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Long-COVID in children and adolescents: a systematic review and meta-analyses

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The objective of this systematic review and meta-analyses is to estimate the prevalence of long-COVID in children and adolescents and to present the full spectrum of symptoms present after acute COVID-19. We have used PubMed and Embase to identify observational studies published before February 10th, 2022 that included a minimum of 30 patients with ages ranging from 0 to 18 years that met the National Institute for Healthcare Excellence (NICE) definition of long-COVID, which consists of both ongoing (4 to 12 weeks) and post-COVID-19 (≥12 weeks) symptoms. Random-effects meta-analyses were performed using the MetaXL software to estimate the pooled prevalence with a 95% confidence interval (CI). Heterogeneity was assessed using I^2 statistics. The Preferred Reporting Items for Systematic Reviewers and Meta-analysis (PRISMA) reporting guideline was followed (registration PROSPERO CRD42021275408). The literature search yielded 8373 publications, of which 21 studies met the inclusion criteria, and a total of 80,071 children and adolescents were included. The prevalence of long-COVID was 25.24%, and the most prevalent clinical manifestations were mood symptoms (16.50%), fatigue (9.66%), and sleep disorders (8.42%). Children infected by SARS-CoV-2 had a higher risk of persistent dyspnea, anosmia/ageusia, and/or fever compared to controls. Limitations of the studies analyzed include lack of standardized definitions, recall, selection, misclassification, nonresponse and/or loss of follow-up, and a high level of heterogeneity.

Abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSS	Cross-sectional study
DM	Diabetes mellitus
QCed	Quality-controlled
IRR	Incidence rate ratios
NICE	National Institute for Health and Care Excellence
MIS-C	Multisystem inflammatory syndrome
ORs	Odds ratios
PCS	Prospective cohort study
PRISMA	Preferred Items for Systematic Reviews and Meta-analyses
RCS	Retrospective cohort study
rt-PCR	Real-time reverse transcription-polymerase chain reaction

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SARS-CoV-2   Severe acute respiratory syndrome coronavirus 2
PASC   Post-acute sequelae of SARS-CoV-2

It has been over 2 years since the coronavirus disease 2019 (COVID-19) pandemic was first declared. Consequently, millions of cases and thousands of deaths have been reported worldwide[1]. Still, treatments have been developed during this time, and effective vaccines have been widely administered to the population, both children and adults, protecting millions from severe disease and death[2]. Until now, the focus was primarily aimed at the acute phase of the disease. However, many individuals experience debilitating COVID-19 symptoms months later, requiring additional medical attention and follow-up.

Severe COVID-19 is less common in children than in adults[3]; however, at least two long-term consequences occur following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children: multisystem inflammatory syndrome (MIS-C) and long-COVID. Both consequences can even appear in asymptomatic patients[4]. MIS-C is a condition where different body parts become inflamed[4], it occurs in less than 0.01% of children infected and requires intensive care support in 68% of cases[5]. Long-COVID is a heterogeneous multisystemic condition for which there is still no precise definition and includes signs and symptoms that persist, develop, or fluctuate after SARS-CoV-2 infection. In October 2021, the WHO proposed a clinical definition for post-COVID-19 through a Delphi consensus stating it generally occurs three months from the onset of COVID-19, with symptoms lasting at least two months and cannot be explained by an alternative diagnosis[6]. On February 2nd, 2022, the National Institute for Health and Care Excellence (NICE) published a guideline defining long-COVID as signs and symptoms that continue or develop after acute COVID-19. This includes ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)[7]. Other organizations, such as the National Institutes of Health (N.I.H.), also define long-COVID as post-acute symptoms after 4 weeks[8]. Many authors have used the following terms interchangeably when referring to long-COVID: long-haulers, COVID-long, post-acute sequelae of COVID-19 (PASC), post-COVID, COVID syndrome, and long-COVID. In the present study, we will use the generic definition from NICE and N.I.H., referring to long-COVID.

To date, most of the published research on long-COVID primarily focuses on adult populations, and there is limited information on pediatric populations[9,10]. The most recent meta-analysis has studied the long-COVID symptoms and their prevalence, risk factors, type, and duration, including studies up to July 2021, encompassing 23,141 children and young people[9]. The most common symptoms were fatigue 47%, dyspnea 43%, and headache 35%. In addition, compared to controls, the prevalence of cognitive difficulties, headache, loss of smell, sore throat, and sore eyes was statistically higher[9]. However, due to the lack of data, this study could only compute the pooled prevalence for 10 symptoms. To date, the potential range of signs and symptoms and their frequency of occurrence in children and adolescents remains unclear[11]. There is a need to create awareness among parents, physicians, and researchers on the afflictions following COVID-19 infection and the health system to better understand the sequelae to provide targeted medical attention and treatment. This systematic review and meta-analyses aim to estimate the prevalence of long-COVID in children and adolescents and identify the full spectrum of symptoms.

Methods

Data sources and search strategy.
This systematic review and meta-analyses were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline[12]. It examines the prevalence of long-COVID signs and symptoms in children under the age of 18 with a diagnosed case of COVID-19 (confirmed via real-time reverse transcription-polymerase chain reaction (rt-PCR), antigen or antibody (or serology tests). To achieve this, two independent investigators (T.W.O. and S.L.L.) searched PubMed and Embase to identify studies that met the following criteria: (1) a minimum of 30 patients, (2) ages ranged from 0 to 18 years, (3) studies published in English, (4) published before February 10th, 2022, and (5) meet the NICE definition of long-COVID, (6) excluding cohorts of children composed of exclusively pre-existing chronic diseases, or exclusively of MIS-C in children, and (7) excluding references of editorials, reviews, and commentaries (Fig. 1).

