Long COVID in Children and Adolescents: A Systematic Review and Meta-analyses.

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ABSTRACT

Objective: To estimate the prevalence of long COVID in children and adolescents and identify the full spectrum of signs and symptoms present after acute SARS-CoV-2 infection.

Methods: Two independent investigators searched PubMed and Embase in order to identify observational studies that met the following criteria: 1) a minimum of 30 patients, 2) ages ranged from 0 to 18 years, 3) published in English, 4) published before February 10th, 2022, and 5) meets 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. For COVID symptoms reported in two or more studies, random-effects meta-analyses were performed using the MetaXL software to estimate the pooled prevalence, and Review Manager (RevMan) software 5.4 was utilized to estimate the Odds Ratios (ORs) 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).

Results: The literature search yielded 68 articles for long COVID in children and adolescents. After screening, 21 studies met the inclusion criteria and were included in the systematic review and meta-analyses. A total of 80,071 children and adolescents with COVID-19 were included. The prevalence of long COVID was 25.24% (95% CI 18.17-33.02), and the most prevalent clinical manifestations were mood symptoms (16.50%; 95% CI 7.37-28.15), fatigue (9.66%; 95% CI 4.45-16.46), and sleep disorders (8.42%; 95% CI 3.41-15.20). When compared to controls, children infected by SARS-CoV-2 had a higher risk of persistent dyspnea (OR 2.69 95%CI 2.30-3.14), anosmia/ageusia (OR 10.68, 95%CI 2.48, 46.03), and/or fever (OR 2.23, 95%CI 1.22-4.07). The main limitation of these meta-analyses is the probability of bias, which includes lack of standardized definitions, recall, selection, misclassification, nonresponse and/or loss of follow-up, and the high level of heterogeneity.

Conclusion: These meta-analyses provide an overview of the broad symptomatology of long COVID in minors, which may help improve management, rehabilitation programs, and future development of guidelines and therapeutic research for COVID-19.

Keywords: Long COVID, post-acute sequelae of SARS-Cov-2 (PASC), pediatric long hauler, post-COVID children, COVID-19 kids, COVID-19 syndrome

INTRODUCTION

It has been two years since the COVID-19 pandemic was first declared. Consequently, millions of cases and thousands of deaths have been reported worldwide [1]. Still, during this time, treatments have been developed rapidly 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, once the acute phase of COVID-19 is over, many individuals experience months of debilitating COVID-19 symptoms that requires additional medical attention and follow-up.

Severe COVID-19 is less common in children than in adults [3]; however, there are two long-term consequences that occur following SARS-CoV-2 infection in children: multisystem inflammatory syndrome (MIS-C) and long COVID. Both of these consequences can even appear in asymptomatic patients [4]. MIS-C is a condition where different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs [4]. It occurs in less than 0.01% of children with COVID-19 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. Until now, many authors have used the following terms interchangeably when referring to long COVID: long haulers, COVID-long, post-acute sequelae of COVID-19 (PASC), long run, post-COVID, COVID syndrome, and long COVID. In this systematic review, we will refer to long-COVID. In addition, given that MIS-C is a severe disease which complications can persist for years, we will exclude MIS-C studies from this systematic review. 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 in the UK (NICE) published a guideline defining long-COVID as signs and symptoms that continue or develop after acute COVID‑19, This includes both 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 (NIH), also define long COVID as post-acute symptoms after 4 weeks [8]. In the present study, we will use the generic definition from NICE and NIH.

To date, most of the published research on long COVID primarily focuses on adult populations. As a result, there is limited information on the long-term effects of COVID-19 in pediatric populations [9,10]. One recent meta-analysis studied the persistent symptoms that occur following SARS-CoV-2 infection and examined their prevalence, risk factors, type, and duration. This meta-analysis included studies up to July 2021, encompassing 23,141

children and young people [9]. The most common symptoms were fatigue 47% (95% CI 7-27), dyspnea 43% (95% CI 18-68), and headache 35% (95% CI 19-51). 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 meta-analysis could only compute the pooled prevalence for 10 symptoms. To date, the potential range of signs and symptoms as well as 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 for the health system to better understand the sequelae in order 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 to identify the full spectrum of signs and symptoms present after COVID-19.

