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Quality of life and mental health in children with long COVID

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Abstract

Background Pediatric Long COVID (PLC) is a heterogeneous condition, which can have a substantial impact on daily life of children and adolescents. This study aimed to evaluate health related quality of life (HRQoL), and mental and social health of children with PLC, in relation to children with other chronic health conditions (CHC) and from the general population (GP) during the pandemic.

Methods Dutch children (8-18 years) with PLC ($n = 106$, 31% male) were included between May 2021 and March 2023. Reference data was available from a CHC-cohort ($n = 90$, 56% male) and GP-cohort ($n = 844$, 47% male) during the first wave of the pandemic (April–May, 2020). Participants completed the Pediatric Quality of Life Inventory (PedsQL) 4.0 and Patient-Reported Outcomes Measurement Information System (PROMIS) instruments (Anxiety, Anger, Depressive symptoms, Sleep-Related Impairment (SRI), and Peer Relationships). Mean scores were analyzed using adjusted ANCOVA. Relative risks (RR (95% CI)) were calculated for impaired HRQoL and severe PROMIS scores.

Results Children with PLC report high proportions of impaired HRQoL (84%, RR = 3.67 (2.35–5.74)), and have significantly lower PedsQL scores than children with CHC. Children with PLC also exhibit worse PROMIS T-scores of Anxiety, Depressive Symptoms, and SRI than children from the CHC- and GP-cohorts (mean difference range 2.2–9.8 (95%CI 0.6–11.7)), and significantly higher risks of severe anxiety (17%), depressive symptoms (18%), and SRI (17%).

Conclusions PLC can severely impact HRQoL and mental and social health in children. Screening of these outcomes and individualized management of children with PLC should be a vital part of clinical care for these highly burdened patients.

Plain language summary

Pediatric Long COVID (PLC) can significantly affect children's daily lives, but its impact on well-being is not yet fully understood. This study investigated the quality of life, mental health, and social well-being of children with PLC compared to those with other chronic conditions and the general population. Using self-report questionnaires, we found that children with PLC experience worse quality of life and are at higher risk of severe anxiety, depression, and sleep problems. These findings highlight the need for better screening and personalized care to support children with PLC. Understanding the challenges they face can help improve medical care and ensure they receive the right support for their recovery and well-being.

The emergence of the COVID-19 pandemic has brought about unprecedented challenges for children and adolescents globally, not only in terms of its direct physical health implications, but also its profound impact on mental health. The pandemic and associated lockdown measures have disrupted daily routines, social interactions, and access to healthcare services, contributing to heightened levels of psychological distress, anxiety, and depression among children worldwide[1–5]. In addition, the pandemic has had a considerable impact on physical, mental, and social functioning, also known as health related quality of life (HRQoL), in children and adolescents globally[6].

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Research has consistently demonstrated that children with various chronic health conditions are already at a higher risk of developing mental health problems such as anxiety and depression[7–9]. The burden of managing a chronic illness, along with the associated physical symptoms, can substantially impact the overall quality of life and mental well-being of these children[10–12]. In addition, having to manage their conditions amidst risk of SARS-CoV-2-exposure and limitations imposed by lockdowns, can lead to more symptoms of depression and anxiety, and has been shown to be associated with worse mental health outcomes[13,14]. However, there is also evidence which suggests that children with chronic somatic diseases may actually be less susceptible to the negative consequences of the pandemic[15–17]. In particular, Zijlmans and Teela et al. reported fewer problems in mental and social health functioning in Dutch children with chronic somatic health conditions during the pandemic when compared to the general population and children with pre-existing psychiatric problems, suggesting they were least negatively affected by the COVID-19 pandemic lockdown regulations[18].

The emergence of a novel phenomenon known as post COVID-19 condition (or 'Long COVID') in children and adolescents has raised concerns about its potential impact on mental health. Pediatric Long COVID (PLC), was defined by the World Health Organization as symptoms lasting or occurring >3 months after SARS-CoV-2 infection with no alternative diagnosis[19]. A recent study by the Dutch National Institute of Public Health and the Environment (RIVM) estimated that about 5% of Dutch young people (aged 12 to 25 years old) are experiencing post-COVID-19 symptoms[20]. PLC is a heterogeneous condition, for which most common symptoms include fatigue, mood symptoms, headache, cognitive difficulties, respiratory symptoms, and loss of smell[14], which can have a significant impact on daily life[21]. Neurological and neuropsychiatric symptoms such as difficulty concentrating and/or difficulties with memory (also known as 'brain fog'), fatigue, headaches, depression, anxiety, and disrupted sleep, have been linked to neuro-inflammation due to a sustained activation of microglia and astrocytes following SARS-CoV-2 infection, and possibly resulting in neurovascular damage[22,23]. However, the exact pathophysiology of PLC remains poorly characterized, resulting in a lack of biomedical treatment options. A systematic review by Malik et al. showed that Long COVID in adults was associated with poor quality of life[24]. However, research on the HRQoL of children and adolescents with PLC is scarce. The potential long-term implications of PLC on the quality of life and mental and social health of children and adolescents are areas of growing concern and require further investigation.

Therefore, this study aims to evaluate HRQoL and mental and social health of children with pediatric Long COVID, in relation to children with other chronic health conditions and children from the Dutch general population during the pandemic. We found that children with pediatric Long COVID experience significantly worse HRQoL and mental health, including higher levels of anxiety, depressive symptoms, and sleep-related problems. Over 80% report poor HRQoL, with a significantly higher risk compared to children with chronic health conditions. These findings highlight the substantial burden of pediatric Long COVID and underscore the need for targeted screening and individualized care to support affected children.