The search terms used to identify publications discussing long-COVID in children were: (COVID-19 OR COVID OR SARSCOV-2 OR coronavirus OR "long-COVID" OR "post COVID") AND (PASC OR haulers OR lingering OR "post-acute" OR persistent OR convalescent OR convalescence OR sequelae OR post-viral) AND (pediatric OR kids OR young OR infant OR children OR adolescents). Given that MedLine was included in the PubMed search, we excluded articles from MedLine in the Embase search along with those not related to COVID-19. Observational studies, including cohorts and cross-sectional studies, were analyzed only when the cases (numerator) were part of a COVID-19 cohort (denominator). Titles, abstracts, and full texts of articles were independently screened. Disagreement on including a full-text article was discussed among all the authors. We developed and registered a review protocol (PROSPERO registration number: CRD42021275408).

Screening and data extraction.
Data were extracted by four authors (A.C., N.C.A., P.R., R.S.) and Quality-Controlled (QCed) data by two authors (T.W.O., N.C.P.). Discrepancies were discussed with a third author. The descriptive variables extracted were country, study design, period of study, collection mode, follow-up time, the severity of COVID-19, sample size, COVID-19 diagnosis, age, percentage of males, outcomes, and names used to describe the long-term effects of COVID-19.

Statistical analysis.
Random-effects meta-analyses were performed for symptoms reported in two or more studies using MetaXL software to estimate the pooled prevalence, which uses a double arcsine transformation[13].
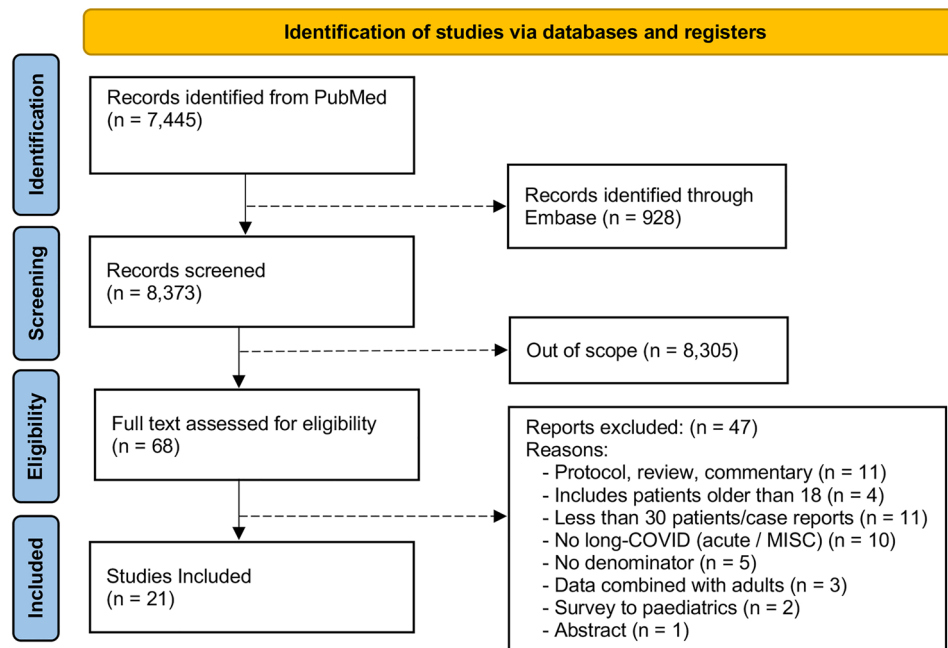
Figure 1. PRISMA diagram with exclusion criteria. Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) screening process flow. Out of 8373 identified studies and after applying the inclusion and exclusion criteria, 21 studies were included in the quantitative synthesis.

Prevalence (presented as percentages) with 95% confidence intervals (C.I.s) was estimated. Numerators represented the number of children with long-COVID, and denominators described the total number of children with acute COVID-19 (with and without long-term effects). To compare cases and controls adjusted for confounders, we used Review Manager (RevMan) software 5.4 to estimate the odds ratios (O.R.s)[14]. A p-value < 0.05 was considered statistically significant. Given the heterogeneity expected, a random-effects model was employed using the I^2 statistics. Values of 25, 50, and 75% for I^2 represented low, medium, and high heterogeneity, respectively. Studies with high precision plotted near the average, and those with low precision are speeded evenly on both sides of the average. Deviation from a funnel shape distribution this shape can indicate publication bias[14]. The quality control of the study was assessed using the QCed data. The MetaXL Guidelines describe and recommend this index, which evaluates the quality of studies assessing prevalence.