METHODS

Search strategy and selection criteria

This systematic review and meta-analyses examine the prevalence of long COVID signs and symptoms in children under the age of 18 with a diagnosed case of COVID-19 (confirmed via PCR, antigen test, or antibody test). To achieve this, two independent investigators searched PubMed and Embase to identify studies that met the following criteria: 1) a minimum of 30 patients with either ongoing symptomatic COVID‐19 (from 4 to 12 weeks) or post‐COVID‐19 syndrome (12 weeks or more) (i.e., patients who met the NICE definition of long COVID) (NICE 2022), 2) ages ranged from 0 to 18 years, 3) published in English, 4) published before February 10th, 2022, and 5) meets 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, 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.

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 by two authors (TWO and SLL). Each article was thoroughly reviewed by both authors in case there was a difference of opinion on the inclusion of a study based on title or abstract. Disagreement on including a full-text article was discussed among all the authors. The study was registered in PROSPERO [CRD42021275408] (https://www.crd.york.ac.uk/PROSPERO).

Screening and data extraction

Data were extracted by four authors (AC, CA, PR, RS) and Quality-Controlled (QCed) by two authors (TWO, CP). Discrepancies were discussed with a third author. The descriptive variables extracted were country, study design, period of study, collection mode, follow-up time, 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. After duplicates were removed, the search identified 68 papers after screening titles and abstracts. Of these, 21 were included after the exclusion criterium (Figure 1).

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 [12]. Prevalence (presented as percentages) with 95% confidence intervals (CIs) 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 the DerSimonian and Laird's random-effects model. Pooled Odds Ratios (ORs) and 95% CIs were calculated [13]. 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. The study's quality control was assessed using the Health States Quality-Controlled data. This index is described and recommended by the MetaXL Guidelines that evaluates the quality of studies assessing prevalence. In addition, the limitations of each study were listed, and they are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

RESULTS

General characteristics of studies

The title and abstract of 8,373 publications were screened. Of these, 68 full publications were reviewed, and 47 were excluded because they did not fulfill the inclusion criteria. Thus, a total of 21 studies were selected for analysis (, Figure 1). The general study characteristics are shown in Table 1. The majority of the studies assessed pre-specified symptoms included in a questionnaire. The process of study selection is presented in Figure 1. There were 18 studies from Europe (e.g., Denmark, Russia, Italy, Germany, Tukey, Latvia, UK, France, Sweden, and Switzerland), 1 from Iran, 1 from Brazil, and 1 from Australia. The studies by Kikkenborg *et. al.* [14] and Borch *et. al*. [15] included an overlapping population (Denmark), as did the studies by Roge *et. al.* [16] and Smane *et. al.* [17] (Latvia). To ensure that no overlapping data were included, only the study with the largest sample size was included for the estimate of 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). Due to a lack of stratification from all the studies, it was not possible to estimate the prevalence for the different severities. It was only possible to evaluate the prevalence of hospitalized patients. 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 effects associated with COVID-19 in children and adolescents in the literature reviewed. Different authors have used the terms “Post-acute COVID”, “long COVID,” “Persistent COVID,” “Persistent COVID Symptoms” as synonyms.

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). For hospitalized patients, the prevalence of long COVID was 29.19% (95% CI, 17.83-41.98). The most common symptoms were mood symptoms (e.g., sadness, tension, anger, depression, and anxiety) (prevalence: 16.50%; 95% CI, 7.37-28.15), fatigue (prevalence: 9.66%; 95% CI, 4.45-16.46), sleep disorders (e.g., insomnia, hypersomnia, and poor sleep quality) (prevalence: 8.42%; 95% CI, 3.41-15.20); headache (prevalence: 7.84%; 95% CI, 4.04-12.70), respiratory symptoms (prevalence: 7.62%; 95% CI, 2.08-15.78), sputum production or nasal congestion (prevalence: 7.53%; 95% CI, 3.78-12.36), cognitive symptoms (e.g., less concentration, learning difficulties, confusion, and memory loss) (prevalence: 6.27%; 95% CI, 4.46-8.35), loss of appetite (prevalence: 6.07%; 95% CI, 3.95-8.59), exercise intolerance (prevalence: 5.73%; 95% CI, 0.00-19.38), and altered smell (e.g.,