Methods

Study design, participants and procedure

This study employed an observational, cross-sectional, multi-cohort design to evaluate HRQoL and mental and social health of children (8-18 years old) with PLC, by comparing them to previously published data of children with other chronic health conditions (CHC) and children from the general population (GP) during the pandemic.

Pediatric Long COVID (PLC) cohort. The PLC cohort consisted of children who participated in the Post COVID Syndrome (POCOS)-study, a prospective, observational cohort study conducted at the Amsterdam University Medical Center (Amsterdam UMC), a tertiary care hospital based in Amsterdam, the Netherlands. The POCOS-study aimed to describe clinical characteristics, investigate underlying mechanisms, and identify biomarkers for PLC[25]. Participants consisted of children with physician-diagnosed Long COVID, according to the WHO definition, which defines Long COVID as a condition of newly onset or persisting symptoms at least three months after SARS-CoV-2 infection, lasting for at least 2 months with no other explanation[19]. Participants were included between May 2021 and March 2023. The Medical Ethics Committee of the Amsterdam UMC, location AMC, approved the study (METc 2021_126). All participants and/or caregivers provided informed consent. The PLC cohort consisted of 106 children, with an age range of 8 to 18 years old, of which 31% were male.

Reference data

Chronic health conditions (CHC) cohort. The CHC cohort consisted of children with chronic somatic diseases treated at the Emma Children's Hospital, Amsterdam UMC. Participants were selected from those already undergoing patient-reported outcome measures (PROMs) as part of their standard care, and invited to complete additional questionnaires in early May, 2020, to evaluate mental and social health during the first COVID-19 lockdown. All children and parents provided informed consent and the study was approved by the Medical Ethics Committee of the Amsterdam UMC. The CHC cohort consisted of 90 children, with an age range of 8 to 18 years old, of which 56% were male[18]. Data used for this study was obtained through collaboration with the Department of Child and Adolescent Psychiatry and Psychosocial Care of the Amsterdam UMC. More details on the CHC cohort *prior* to the pandemic can be found in Table 2 of the publication by van Muilekom et al.[26].

General population (GP) cohort. Data from Dutch children during the COVID-19 pandemic were collected through an independent online research agency, "Panel Inzicht," between April 10 and May 5, 2020, to evaluate mental and social health during the first COVID-19 lockdown. The sample was representative of the Dutch general population within 2.5% on most key demographics (age, gender, ethnicity, region, and educational level). Additionally, as a reference group, mean scores from the same sample of Dutch children *before* the pandemic (2018) have been added, but no statistical tests were conducted with this data. All children and parents provided informed consent and the studies were approved by the Medical Ethics Committee of the Amsterdam UMC. The GP cohort consisted of 844 children, with an age range of 8 to 18 years old, of which 47% were male[1]. Data used for this study was obtained through collaboration with the Department of Child and Adolescent Psychiatry and Psychosocial Care of the Amsterdam UMC.

Data collection and outcome measures

Data from all cohorts were primarily collected via online questionnaires administered through the research website of the KLIK Patient-Reported Outcome Measures (PROM) portal[27]. The Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0) PROM was completed by the PLC- and CHC-cohorts, and the Patient-Reported Outcomes Measurement Information System (PROMIS) measures assessing anxiety, anger, depressive symptoms, sleep-related impairment, and peer relationships, were completed by all three cohorts. For children from the PLC-cohort, because PROMs were collected for standard clinical care, patients received questionnaires before their outpatient visit, and results were discussed during the visit.

Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0)

Domains and scoring. The Dutch PedsQL 4.0 is a comprehensive PROM comprising 23 items intended to evaluate the self-reported HRQoL of children. The PedsQL is available in versions for certain age categories, of which two have been used in this study: 8-12 years old and 13-18 years old. It encompasses four domains of HRQoL: Physical Health (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). Employing a recall period of one week, respondents rated items on

a scale from 1 (Never a problem) to 5 (Almost always a problem). These responses were then linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), with higher scores indicating better functioning and better HRQoL. The Total PedsQL score was calculated as the mean of all items across the entire questionnaire, also ranging from 0 to 100. The Psychosocial Functioning PedsQL score was calculated as the mean of the Emotional, Social and School scores. Validation studies have confirmed the suitability of the Dutch PedsQL for clinical use in the Netherlands[28].

Severity cutoffs. Cut-off points for at-risk status of impaired HRQoL by the PedsQL 4.0 were set at 1 standard deviation (SD) below the population mean[29]. The population mean and SD used to create categories of Normal and Impaired HRQoL for this study were based on psychometric properties of PedsQL 4.0 in the Dutch pediatric population[28].

Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires

Domains and scoring. PROMIS item banks and scales, developed and validated using modern psychometric techniques, measure generic unidimensional domains across physical, social, or mental health. These measures were administered as Computerized Adaptive Tests (CAT) format, in which subsequent questions are chosen based on the answers given earlier, resulting in reliable scores with a minimal number of items. Five Dutch PROMIS pediatric measures, including Anxiety, Anger, Depressive Symptoms, Sleep-related Impairment (SRI), and Peer Relationships, were completed by all children and adolescents aged 8 to 18 years. Two additional Dutch PROMIS pediatric measures, Fatigue and Mobility, were completed by the PLC cohort. These measures, recognized by the American Psychiatric Association (APA) as level-2 assessment tools for psychiatric disorder monitoring from DSM-V, utilize a 7-day recall period and are scored on a five-point Likert scale. Total scores were derived by transforming item scores into T-scores ranging from 0 to 100. For PROMIS Anxiety, Anger, Depressive Symptoms, Sleep-related Impairment, and Fatigue, higher scores indicate more symptoms and/or worse functioning. For PROMIS Peer Relationships and Mobility, lower scores indicate more symptoms and/or worse functioning.