Results

General characteristics of studies. The title and abstract of 8373 publications were screened. After duplicates were removed, the search identified 68 publications after screening titles and abstracts, and 47 were excluded because they did not fulfill the inclusion criteria. A total of 21 studies were selected for the analyses (Fig. 1). The general study characteristics are shown in Table 1. Different authors have used the terms "Post-acute COVID", "long-COVID", "Persistent COVID", and "Persistent COVID Symptoms" as synonyms. Most of the studies assessed pre-specified symptoms included in a questionnaire. 18 of the selected studies come from European cohorts (Denmark, Russia, Italy, Germany, Tukey, Latvia, UK, France, Sweden, and Switzerland), one from Iran, one from Brazil, and one from Australia. The studies by Kikkenborg[15] and Borch[16] included an overlapping population (Denmark), as did Roge[17] and Smane[18] (Latvia). To ensure that no overlapping data were included, only the study with the largest sample size was included to estimate long-COVID and for outcomes reported in both studies. Still, several outcomes were only presented in one of the studies, therefore both studies were included in the overall meta-analysis. Four studies included only hospitalized patients, and the rest included all COVID-19 severities (asymptomatic, mild, moderate, and severe). The number of patients included in the studies ranged from 53 to 57,763, and ages ranged from 0 to 18 years. A total of 80,071 children and adolescents with COVID-19 were included in the meta-analyses. We identified more than 40 long-term clinical manifestations associated with COVID-19 in the literature reviewed (Table 2).

Meta-analyses of the prevalence of long-COVID. The prevalence of long-COVID in children and adolescents, as defined by the presence of one or more symptoms more than 4 weeks following a SARS-CoV-2 infection, was 25.24% (95% CI 18.17–33.02, I^2 99.61%) (Figs. 2, 3). For hospitalized patients, the prevalence of long-COVID was 29.19% (95% CI 17.83–41.98, I^2 80.84%). The most common symptoms and percentage of prevalence associated were mood symptoms (e.g., sadness, tension, anger, depression, and anxiety) (16.50%; 95% CI 7.37–28.15, I^2 97.49%), fatigue (9.66%; 95% CI 4.45–16.46, I^2 99.12%), sleep disorders (e.g., insomnia, hypersomnia, and poor sleep quality) (8.42%; 95% CI 3.41–15.20, I^2 93.49%); headache (7.84%; 95% CI 4.04–12.70, I^2 98.49%), respiratory symptoms (7.62%; 95% CI 2.08–15.78, I^2 99.15%), sputum production or nasal

Author	Country	Study design	Collection mode	Follow-up time included in M.A.	Severity%	N cases (denominator)	N controls	COVID-19 diagnoses	Control definition	Age range	Sex% Male	Term
Asadi-Pooya[19]	Iran	CSS	Phone (question-naire)	>3 months	Hospital-ized	58	NA	PCR	NA	6 to 17	48	Long COVID
Blankenburg[20]	Germany	CSS	Schools (survey)	>3 months	NR	188	1365	IgG	IgG nega-tive	14 to 16	45	Long-COVID19
Borch[16]	Denmark	RCS	Electronic (question-naire)	>1 month	Asympto-matic	15,041	15,080	PCR	Not a PCR positive in the past	0 to 17	NR	Long COVID
Buonsenso[21]	Italy	CSS	Phone or inpatient (question-naire)	>4 months	All severi-ties	129	NA	PCR	NA	>18	52	Long COVID
Erol[22]	Turkey	RCS	Clinical	5.6 months average	All severi-ties	121	95*	"Tested positive"	Not having contact with some-one with COVID-19.19	>18	54	Long COVID
Fink[23]	Brazil	PCS	Outpa-tient and inpatients validated instru-ments and clinic	4.4 months average	Symp-tomatic (Outpa-tient and inpatients)	53	52*	PCR or antibody	Negative PCR or antibody*	8 to 18	42	Post-COVID-19/long term PASC/long COVID-19
Kikkenborg Berg*[15]	Denmark	CSS	Electronic (survey)	2 months	All severi-ties	6630	21,640	Tested positive	Not tested positive	15 to 18	58	Long COVID
Knoke[24]	Germany	CSS	Outpatient (question-naire and pulmonary function testing)	2.6 months average	Asympto-matic	73	45	PCR or antibody	No antibodies, 31% other infection	5 to 18	48	Long term COVID/ persistent symptoms
Matteudi[25]	France	PCS	Phone (question-naire)	10 to 13 months	All severi-ties	137	NA	PCR	NA	0 to 15	NR	Long-term conse-quences/ persisting symptoms/ long COVID
Miller[26]	U.K.	PCS	Electronic (weekly survey)	≥1 month	NR	174	NA	"Nasal swab"	NA	≤17	45	Persistent symptoms/ long COVID
Molteni[27]	U.K.	PCS	Electronic App	>2 months	NR	1734	NA	PCR IgG	NA	5 to 17	50	Persistent symptoms
Osmanov[28]	Russia	PCS	Phone (SARIC COVID-19 Health and Wellbeing Follow-Up Survey for Children)	>5 months	Hospital-ized	518	NA	PCR	NA	3 to 15	47	Long term/ long covid/ persistent symtoms
Radtke[29]	Switzer-land	PCS	Online (question-naire)	>3 months	Asympto-matic and mild	109	1246	Serology	Seronega-tive	6 to 16	46	Long COVID/ SARS-Cov-2 postviral syndromes
Roge[17]	Latvia	PCS and RCS	Phone (question-naire)	1 to 6 months	All severi-ties	236	142	PCR or serocon-version	Other infections	0 to 18	55.50	Persistent symp-toms/long COVID/ long-term conse-quences/ long-lasting symptoms/ long-term persistent symptoms/ late sequelae of COVID-19
Continued												