hyposmia, anosmia, hyperosmia, parosmia, and phantom smell) (prevalence: 5.60%; 95% CI, 3.13-8.69). All other symptoms had less than 5.00% prevalence (Figure 2 and 3).

Meta-analyses of ORs (cases vs. controls)

It was only possible to perform meta-analyses of ORs comparing cases and controls for 13 symptoms (Supplementary Figure 1). Cases were defined as patients that had a confirmed COVID infection, and controls as patients without COVID. When compared to controls, children with long COVID had a higher risk of persistent dyspnea (OR: 2.69; 95%CI, 2.30-3.14), anosmia/ageusia (OR: 10.68; 95% CI, 2.48, 46.03), and/or fever (OR: 2.23; 95% CI, 1.2-4.07). There was significant heterogeneity for 5 out of the 13 meta-analyses.

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: 1) children with other infections (e.g., common cold, pharyngotonsillitis, gastrointestinal, urinary tract infections, pneumonia of bacteria or unknown origin) [16]; 2) children with no antibodies testing [18] mixed with other children with other infections [16]; 3) children with a negative antibody test [19], 4) children with a negative PCR test that were symptomatic [20]; and 5) children who did not have a positive test recorded in the database [14].

The adjustments among studies also varied. Several studies adjusted their OR by age, sex, ethnicity, socioeconomic status, and comorbidities [20]. However age and sex [14] only adjusted for sex, only age [16] only adjusted for age, and Knoke et al did not adjust , or by OR without adjusting previous conditions [18] (Supplemental Figures 2 and 3).

Other Findings

The prevalence of symptoms over the course of long COVID for cases and controls is showed in Supplementary Table 1. Given the heterogeneity in the definition of controls and the low number of subjects, no formal statistical comparison was done for the crude prevalence.

Symptoms that were presented in a single study and, therefore, unable to be incorporated into the meta-analyses included: orthostatic intolerance, cold hands/feet, chapped lips, adenopathy, fainting, twitching of fingers and toes, chills, swollen toes/fingers, and hallucinations. 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 [21]. 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 evaluated whether certain variables increased the risk of long COVID-19 and found that age, sex, severe acute-COVID-19, obesity, allergic disease, and long-term health conditions were associated with high risk to develop long COVID-19 [22-25]. 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 (varied with age) within 1–5 months [15]. Another, from England, which used the UK ZOE COVID Symptom Study app, 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 [24].

Quality of studies

Regarding the quality of studies, all had a score of 7 or more. Supplementary Table 1 presents a list of methodological strengths or, conversely, limitations for each study. All studies included laboratory-confirmed COVID-19 infection, PCR or antibody test. Two-thirds of the studies included over 100 children. Six meta-analyses had low heterogeneity (I^2<25%) for the following symptoms: vomiting and nausea, nasal congestion, dysphonia, urinary problems, neurological abnormalities, and dysphagia. Three meta-analyses 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%). It was not possible to stratify by any variable (e.g., age, sex, country, past comorbidities, or severity) to evaluate where the heterogeneity originated.

DISCUSSION

The prevalence of long COVID in children and adolescents, following a COVID-19 infection 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. When compared to controls, persons with COVID-19 had a higher risk of presenting persistent dyspnea, anosmia/ageusia, and/or fever.

The most frequent symptoms reported were related to mood. COVID-19 pandemic has initiated an explosion of future mental illnesses [26], that is affecting both society as a whole as well as those who recover from COVID-19. 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 [27]. The presence of these symptoms in the general population, regardless of COVID-19 status, has been coined long-Pandemic Syndrome [28].