Severity cutoffs. Severity cutoffs were determined per PROMIS domain based on psychometric properties of PROMIS questionnaires in Dutch populations[30–33]. For domains where higher scores reflect poorer functioning, severity groups were defined as Minimal (<75th percentile), Moderate (75–94th percentile), and Severe (≥95th percentile). For domains where higher scores reflect greater functioning, severity cutoffs were defined as Good (>25th percentile), Fair (6th–25th percentiles), and Poor (≤5th percentile).

Statistics and reproducibility

IBM Statistical Package for Social Sciences (SPSS) version 28.0 was used to perform statistical analyses. Descriptive analyses were performed to summarize participant characteristics and mean with standard deviation (SD) were calculated for PedsQL and PROMIS T-scores for all three cohorts.

A one-way analysis of covariance (ANCOVA) was conducted to compare the mean PedsQL scores between the PLC- and CHC-cohorts, and the mean PROMIS T-scores between the PLC-, CHC-, and GP-cohorts whilst controlling for age and sex. Levene's test and normality checks were carried out and the assumptions met. Chi-squared tests were conducted to compare severity categories between cohorts and the relative risk (RR) with 95% confidence intervals (95% CI) were reported. The RR represents the risk of a child with PLC having a severe score compared to a child with a CHC or a child from the GP-cohort. A ratio higher than 1 indicated more risk. Bonferroni-corrected post-hoc t-tests were performed to determine which cohorts differed significantly (defined as a p-value < 0.05) from each other.

Comparative analyses for PROMIS T-scores between the CHC- and GP-cohort have been previously published[18] and will therefore not be performed in the current study. Each participant was considered a biological replicate, and no technical replicates were used. All statistical tests were two-sided and reproducibility of the analyses was ensured through use of predefined protocols and consistent data processing across cohorts.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Cohort demographics

In total, 106 children with PLC were included in the study. Reference data of 90 children with CHC and 844 children from the GP-cohort during the pandemic was available for comparison, and pre-pandemic PROMIS outcomes of 1319 children from the general population were added to Supplementary Table S1. A timeline of administration of questionnaires per cohort can be found in Supplementary Fig. S1. Demographics of all participants are presented in Table 1. Participants of the PLC-cohort were between 8 and 18 years old, with a median age of 15 years (IQR 12–17 years), and consisted of mostly girls (68.9%). Atopic (48.5%) and psychological (20.4%) comorbidities were common in the PLC cohort. All children with PLC had mild to moderate acute COVID-19; none were admitted to the hospital during the acute phase. Data on medical history and comorbidities were not available for the GP cohort. Additional demographic information for the CHC- and GP- cohorts can be found in Supplementary Table S2.

Outcomes scores for PedsQL in the PLC- and CHC-cohorts

In total, 106 children with PLC and 89 children with CHC completed PedsQL questionnaires. Table 2 shows adjusted mean outcome scores and mean differences per age category for both cohorts. After controlling for covariates sex and age, children with PLC scored significantly worse on all PedsQL domains than children with CHC during the pandemic ($p < 0.03$, η^2 0.07–0.40). Largest differences were found in Physical Functioning and in School Functioning.

Figure 1 and Table 3 report percentages of children with PLC and CHC with impaired HRQoL (defined as ≤1 SD below Dutch norm values) per PedsQL domain. A high proportion of children with PLC (84.4%) reported impaired PedsQL total scores. Additionally, significantly more children with PLC reported impaired PedsQL scores compared to children with CHC on the following domains: for Physical Functioning (85.8% versus 28.1%; RR: 4.13; 95% CI 2.59–6.58), Emotional Functioning (48.1% versus 24.7%; RR: 1.55; 95% CI 1.21–1.98), Social Functioning (55.7% versus 16.9%; RR: 2.05; 95% CI 1.60–2.64), School Functioning (80.2% versus 34.8%; RR: 2.76; 95% CI 1.88–4.04), and Psychosocial Functioning (75.5% versus 32.6%; RR: 2.43; 95% CI 1.73–3.41).

Sub-analyses were performed to evaluate HRQoL in a subgroup of children with pre-existing psychological and/or psychiatric conditions ($n = 15$) from the PLC-cohort. The mean PedsQL total score for this subgroup was 52.80, compared to 58.07 for children without psychological and/or psychiatric conditions ($n = 92$) (mean difference: −5.27, 95% CI = −14.16 to 3.60). The proportion of impaired HRQoL was 100% for children with psychological and/or psychiatric conditions, versus 82.6% for the group without (Pearson Chi-Square p-value = 0.09).

Outcomes scores for PROMIS in the PLC-, CHC-, and GP-cohorts

In the PLC cohort, 86 children completed PROMIS Peer Relationships, and 105 children completed PROMIS Anxiety, Anger, Depressive Symptoms, Sleep Related Impairment, Fatigue, and Mobility. T-scores for PROMIS Anxiety, Anger, Depressive Symptoms, Peer Relationships, and Sleep Related Impairment, were compared to previously collected PROMs of 90 children with CHC and 815 children from the GP. Adjusted mean outcome scores for all cohorts are shown in Table 4. After controlling for covariates sex and age, there was a significant difference in mean PROMIS T-scores for Anxiety, Anger, Depressive Symptoms, Sleep Related Impairment, and Peer