Author	Country	Study design	Collection mode	Follow-up time included in M.A.	Severity%	N cases (denominator)	N controls	COVID-19 diagnoses	Control definition	Age range	Sex% Male	Term
Roessler[30]	Germany	RCS	Health Insurance data	≥ 3 months	All severities	57,763	288,815*	Laboratory virus detection	Non-laboratory virus detection	0 to 17	51.30	Post COVID19/long term health sequelae/post-acute COVID-19 syndrome/post COVID-19 condition
Rusetsky[31]	Russia	PCS	Phone	At 2 months	Hospitalized	79	NA	PCR	NA	9.5–16.3	47	Persistent
Say[32]	Australia	PCS	Clinical	3 to 6 months	All severities	151	NA	PCR	NA	0 to 12	58	Post-acute COVID-19
Smane*[18]	Latvia	RCS	Clinical	1 to 3 months	Hospitalized	92	NA	NR	NA	8 to 15	61	Post-acute COVID/long-term consequences
Stephenson[33]	U.K.	PCS	Paper questionnaire	At 3 months	Non-hospitalized	3065	3739	PCR	PCR negative	11 to 17	37	Long COVID/post-COVID symptomatology/long haulers/post-acue COVID syndrome)
Sterky[34]	Sweden	PCS	Phone questionnaire	Median 7.3, range 4.1 to 10.8 months	Hospitalized	55	NA	PCR	NA	0 to 18	58	Persistent/long COVID/long term health issues
Zavala[35]	U.K.	RCS	Paper questionnaire	At 1 month	All severities	387	472	PCR	PCR negative	0 to 16	51	Persistent

Table 1. General characteristics of studies. Controls: did not present numbers, therefore it could not be used *CSS* cross-sectional study, *DM* diabetes mellitus, *NA* not applicable, *NR* not reported, *MA* meta-analysis, *M* months, *PCS* prospective cohort study, *RCS* retrospective cohort study. *Part of the population duplicated.

congestion (7.53%; 95% CI 3.78–12.36, I^2 0%), cognitive symptoms (e.g., less concentration, learning difficulties, confusion, and memory loss) (6.27%; 95% CI 4.46–8.35, I^2 91.32%), loss of appetite (6.07%; 95% CI 3.95–8.59, I^2 93.54%), exercise intolerance (5.73%; 95% CI 0.00–19.38, I^2 87.77%), and altered smell (e.g., hyposmia, anosmia, hypersomnia, parosmia, and phantom smell) (5.60%; 95% CI 3.13–8.69, I^2 97.11%). All other symptoms had less than 5.00% prevalence (Table 2, Fig. 2, Supplementary Fig. 1).

Meta-analyses of O.R.s (cases vs. controls). It was only possible to perform meta-analyses of O.R.s comparing cases and controls for 13 symptoms (mood, fatigue, headache, dyspnea, concentration problems, anosmia/ageusia, loss of appetite, rhinitis, myalgia/arthralgia, cough, fever, sore throat, and nausea/vomiting) (Fig. 4). When compared to controls, children with long-COVID had a higher risk of persistent dyspnea (OR 2.69; 95% CI 2.30–3.14, I^2 0%), anosmia/ageusia (OR 10.68; 95% CI 2.48, 46.03, I^2 0%), and/or fever (OR 2.23; 95% CI 1.2–4.07, I^2 12%). There was significant heterogeneity for 4 out of the 13 meta-analyses (Fig. 4). The controls were chosen in a very different way among studies, which might have introduced significant heterogeneity. The following were the different definitions of controls, children and adolescents with: (1) other infections (e.g., common cold, pharyngotonsillitis, gastrointestinal, urinary tract infections, pneumonia of bacteria or unknown origin)[17]; (2) no antibodies testing[24] mixed with other infections[17]; (3) a negative antibody test[29], (4) a negative rtPCR test among symptomatic children[35]; and (5) children who did not have a positive test recorded in the database[15] (Supplementary Fig. 2). The adjustments among studies also varied. Several studies adjusted their OR by age, sex, ethnicity, socioeconomic status, and comorbidities[35]. However, age and sex[15] only adjusted for sex, only for age[17], did not adjust, or by OR without adjusting previous conditions[24].

Other findings. The prevalence of symptoms over the course of long-COVID for cases and controls is shown in Supplementary Fig. 2. Given the heterogeneity in the definition of controls and the low number of subjects, no formal statistical comparison was done for the crude prevalence. The symptoms that were presented in a single study and, therefore, unable to be incorporated into the meta-analyses, include: orthostatic intolerance, cold hands/feet, chapped lips, adenopathy, fainting, twitching of fingers and toes, chills, swollen toes/fingers, and hallucinations.