Interestingly, many of the symptoms identified in these meta-analyses, 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 [29]. Dysautonomia is defined as a dysfunction of the sympathetic and/or parasympathetic autonomic nervous system Postural orthostatic tachycardia syndrome, chronic fatigue syndrome (CFS), and myalgic encephalomyelitis (ME) are subclassifications of this condition [30]. Moreover, the constellation of symptoms because of long COVID can vary from patient to patient, fluctuating in their frequency and severity [31]. Several viruses have been shown to trigger ME/CFS, including the Epstein Barr Virus, Ross River virus, and earlier coronaviruses (e.g., SARS and MERS) [32]. However, it remains unclear whether dysautonomia may occur as a direct result of the SARS-CoV-2 infection, interaction with other viruses, or due to immune-mediated processes such as cytokines, which are known mediators of the inflammatory response [33-36].

Similar to adults, the following risk factors in the pediatric population were associated with long COVID: 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 ACE2 receptors, and active thymic function, which leads to the increased presence and decreased depletion of T cells which recognize viral proteins. Further protections include a range of environmental or non-inheritable factors such as vaccines, past infections, nutrition, and/or the gut microbiome [22-25,37].

The prevalence of symptoms is highly dependent on how much time has passed after having acute COVID-19. The follow-up time in our meta-analyses varied between 1 to 13 months. Even though most symptoms improve with time [38], there is evidence in adult studies that suggests some symptoms can persist one year after COVID-19 diagnosis [39]. It is important to understand which symptoms are associated with certain periods of time, so future studies should assess the prevalence of each symptom at different time points (e.g., 6 months, 12 months, 2 years) to determine which symptoms are associated with which time period.

As with other meta-analyses, the strength of this study centers on the large sample size [40] which helps provide identify the signs and symptoms present after acute SARS-CoV-2 infection.. Further, there were some limitations to our meta-analyses. The quality of the meta-analyses results depends 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. Another limitation relates to the high level of heterogeneity. To account for heterogeneity, we used a random-effects model [41]. However, ideally one should stratify the meta-analysis to identify what is causing the heterogeneity. This was not possible because most studies did not include data on different groups. 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 on pre-existing comorbidities, and prior receipt of COVID-19 therapeutics and vaccines. Only four studies mentioned what percentage of the population was already vaccinated [14,15,23,28] (Table 3). It has been shown that vaccines reduce the risk of long COVID. A study in Israel compared the prevalence of symptoms of long COVID and found that fully vaccinated participants who had COVID-19 were 54% less likely to report headaches, 64% less likely to report fatigue, and 68% less likely to report muscle pain than were their unvaccinated control group [42]. More studies are needed to analyze the relationship between vaccines in children and long COVID.

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. If we had analyzed these types of factors separately, we would have been able to discover the variations in the prevalence of long COVID. 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 of the cases are recorded in databases (e.g., home tests), tests can be false negative or positive, or children can be asymptomatic. Proposed control groups for future studies 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.

Protective measures are essential to prevent long COVID in children. We need to understand the long COVID pathophysiology and symptomatology in relation to other post-infectious syndromes 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 appropriated control cohorts in studies to have a better knowledge of 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.

Conflict of interest statement.

SLL is an employee of Novartis Pharmaceutical Company; the statements presented in the paper do not necessarily represent the position of the company. The remaining authors have no competing interests to declare.

Funding/Support

This work was supported by funds from Houston Methodist Research Institute, Houston, TX.

LEGENDS

Figure 1. Flow diagram of long COVID studies in children and adolescents. Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) flow of the screening process. Out of 8,373 identified studies and after applying the inclusion and exclusion criteria, 21 studies were included in the quantitative synthesis.

Figure 2. Long-term symptoms of COVID-19 in children and adolescents. Meta-analyses revealed that the prevalence of long COVID in children and adolescents, as defined by the presence of one or more symptoms following a COVID-19 infection, was 25.24%. This figure was created using Biorender.