relationships ($p < 0.001$, $\eta^2 = 0.02–0.07$) between the three cohorts. Post-hoc tests showed (Supplementary Table S3) there was a significant mean difference between the PLC- and CHC-cohort for PROMIS Anxiety (ΔM = 6.9, 95% CI = 4.4–9.4, $\eta^2 = 0.14$), PROMIS Anger (ΔM = 3.6, 95% CI = 0.7–5.6, $\eta^2 = 0.05$), PROMIS Depressive Symptoms (ΔM = 7.8, 95% CI = 4.1–9.2, $\eta^2 = 0.12$), and PROMIS SRI (ΔM = 9.8, 95% CI = 6.6–11.7, $\eta^2 = 0.21$), but not for PROMIS Peer Relationships (p = 0.74). Post hoc tests also revealed statistically significant differences in means between the PLC- and GP-cohort (Supplementary Table S4) for PROMIS Anxiety, Depressive Symptoms, SRI, and Peer Relationships, but with lower effect sizes (0.01–0.07).

Table 1 | Demographics and clinical characteristics of participants per cohort

	PLC (*n* = 106)	CHC (*n* = 90)	GP (*n* = 844)
Sex; male (*n*, %)	32 (31.1%)	50 (55.6%)	400 (47.4%)
Age (median, IQR)	15 (12, 17)	12 (10, 16)	13 (11, 16)
Medical history and comorbidities (n, %)			[b]
Atopic[a]	50 (48.5%)	0 (0.0%)	
Auto-immune	0 (0.0%)	18 (20.0%)	
Congenital	1 (1.0%)	18 (20.0%)	
Endocrinological	0 (0.0%)	7 (7.8%)	
Hematological	0 (0.0%)	14 (15.5%)	
Pulmonary	12 (11.7%)	6 (6.7%)	
Psychological	15 (14.5%)	0 (0%)	
Gastro-intestinal	0 (0.0%)	10 (11.1%)	
Other	19 (18.4%)	17 (18.9%)	
None	32 (31.1%)	0 (0.0%)	
Months since SARS-CoV-2 infection (median, IQR)	16 (10, 22)	n.a.	n.a.

PLC Pediatric Long COVID, *CHC* Chronic Health Conditions, *GP* General Population, *n.a.* Not applicable.
[a]Includes allergies (dust mite, food and hay fever) and eczema. Asthma was included as Pulmonary.
[b]Medical history and comorbidities were not available for the GP cohort.

There seems to be an indication of increased fatigue in children with PLC compared to children from the GP *before* the pandemic (mean PROMIS Fatigue T-score: 62.9 versus 39.8) and decreased mobility (mean PROMIS Mobility score: 39.3 versus 57.9), however, no statistical tests were performed to compare these scores.

Figure 2 and Table 5 report percentages of children from the PLC-, CHC- and GP-cohorts minimal, moderate, and severe PROMIS scores per domain. For PROMIS Anxiety and PROMIS Anger, significantly more children with PLC had severe scores than children from the GP (17.0% versus 5.2%, RR: 2.97; 95% CI 1.89–4.66, and 8.0% versus 2.8%, RR: 2.48; 95% CI 1.32–4.66, respectively). For PROMIS Depressive Symptoms, children with PLC had a significantly higher percentage of severe scores than children with CHC (18.0% versus 1.1%, RR: 1.98; 95% CI 1.64–2.39), and than children from the GP (18.0% versus 2.7%, RR: 4.84; 95% CI 3.23–7.23). For PROMIS Sleep Related Impairment, children with PLC had a significantly higher percentage of severe scores than children with CHC (16.8% versus 2.2%, RR: 1.83; 95% CI 1.47–2.28), and than children from the GP (16.8% versus 2.0%, RR: 5.42; 95% CI 3.66–8.03). For PROMIS Peer Relationships, no children with PLC reported severe scores.

Discussion

This study showed that Dutch children and adolescents with PLC reported worse HRQoL and mental health than children and adolescents with CHC and children and adolescents from the general population during the pandemic. Over 80% of children with PLC reported impaired HRQoL, and were at significantly higher risk of having impaired HRQoL than children with CHC during the pandemic.

Similarly, we observed significantly decreased self-reported mental health in children and adolescents with PLC, who reported more anxiety, depressive symptoms, and sleep related problems than children with CHC and children from the general population during the pandemic. This was also reflected by the increased risk of severe anxiety, anger, depressive symptoms, and sleep related impairment in children with PLC compared to children with CHC and children from the general population.

These results show the substantial impact of PLC on quality of life and mental health of children and adolescents. This may be attributed to the drastic decline in physical and daily life functioning; most children went

Table 2 | Mean PedsQL scores from PLC- and CHC-cohorts during the pandemic

	PLC	CHC	η^2	Mean difference (95% CI)	*p*-value[a]
	Mean (SD)[b]	Mean (SD)[b]			
PedsQL scores: 8 to 12 years	(*n* = 31)	(*n* = 46)			
Total score	63.6 (13.8)	81.3 (13.7)	0.26	−16.9 (−23.6, −10.3)	0.001
Physical functioning	59.6 (18.5)	85.1 (16.8)	0.30	−23.3 (−31.4, −15.0)	0.001
Emotional functioning	64.7 (18.6)	74.6 (18.5)	0.07	−10.2 (−19.1, −1.3)	0.025
Social functioning	74.4 (14.4)	86.4 (16.3)	0.12	−11.8 (−19.3, −4.3)	0.003
School functioning	58.2 (19.0)	77.0 (17.2)	0.20	−18.8 (−27.5, −10.1)	0.001
Psychosocial functioning	65.8 (14.5)	79.3 (14.6)	0.17	−13.6 (−20.7, −6.5)	0.001
PedsQL scores: 13 to 18 years	(*n* = 75)	(*n* = 43)			
Total score	54.8 (15.7)	80.2 (12.7)	0.40	−24.3 (−29.9, −18.8)	0.001
Physical functioning	50.8 (21.4)	82.3 (17.1)	0.35	−30.4 (−38.1, −22.8)	0.001
Emotional functioning	60.3 (21.0)	78.3 (16.0)	0.14	−15.3 (−22.5, −8.2)	0.001
Social functioning	69.0 (18.3)	84.9 (15.8)	0.16	−15.7 (−22.3, −9.0)	0.001
School functioning	41.5 (21.5)	74.2 (16.1)	0.38	−32.3 (−40.0, −24.6)	0.001
Psychosocial functioning	56.9 (16.2)	79.1 (12.8)	0.32	−21.1 (−26.8, −15.4)	0.001