Clinical manifestations	Studies	Cases	Sample size	I²	Prevalence % (95% CI)
Mood (sad, tense, angry, depression, anxiety)	5	730	6047	97.49	16.50 (7.37–28.15)
Fatigue	16	3015	21,592	99.12	9.66 (4.45–16.46)
Sleep disorder (insomnia, hypersomnia, poor sleep quality)	8	153	1592	93.49	8.42 (3.41–15.20)
Headache	13	1875	21,108	98.49	7.84 (4.04–12.70)
Respiratory symptoms	9	1387	19,013	99.15	7.62 (2.08–15.78)
Sputum/nasal congestion	2	11	150	0	7.53 (3.78–12.36)
Cognition (less concentration, learning difficulties, confusion, memory loss)	11	1223	19,803	91.31	6.27 (4.46–8.35)
Loss of appetite	5	747	9379	93.54	6.07 (3.95–8.59)
Exercise intolerance	2	8	150	87.77	5.73 (0.00–19.38)
Altered smell (hyposmia, anosmia, hypersomnia, parosmia, phantom smell)	10	2048	20,818	97.11	5.60 (3.13–8.69)
Hyperhidrosis	2	36	738	93.59	4.66 (0.00–13.85)
Chest pain	6	467	18,777	98.24	4.62 (1.52–9.11)
Dizziness	6	791	9340	97.77	4.40 (1.50–8.59)
Rhinorrhea	5	65	1032	94.10	4.15 (0.10–11.89)
Cough	10	570	19,688	86.60	3.80 (2.61–5.19)
Myalgia/arthralgia	9	547	19,564	93.67	3.76 (2.18–5.75)
Body weight changes	3	30	865	96.82	3.99 (0.00–14.00)
Altered taste	5	1273	16,005	92.23	3.65 (1.35–6.92)
Otalgia (tinnitus, earache, vertigo)	3	207	3773	92.65	3.41 (0.84–7.35)
Ophthalmologic (conjuntivitis, dry eye, problems seeing/blurred vision, photophobia, pain)	6	384	9411	91.07	3.00 (1.66–4.69)
Abdominal pain	8	277	9611	73.94	2.91 (2.04–3.92)
Dermatologic (dry skin, itchy skin, rashes, hives)	6	218	9322	78.68	2.61 (1.73–3.67)
Sore throat	6	401	10,311	98.46	2.47 (0.25–6.23)
Chest tightness	5	293	6319	92.81	2.45 (0.58–5.35)
Variations in heart rate	2	18	729	88.54	2.29 (0.00–7.36)
Constipation	3	20	1101	81.01	2.05 (0.39–4.75)
Dysphonia	2	62	3301	0	1.89 (1.45–2.38)
Fever	5	167	18,709	96.27	1.87 (0.50–3.99)
Musculoskeletal other	3	383	15,618	87.72	1.72 (0.41–3.78)
Diarrhea	7	218	19,337	81.01	1.68 (0.63–3.18)
Vomiting/nausea	5	260	16,144	24.91	1.53 (1.09–2.03)
Changes in menstruation	3	10	866	43.98	1.27 (0.38–2.60)
Palpitations	4	165	6178	93.55	1.27 (0.00–3.83)
Hair loss	3	16	1209	80.31	1.17 (0.10–3.10)
Neurological abnormalities (pins and needles, tremor, numbness)	3	8	997	0	0.86 (0.37–1.55)
Urinary symptoms	3	6	1060	0	0.63 (0.23–1.21)
Dysphagia	3	5	1207	0	0.46 (0.14–0.93)
Speech disturbances	3	5	1197	40.41	0.44 (0.05–1.10)

Table 2. Pooled prevalence of symptoms in children and adolescents.

One study reported statistically significant differences between clinical cases and controls for systolic blood pressure, left ventricular ejection fraction, relative myocardial wall thickness, and tricuspid annular plane systolic excursion[22]. However, given that these variables were only evaluated in this study, we could not perform a meta-analysis for these outcomes. Studies included in the meta-analyses found that certain variables, such as age, sex, severe acute-COVID-19, obesity, allergic disease, and long-term health conditions[19,26,28,36], increased the risk of long-COVID. Further, two of the studies evaluated the duration of symptoms. A study from Denmark reported that symptoms resolved in a minimum of 54–75% of children and adolescents within 1–5 months[16]. Another from England, reported that 4.4% of children still had symptoms four weeks after COVID-19 onset, which decreased to 1.8% at 8 or more weeks[27].