Figure 3. Estimated incidence rate ratios with 95%-confidence intervals in children and adolescents by long COVID symptoms and domain.

Supplementary Figure 1. Prevalence of symptoms reported over the course of long COVID in children and adolescents who tested positive or negative for SARS-CoV-2 infection.

Supplementary Figure 2. Forest plots for individual long COVID-19 symptoms in children and adolescents (1-17). ORs and 95% CIs for the presence of any category of persistent symptoms for each long COVID study.

Supplementary Figure 3. Forest plots for individual long COVID-19 symptoms in children and adolescents (18-38). ORs and 95% CIs for the presence of any category of persistent symptoms for each long COVID study.

Table 1. General Characteristics of Studies.

Author	Country	Study Design	Collection mode	Follow up time included in MA	Severity %	N cases (denominator)	N controls	COVID diagnoses	Control definition	Age range	Sex % Male	Term
Asadi‐Pooya [22]	Iran	CSS	Phone (questionnaire)	>3 months	Hospitalized	58	NA	PCR	NA	6 to 17	48%	Long COVID
Blankenburg [28]	Germany	CSS	Schools (survey)	>3 months	NR	188	1365	IgG	IgG negative	14 to 16	45%	Long-COVID19
Borch [15]	Denmark	RCS	Electronic (questionnaire)	>1 month	Asymptomatic	15,041	15,080	PCR	Not a PCR positive in the past	0 to 17	NR	Long COVID
Buonsenso [43]	Italy	CSS	Phone or inpatient (questionnaire)	>4 months	All severities	129	NA	PCR	NA	>18	52%	Long COVID
Erol [21]	Turkey	RCS	Clinical	5.6 months average	All severities	121	*95	“tested positive”	Not having contact with someone with Covid.19	>18	54%	Long Covid
Fink [44]	Brasil	PCS	Outpatient and inpatients validated instrument and clinic	4.4 months average	Symptomatic (Outpatient 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* [14]	Denmark	CSS	Electronic (survey)	2 months	All severities	6,630	21,640	Tested positive	Not tested positive	15 to 18	58%	Long COVID
Knoke [18]	Germany	CSS	Outpatient (questionnaire and pulmonary function testing)	2.6 months average	Asymptomatic	73	45	PCR or antibody	No antibodies, 31% other infection	5 to 18	48%	Long term COVID /persistent symptoms
Matteudi [45]	France	PCS	Phone (questionnaire)	10 to 13 months	All severities	137	NA	PCR	NA	0 to 15	NR	Long-term consequences/persisting symptoms/ Long COVID
Miller [25]	UK	PCS	Electronic (weekly survey)	≥ 1 month	NR	174	NA	“nasal swab”	NA	≤17	45%	Persistent symptoms/ long covid

Molteni [24]	UK	PCS	Electronic App	>2 months	NR	1734	NA	PCR IgG	NA	5 to 17	50%	Persistent symptoms
Osmanov [23]	Russia	PCS	Phone (SARIC COVID-19 Health and Wellbeing Follow-Up Survey for Children)	>5months	Hospitalized	518	NA	PCR	NA	3 to 15	47%	Long Term /long covid/ persistent symtoms
Radtke [19]	Swtizerland	PCS	Online (questionnaire)	>3 months	Asymptomatic and mild	109	1246	Serology	Seronegative	6 to 16	46%	Long COVID/ SARS-Cov-2 postviral syndromes
Roge [16]	Latvia	PCS and RCS	Phone (questionnaire)	1 to 6 months	All severities	236	142	PCR or seroconversion	Other infections	0 to 18	55.50%	Persistent Symptoms/ long COVID/ long-term consequences/ long-lasting symptoms/ long-term persistent symtoms/ late sequelae of COVID-19
Roessler [46]	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 [47]	Russia	PCS	Phone	At 2 months	Hospitalized	79	NA	PCR	NA	9.5-16.3	47%	Persistent
Say [48]	Australia	PCS	Clinical	3 to 6 months	All severities	151	NA	PCR	NA	0 to 12	58%	Post-acute COVID-19
Smane* [17]	Latvia	RCS	Clinical	1 to 3 months	Hospitalized	92	NA	NR	NA	8 to 15	61%	Post-acute COVID/ long-term consequences
Stephenson [49]	UK	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 [50]	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 [20]	UK	RCS	Paper questionnaire	At 1 month	All severities	387	472	PCR	PCR negative	0 to 16	51%	Persistent

Controls: did not presented 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.