PLC Pediatric Long COVID, *CHC* Chronic Health Conditions, *SD* Standard Deviation, *CI* Confidence Interval, *Psychosocial* Emotional + Social + School functioning combined.
η^2 = Amount of variance explained by group membership.
[a]*P*-value of the main effect of ANCOVA.
[b]Adjusted means and standard deviation (SD) from ANCOVA (adjusted for sex and age).

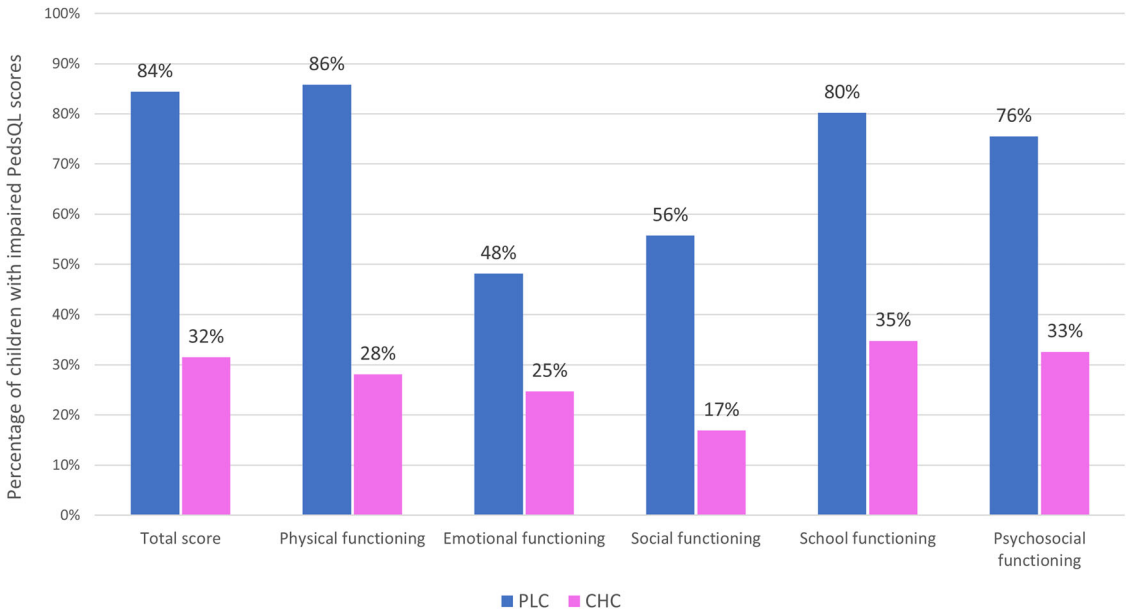

Fig. 1 | Percentage of impaired HRQoL per domain for children with PLC vs. children with CHC during the pandemic. PLC Pediatric Long COVID ($n = 106$), CHC Chronic Health Conditions ($n = 89$), *Psychosocial* Emotional + Social + School functioning combined.

Table 3 | Portion of children with impaired scores of PedsQL domains in PLC- and CHC-cohorts during the pandemic

	PLC ($n = 106$)	CHC ($n = 89$)	Relative Risk[a] (95% CI)	*p*-value[b]
PedsQL - Total score	90 (84.4%)	28 (31.5%)	3.67 (2.35, 5.74)	0.001
PedsQL - Physical functioning	91 (85.8%)	25 (28.1%)	4.13 (2.59, 6.58)	0.001
PedsQL - Emotional functioning	51 (48.1%)	22 (24.7%)	1.55 (1.21, 1.98)	0.001
PedsQL - Social functioning	59 (55.7%)	15 (16.9%)	2.05 (1.60, 2.64)	0.001
PedsQL - School functioning	85 (80.2%)	31 (34.8%)	2.76 (1.88, 4.04)	0.001
PedsQL - Psychosocial functioning	80 (75.5%)	29 (32.6%)	2.43 (1.73, 3.41)	0.001

PLC Pediatric Long COVID, *CHC* Chronic Health Conditions, *CI* Confidence Interval, *Psychosocial* Emotional + Social + School functioning combined.
[a] Relative risk of having impaired quality of life when suffering from PLC compared to when suffering from a chronic health condition.
[b] *P*-value from Chi-squared test.