Quality of studies. Regarding the quality of studies, all had a score of 7 or more (Supplementary Table 1). Table 3 presents a list of methodological strengths or limitations for each study. All studies included laboratory-confirmed COVID-19 infection, rt-PCR, antigen, or antibody test. Two-thirds of the studies included over 100 children. Six meta-analyses had low heterogeneity (I² < 25%) for the following symptoms: vomiting and nausea, nasal congestion, dysphonia, urinary problems, neurological abnormalities, and dysphagia. Three meta-analyses
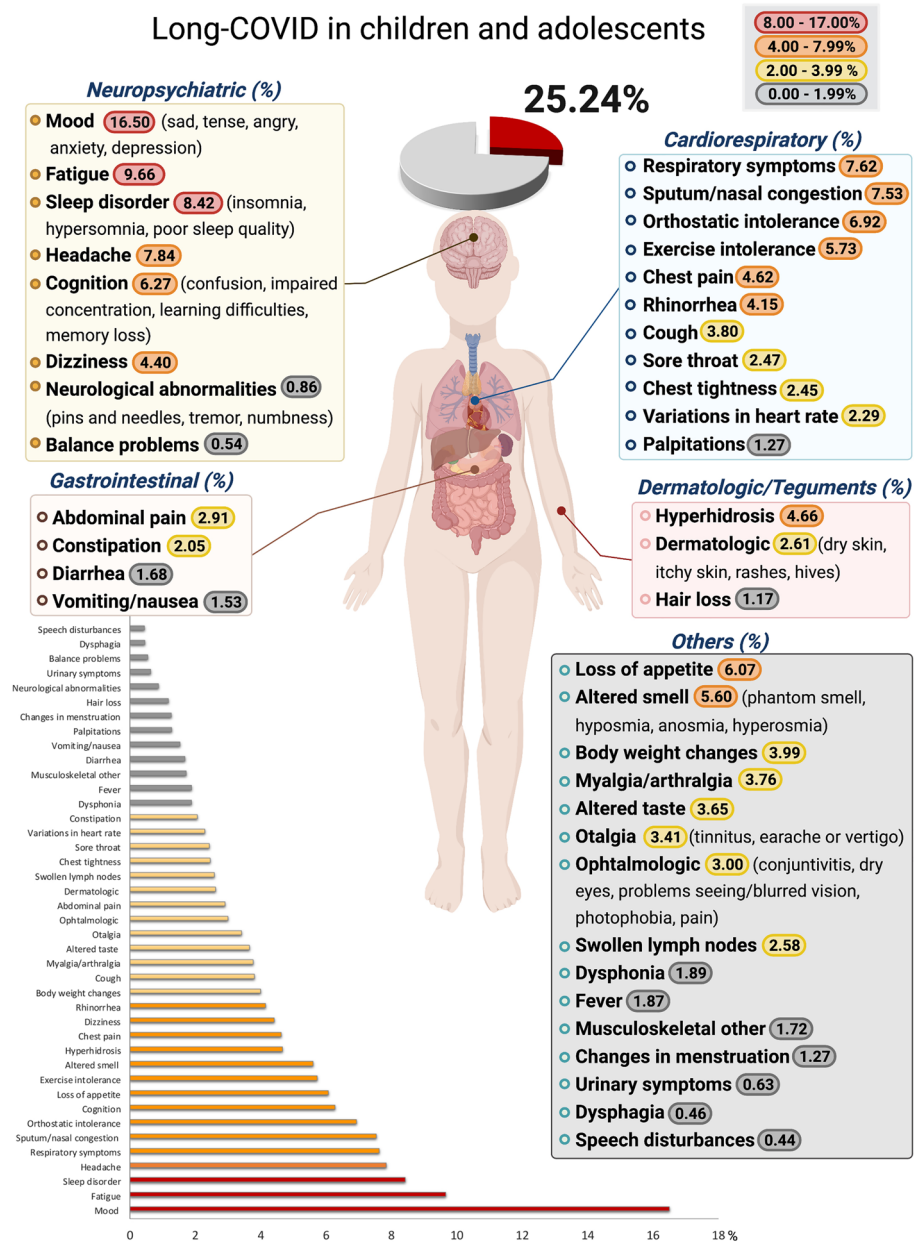
Figure 2. The pooled prevalence of long-COVID by symptoms in children and adolescents. Meta-analyses revealed that the prevalence of more than 40 long-COVID symptoms in children and adolescents. The presence of one or more symptoms following a SARS-CoV-2 infection was 25.24%.

had medium heterogeneity for the following symptoms: abdominal pain, changes in menstruation, and speech disturbances. All other meta-analyses had high heterogeneity ($I^2 > 75\%$). Given that very few studies stratified by the different variables (e.g., age, sex, country, or past comorbidities), there were not enough studies that included this information to evaluate where the heterogeneity originated.

Discussion

The prevalence of long-COVID in children and adolescents was 25.24%. The five most prevalent clinical manifestations were mood symptoms (16.50%), fatigue (9.66%), sleep disorders (8.42%), headache (7.84%), and respiratory symptoms (7.62%). It was only possible to perform meta-analyses of ORs comparing cases and controls for 13 symptoms, with a higher risk of persistent dyspnea, anosmia/ageusia, and/or fever. Studies have shown that the pandemic has profoundly impacted society by affecting children's development through isolation, poverty, food insecurity, loss of parents and caregivers, loss of time in education, and increased stress[37]. COVID-19 pandemic has initiated an explosion of future mental illnesses[38], affecting both society as a whole and those who recover from long-COVID. The presence of these symptoms in the general population, regardless of COVID-19 status, has been coined long-Pandemic Syndrome[20].
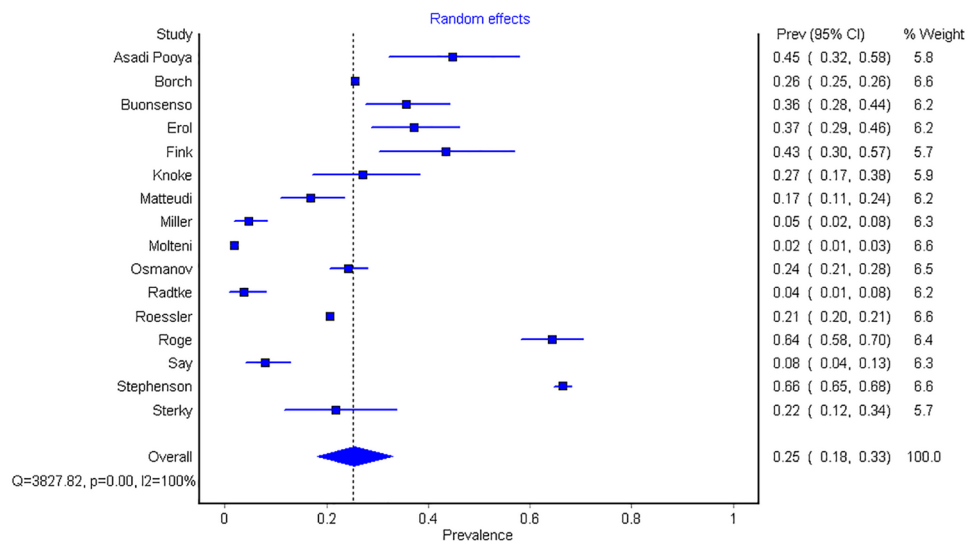
Figure 3. Forest plot of pooled prevalence of long-COVID overall in children and adolescents.

Interestingly, many of the symptoms identified in these meta-analyses associated to long-COVID, such as mood, fatigue, sleep disorders, orthostatic intolerance, decreased concentration, confusion, memory loss, balance problems, exercise intolerance, hyperhidrosis, blurred vision, body temperature dysregulation, dysfunction on heart, rate variability and palpitations, constipation or diarrhea, and dysphagia, are commonly present in dysautonomia[39]. Dysautonomia is a dysfunction of the sympathetic and/or parasympathetic autonomic nervous system. However, it remains unclear whether dysautonomia may be a direct result of the SARS-CoV-2 infection, interaction with other viruses, or immune-mediated processes such as cytokines, which are known mediators of the inflammatory response[40–43].

Moreover, the constellation of symptoms because of long-COVID can vary from patient to patient, fluctuating in their frequency and severity[44]. Like adults, the pediatric population's risk factors associated with long-COVID are older age, female gender, severe COVID-19, overweight/obesity, comorbid allergic diseases, and other long-term co-morbidities. Protective factors leading to milder severity and duration of COVID-19, and possibly also long-COVID in children, include fewer comorbidities, strong innate immune responses, reduced expression of angiotensin-converting enzyme-2 (ACE2) receptors, and active thymic function, which leads to the increased presence and decreased depletion of T cells. Further protections include a range of environmental or non-inheritable factors such as vaccines, past infections, nutrition, and/or the gut microbiome[19,26,28,36,45]. Concerning age, most of the studies did not discriminate between children (< 12-year-old) and adolescents. Given that the risk increases with age, there is a need for future studies to stratify by age. In addition, the evaluation of self-reporting symptoms can be significantly biased by age as younger children might not be able to express their emotional and functional status relevant to post-COVID-19 adequately. Further studies targeting age groups are required.

The prevalence of symptoms is highly dependent on how much time has passed after having acute COVID-19. The follow-up time in these meta-analyses varied between 1 and 13 months. Even though most symptoms improve with time[46], there is evidence in adult studies that suggests some symptoms can persist one year after COVID-19 diagnosis[47]. It is important to understand which symptoms are associated with certain periods of time (e.g., 6 months, 12 months, 2 years).

The strength of this meta-analyses focuses on the large sample size[48] which helps identify the signs and symptoms present after acute SARS-CoV-2 infection. Further, there were some limitations such as the quality of the meta-analyses results depending on the quality of the studies included. Table 3 contains a list of all the methodological aspects that future studies need to consider. We can observe that all studies had a high probability of bias, including lack of standardized definitions, recall, selection, misclassification, nonresponse, and/or loss of follow-up. Additionally, the included studies have the limitations inherited in all observational studies, including bias due to residual and unmeasured confounding, and a high level of heterogeneity. To account for heterogeneity, we used a random-effects model[49]. The differences between studies were likely due to differences in study designs, settings, populations, follow-up time, symptom ascertainment methods, inconsistent terminology, little details on stratification of pre-existing comorbidities, and prior receipt of COVID-19 therapeutics and vaccines. Only four studies mentioned what percentage of the population was already vaccinated[15,16,20,28] (Table 3). It has been shown that vaccines reduce the risk of long-COVID in adults[50]. More studies are needed to analyze the relationship between vaccines in children with long COVID.