Table 4 | Mean PROMIS T-scores from all cohorts

	PLC ($n = 86$–105)*	CHC ($n = 90$)	GP ($n = 815$)	η^2	*p*-value**
	Mean (SD)***	Mean (SD)***	Mean (SD)***		
PROMIS Anxiety[a]	52.7_a (8.8)	44.8_b (8.0)	50.5_c (7.6)	0.05	0.001
PROMIS Anger[a]	47.3_a (9.8)	43.7_b (9.0)	$47.3_{a,c}$ (8.2)	0.02	0.001
PROMIS Depressive Symptoms[a]	53.0_a (9.4)	45.2_b (8.0)	49.4_c (8.0)	0.04	0.001
PROMIS Sleep Related Impairment[a]	57.3_a (8.8)	47.5_b (8.2)	49.9_c (8.7)	0.07	0.001
PROMIS Peer Relationships[b]	49.3_a (6.7)	$49.3_{a,b}$ (8.2)	44.3_c (7.0)	0.07	0.001
PROMIS Fatigue[a]	62.9 (10.2)	n.a.	n.a.	n.a.	n.a.
PROMIS Mobility[b]	39.3 (6.0)	n.a.	n.a.	n.a.	n.a.

PLC Pediatric Long COVID, *CHC* Chronic Health Conditions, *GP* General Population, *SD* Standard Deviation.
η^2 = Amount of variance explained by group membership.
n.a. Not applicable: PROMIS Fatigue and Mobility were only available for the PLC-cohort.
[a]Higher scores indicate more symptoms.
[b] Higher scores indicate better functioning.
*Number of completed questionnaires differed between domain, $n = 86$ for PROMIS Peer Relationships, and $n = 105$ for other PROMIS measures in PLC cohort.
**P-value of the main effect of ANCOVA.
***Adjusted means and SD from ANCOVA (adjusted for sex and age). [a,b,c]Represent significant differences ($p < 0.05$, Bonferroni corrected) between samples as indicated by post-hoc Tukey tests.

from being physically healthy before SARS-CoV-2 infection, to being severely affected, leading to decreased ability to engage in school, sports, social activities, and family life. In addition, children with PLC and their parents have often had a long journey towards diagnosis and appropriate management, which is reflected by our PLC-cohort (average time between infection and study visit was 16 months). They've faced challenges such as a lack of awareness or compassion for PLC, misinterpretation of symptoms, or neglect from healthcare professionals[34]. A recent study[35] found that children with PLC experience a negative social stigma towards their condition, and although this has not yet been studied further in children, these

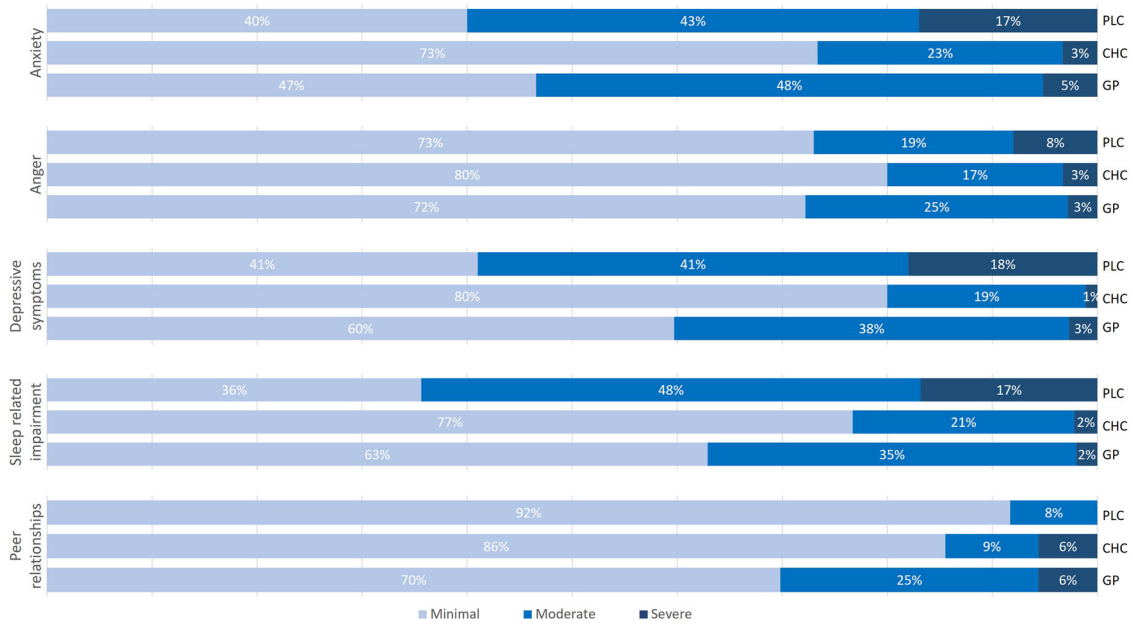

Fig. 2 | Severity categories of PROMIS domains for children from the PLC-, CHC-, and GP-cohorts during the pandemic. PLC Pediatric Long COVID ($n = 105$), CHC Chronic Health Conditions ($n = 90$); GP General Population ($n = 815$)

stigmas have been associated with worse mental health outcomes in adults with Long COVID[36]. Furthermore, although symptom management and rehabilitation strategies are being employed, there is a lack of biomedical treatment options for PLC, which may induce feelings of hopelessness and frustration, and thereby negatively affect mental health. Additionally, about 15% of children from the PLC-cohort reported psychological and/or psychiatric comorbidities such as diagnosed autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and generalized anxiety disorder. Their PLC-symptoms and impairments in daily functioning might be influenced by their pre-existing mental health condition, which could explain the trend towards worse HRQoL scores we found in this subgroup. However, this was not statistically significant, possibly because the subgroup only comprised 15 children. Another important finding of our study is that children with PLC show worse HRQoL and mental health compared to children with other CHC during the pandemic. This CHC-cohort also reported less problems in mental and social health functioning during the pandemic compared to the general population and children with pre-existing psychiatric problems[18]. Research has shown that children with CHC, although facing ongoing health challenges, can maintain an acceptable level of life satisfaction[37]. Furthermore, when managing their disease, these children are more often confronted with stressful situations directly impacting their physical health and daily, which might contribute to more effective coping mechanisms, leading to better PedsQL and PROMIS scores. In children with PLC, these coping mechanisms may not (yet) be in place, since they have only recently been confronted with their chronic illness, instead of having adapted to it throughout their lives like children with other CHC. Moreover, the consequences of the COVID-19 pandemic, such as lockdown and social distancing, may have been less disruptive for some children with CHC, as they might already be accustomed to activities like home schooling and social distancing, minimalizing the impact on their quality of life and mental health[15–18].