In our analyses, we included 2 pre-publication articles that are still not peer-reviewed[26,30]. The limitations of the study of Roessler et al.[30] are inherited from all observational studies and are mentioned above. However its strengths are that it includes a large population (n = 11,950), that physicians and psychotherapists validate the cases, and that they estimate the incidence rate ratios (IRR), controlling for age, sex, and prevalent medical conditions by applying propensity score matching. They report that symptoms were statistically higher in the acute COVID-19 cohort (IRR = 1.30) than in the controls without COVID-19. The study by Miller et al.[26] included
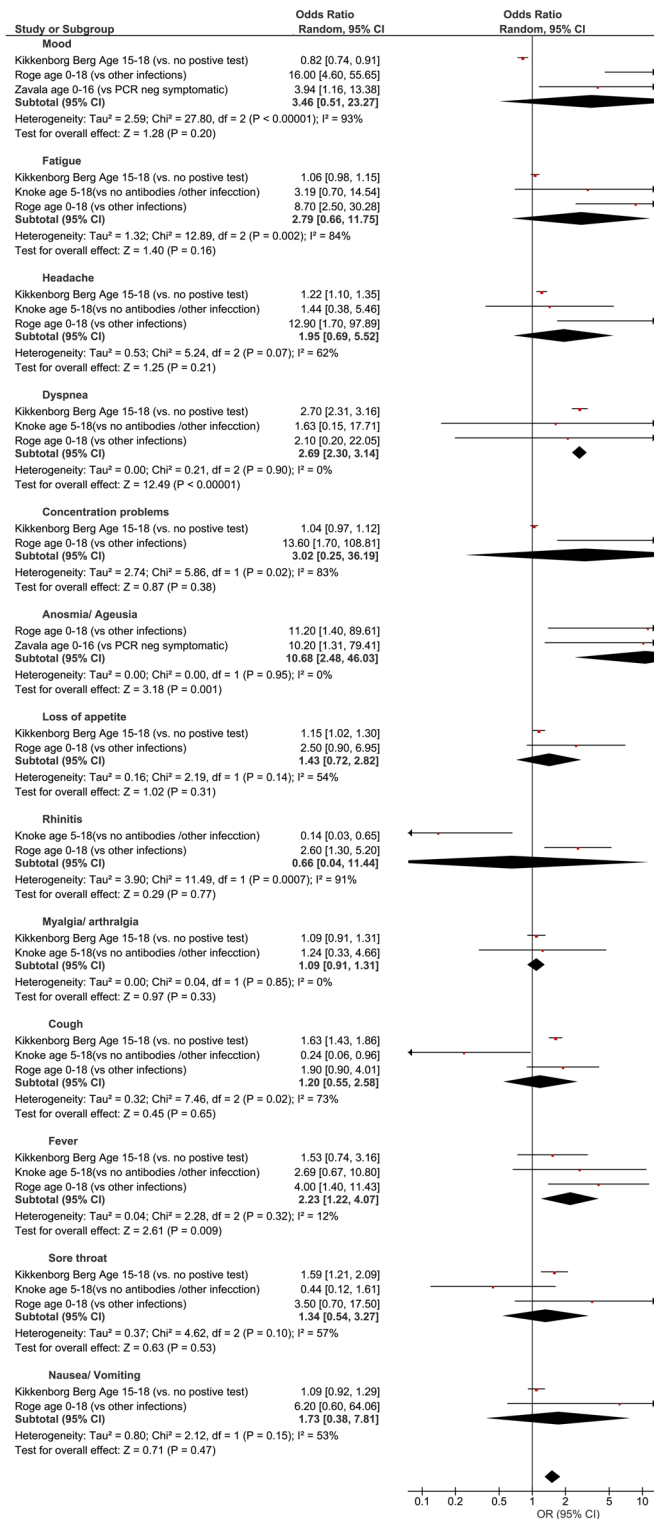
Figure 4. Pooled odds ratios with 95% CI in cases vs. controls. The size of each box indicates the effect of each study by symptom assigned using the odds ratios (95% CI) by age and domain.

children participating in VirusWatch, a household cohort in England and Wales that recruited households via postcards, social media, and SMS that had as an objective to study acute COVID-19. Long-COVID was defined as answering "YES" to the following question—"Have you presented any new symptoms that have lasted for four or more weeks even if these symptoms come and go and cannot be explained by something else?". Given the nature of the survey, it has a possibility of introducing bias to the results (recall bias, selection bias, misclassification bias, and nonresponse bias). The study does not present the frequencies for each symptom, and therefore it was not

	No of studies (N = 21)	Prevalence (%)
Study methodological strength		
COVID cases lab confirmed (PCR or antibody)	21	100
More than 100 COVID patients	14	66.66
Timing of COVID well specified	14	66.66
Long COVID defined > 3 months	8	38.10
Point in time specific and well defined	10	42.11
Control added	8	31.60
Control group with negative antibody test	2	10.50
Clinical assessment (not self/parent reported)	7	36.84
New symptoms on or after COVID	6	31.58
Specify if persistent symptom or if it is symptoms months after acute COVID	2	9.52
Exclude vaccinated/no vaccinated in sample	4	19.05
Duration (end) of symptoms specified	3	14.29
Validated questionnaires or clinical evaluation for symptoms	5	23.81
Bias		
Low chance of recall bias	7	33.33
Low chance of selection bias	4	19.05
Low chance of misclassification bias	3	14.29
Low chance of nonresponse bias/loss of follow up	3	14.29
Stratifications		
Stratify by severity/only one severity	4	19.05
Stratified by age/only one age group studied	6	28.57
Stratified by preexisting medical conditions	1	4.76
Stratified by sex	2	9.52
Stratify by vaccination status	0	0

Table 3. Study methodological strengths and limitations.

included in the meta-analyses of each symptom. We only included this study in the meta-analysis of overall long-COVID. The authors estimated a prevalence of 4.6%, which, compared to the other studies, is underestimated.

Future prospective studies should include a control cohort and stratify and/or adjust their results by age, sex, race, severity of acute COVID-19 infection paired with clinical evaluation, vaccination status, preexisting medical conditions, and, if possible, SARS-CoV-2 variant. Retrospective studies using large population-based databases with historical controls and secondary data sources (e.g., claims and medical records) should also be used. The selection of controls will be difficult in the future because not all the cases are recorded in databases (e.g., home tests), tests can be false, negative, or positive, or children can be asymptomatic. Future studies' proposed control groups include a negative N protein antibody test without vaccination, a negative antibody test with vaccination, or historical cohorts that include children who have neither been vaccinated nor exposed to the virus.

Conclusion
Protective measures are essential to prevent long-COVID in children. We need to understand the long-COVID pathophysiology and symptomatology to support clinical management systems, establish rehabilitation programs, and design guidelines and therapeutic research. Long-COVID represents a significant public health concern, and there are no guidelines to address its diagnosis and management. Our meta-analyses further support the importance of continuously monitoring the impact of long-COVID in children and adolescents and the need to include all variables and appropriate control cohorts in studies to better understand the real burden of pediatric long-COVID.

Data availability
All data relevant to the study are included in the article or uploaded as Supplementary Information. In addition, the datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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