Surprisingly, no children and adolescents with PLC reported severe scores for the PROMIS Peer Relationships. Mean PROMIS Peer Relationship scores were comparable between the PLC- and CHC-cohort, but were worse in the general population during the pandemic. This might be due to the fact that PROMs for the GP-cohort were administered in the first wave (April-May 2020) of the pandemic, when strict lockdowns and quarantine measures were in place in The Netherlands[38]. These severe restrictions heavily impacted children's relationships during this time[1]. In contrast, for the PLC-cohort, PROMIS questionnaires were administered between May 2021 and March 2023, when most social restrictions were lifted, possibly leading to a lower impact on relationships with peers. For the CHC-cohort, PROMs were also administered during the first lockdown, but were not worse than in the PLC-cohort. This might, in addition to the beforementioned coping strategies, be explained by these children already being more used to having online contact with friends[18]. Children with PLC were at increased risk of severe anxiety, anger, depressive symptoms, and sleep related impairment. These symptoms have previously been found to be associated with neuroinflammation after COVID-19 in adults[22,23,39], and may be part of the reason why neurocognitive and neuropsychiatric symptoms are more prevalent in children with Long COVID than in children with other chronic diseases, which do not involve a neuroimmune response and/or neurovascular damage.

Our findings are in line with an article by Chen et al. (2023), who reported significantly lower HRQoL in American children and adolescents with PLC than previously published controls[40]. A systematic review on the prevalence of mental health problems among children with PLC, found that children with previous COVID-19 were more than two times at higher odds of having anxiety and depression than children who were not infected with SARS-CoV-2[41]. Similar findings have been described in adults with Long COVID, reporting a deterioration in quality of life[42], and highlighting the considerable burden of mental health issues, including depression, anxiety, and sleep disorders[43,44]. However, what makes our study unique, is its account of HRQoL and mental and social health in children with PLC who were not admitted to the hospital during acute COVID-19, and its comparison to reference groups of children with other CHC and children from the general population during the pandemic.

Some limitations of this study need to be taken into account. Firstly, because this was a cross-sectional study, there is no longitudinal information on HRQoL and mental health status for our PLC-cohort. It was therefore not possible to evaluate the causality of pre-existing HRQoL impairment or mental and social health problems and current outcomes. Secondly, this study only included patients with PLC with severe symptoms, who were referred to a tertiary care center, creating a selection bias and thereby possibly lowering the generalizability of our results. Thirdly, questionnaires were administered at different time

Table 5 | Severity categories of the PROMIS domains for all cohorts

	PLC (n = 86 –105)*	CHC (n = 90)	GP (n = 815)	Relative Risk* (95% CI)	p-value**
PROMIS Anxiety[w]					0.001
Minimal	40 (40.0%)$_a$	66 (73.3%)$_b$	392 (46.6%)$_a$	1.74 (1.37, 2.21)[y]	
Moderate	43 (43.0%)$_a$	21 (23.3%)$_b$	408 (48.3%)$_a$	2.97 (1.89, 4.66)[z]	
Severe	17 (17.0%)$_a$	3 (3.3%)$_{a,b}$	44 (5.2%)$_b$		
PROMIS Anger[w]					0.025
Minimal	73 (73.0%)$_a$	72 (80.0%)$_a$	609 (72.2%)$_a$	1.42 (0.96, 2.09)[y]	
Moderate	19 (19.0%)$_a$	15 (16.7%)$_a$	211 (25.0%)$_a$	2.48 (1.32, 4.66)[z]	
Severe	8 (8.0%)$_a$	3 (3.3%)$_{a,b}$	24 (2.8%)$_b$		
PROMIS Depressive Symptoms[w]					0.001
Minimal	41 (41.0%)$_a$	72 (80.0%)$_b$	504 (59.7%)$_c$	1.98 (1.64, 2.39)[y]	
Moderate	41 (41.0%)$_a$	17 (18.9%)$_b$	317 (37.6%)$_a$	4.84 (3.23, 7.23)[z]	
Severe	18 (18.0%)$_a$	1 (1.1%)$_b$	23 (2.7%)$_b$		
PROMIS Sleep Related Impairment[w]					0.001
Minimal	36 (35.6%)$_a$	69 (76.7%)$_b$	531 (62.9%)$_c$	1.83 (1.47, 2.28)[y]	
Moderate	48 (47.5%)$_a$	19 (21.1%)$_b$	296 (35.1%)$_c$	5.42 (3.66, 8.03)[z]	
Severe	17 (16.8%)$_a$	2 (2.2%)$_b$	17 (2.0%)$_b$		
PROMIS Peer Relationships[w]					0.001
Good	77 (91.7%)$_a$	77 (85.6%)$_a$	589 (69.8%)$_b$	n.a.	
Fair	7 (8.3%)$_a$	8 (8.9%)$_a$	208 (24.6%)$_b$	n.a.	
Poor	0 (0.0%)$_a$	5 (5.6%)$_a$	47 (5.6%)$_a$		
PROMIS Fatigue[w]					
Minimal	9 (8.6%)	n.a.	n.a.	n.a.	n.a.
Moderate	32 (30.5%)				
Severe	64 (61.0%)				
PROMIS Mobility[x]					
Good	6 (5.9%)	n.a.	n.a.	n.a.	n.a.
Fair	18 (17.6%)				
Poor	78 (76.5%)				

PLC Pediatric Long COVID, *CHC* Chronic Health Conditions, *GP* General Population, *CI* Confidence Interval, *n.a.* Not applicable: PROMIS Fatigue and Mobility were only available for the PLC-cohort. *Number of completed questionnaires differed between domain, n = 86 for PROMIS Peer Relationships, and n = 105 for other PROMIS questionnaires in PLC-cohort. **P-value from Chi-squared test. [a,b,c]Represent significant differences ($p < 0.05$, Bonferroni corrected) between samples as indicated by post-hoc Tukey tests.[w] Cutoffs defined by Luijten et al. based on Dutch children. [x]Cutoffs defined by Carle et al. based on American children. [y]Relative risk of being in Severe PROMIS category for children with PLC compared to children with CHC. [z]Relative risk of being in Severe PROMIS category for children with PLC compared to GP children.

points by the cohorts, with the PLC-group completing questionnaires between May 2021 and March 2023, and the CHC and GP group completing questionnaires between April and May 2020. This was in the early period of the COVID-19 pandemic, when the lockdown had been introduced a month prior, and may therefore not bring out some of the longer-term pandemic-related impacts on children, particularly on mental health.

This study highlights the risk of impaired HRQoL and mental health burden of children and adolescents with PLC. At this time, a definitive, all-encompassing screening tool has not yet been established for PLC. Seylanova et al.[45] found four critical outcome measurement instruments for pediatric Long COVID through Delphi consensus. These were the 'PedsQL Multidimensional Fatigue Scale' for measuring fatigue; the 'PedsQL Gastrointestinal Symptom Scales' for evaluating gastrointestinal outcomes; the 'PedsQL Cognitive Functioning Scale' for assessing neuro-cognitive outcomes; and the 'EQ5D family' for physical functioning assessments. These instruments gives some important direction in identifying and diagnosing PLC, but do not cover the complete picture. From our experiences in caring for children with CHC, we find it is important to structurally monitor HRQoL by using the PedsQL and PROMIS measurements, and discuss the results with patients in daily clinical practice[26]. Future research implications include long-term evaluation of mental and social health in children suffering from PLC. Participants in our PLC-cohort received follow-up questionnaires at 6 and 12 months after their initial questionnaire, which will give insight into the longitudinal impact of PLC on HRQoL and mental and social health, and might increase understanding of possible predictors and risk factors. Furthermore, our study suggests that HRQoL can be a valuable outcome measure for research studies concerning the impact of PLC, and should, as previously described by Buonsenso et al.[46], be taken into consideration for clinical studies besides self-reported symptoms.

In conclusion, pediatric Long COVID can severely impact HRQoL and mental health in children and adolescents. Children with PLC are at higher risk of developing impaired HRQoL and severe anxiety, anger, depressive symptoms, and sleep related problems than children with CHC and children from the general population during the pandemic. Mental health screening and individualized management of children with PLC should be a vital part of clinical care for these highly burdened patients.

Data availability

The data used in this manuscript is from the Emma Children's Hospital of the Amsterdam UMC. Due to the sensitive nature of this data, it is not publicly available. Anonymized datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. The source data for all Tables and Figures is available at Figshare (https://doi.org/10.6084/m9.figshare.29161532.v1).

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Author contributions

S.W.J.T.-L. conceived the study. L.C.E.N., C.R.L., S.H., L.T., K.J.O., M.A.vH., G.B., L.H. and S.W.J.T.-L.; M.A.J.L. conceptualized and designed the study. Material preparation, data collection and analysis were performed by L.C.E.N., C.R.L., M.A.J.L., L.T., K.J.O., M.W.A., G.B., L.H. and S.W.J.T.-L.; The first draft of the manuscript was written by L.C.E.N. and all authors commented on previous versions of the manuscript. S.H., M.A.vH., G.B., A.H.M.-Z., J.B.vG. and S.W.J.T.-L. supervised the process. All authors read and approved the final manuscript.

Competing interests

The authors declare the following competing interests: AHM-Z is the PI of a public private consortium [P4O2 (Precision Medicine for More Oxygen)] sponsored by Health Holland involving many private partners that contribute in cash and/or in kind (AbbVie. Boehringer Ingelheim, Breathomix, Clear, Fluidda, Ortec Logiqcare, Olive, Philips, Quantib-U, Smartfish, Clear, SODAQ, Thirona, Roche, TopMD, Novartis, RespiQ). She received unrestricted research grants from GSK and Boehringer Ingelheim and received the Vertex innovation award grant, and had honoraria paid to institution by GSK, Boehringer Ingelheim and Astra Zeneca. AHM-Z is also the chair of DSMB of a study on BPD in neonates and the president of FIGON (Federation Innovative drug research in the Netherlands). JBvG has received a grant from Danone Research and has a patent planned for amino acid composition of infant formulas. He is a member of the national health council (unpaid) and the director of the national Human Milk Bank (unpaid). L.C.E.N., C.R.L., M.A.J.L., S.H., L.T., K.J.O., M.W.A., M.A.v.H., G.B., L.H. and SWJT-L declare no competing interests.

Ethical approval

The medical ethics committee of the Amsterdam UMC, location AMC, approved the study (METc 2021_126). All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent to participate in the study has been obtained from all participants (or their parent or legal guardian in the case of children under 16).

Additional information

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