Table 2. Clinical manifestations of Long-COVID in children and adolescents.

CLINICAL MANIFESTATIONS	Studies	Cases	Sample Size	Prevalence % (95%CI)
Mood (sad, tense, angry, depression, anxiety)	5	730	6047	16.5 (7.37-28.15)
Fatigue	16	3015	21592	9.66 (4.45-16.46)
Sleep disorder (insomnia, hypersomnia, poor sleep quality)	8	153	1592	8.42 (3.41-15.20)
Headache	13	1875	21108	7.84 (4.04-12.70)
Respiratory symptoms	9	1387	19013	7.62 (2.08-15.78)
Sputum/nasal congestion	2	11	150	7.53 (3.78-12.36)
Cognition (less concentration, learning difficulties, confusion, memory loss)	11	1223	19803	6.27 (4.46-8.35)
Exercise intolerance	2	8	150	5.73 (0.00-19.38)
Altered smell (hyposmia,	10	2048	20818	5.60 (3.13-8.69)

anosmia, hyperosmia, parosmia, phantom smell)				
Chest pain	6	467	18777	4.62 (1.52-9.11)
Loss of appetite	5	747	9379	6.07 (3.95-8.59)
Rhinorrhea	5	65	1032	4.15 (0.10-11.89)
Dizziness	6	791	9340	4.40 (1.50-8.59)
Myalgia/arthralgia	9	547	19564	3.76 (2.18-5.75)
Cough	10	570	19688	3.80 (2.61-5.19)
Hyperhidrosis	2	36	738	4.66 (0.00-13.85)
Ophthalmologic (conjuntivitis, dry eye, problems seeing/blurred vision, photophobia, pain)	6	384	9411	3.00 (1.66-4.69)
Otalgia (tinnitus, earache, vertigo)	3	207	3773	3.41 (0.84-7.35)
Altered taste	5	1273	16005	3.65 (1.35-6.92)

Body weight changes	3	30	865	3.99 (0.00-14.00)
Fever	5	167	18709	1.87 (0.50-3.99)
Abdominal pain	8	277	9611	2.91 (2.04-3.92)
Sore Throat	6	401	10311	2.47 (0.25-6.23)
Dermatologic (dry skin, itchy skin, rashes, hives)	6	218	9322	2.61 (1.73-3.67)
Variations in heart rate	2	18	729	2.29 (0.00-7.36)
Diarrhea	7	218	19337	1.68 (0.63-3.18)
Constipation	3	20	1101	2.05 (0.39-4.75)
Dysphonia	2	62	3301	1.89 (1.45-2.38)
Chest tightness	5	293	6319	2.45 (0.58-5.35)
Musculoskeletal other	3	383	15618	1.72 (0.41-3.78)
Vomiting/nausea	5	260	16144	1.53 (1.09-2.03)

Changes in menstruation	3	10	866	1.27 (0.38-2.60)
Hair loss	3	16	1209	1.17 (0.10-3.10)
Palpitations	4	165	6178	1.27 (0.00-3.83)
Neurological abnormalities (pins and needles, tremor, numbness)	3	8	997	0.86 (0.37-1.55)
Urinary symptoms	3	6	1060	0.63 (0.23-1.21)
Dysphagia	3	5	1207	0.46 (0.14-0.93)
Speech Disturbances	3	5	1197	0.44 (0.05-1.10)

Table 3. Study methodological strength.

Study methodological Strength	N° of studies (N=21)	Prevalence (%)
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	31.6%
Control group with negative antibody test	2	10.5
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

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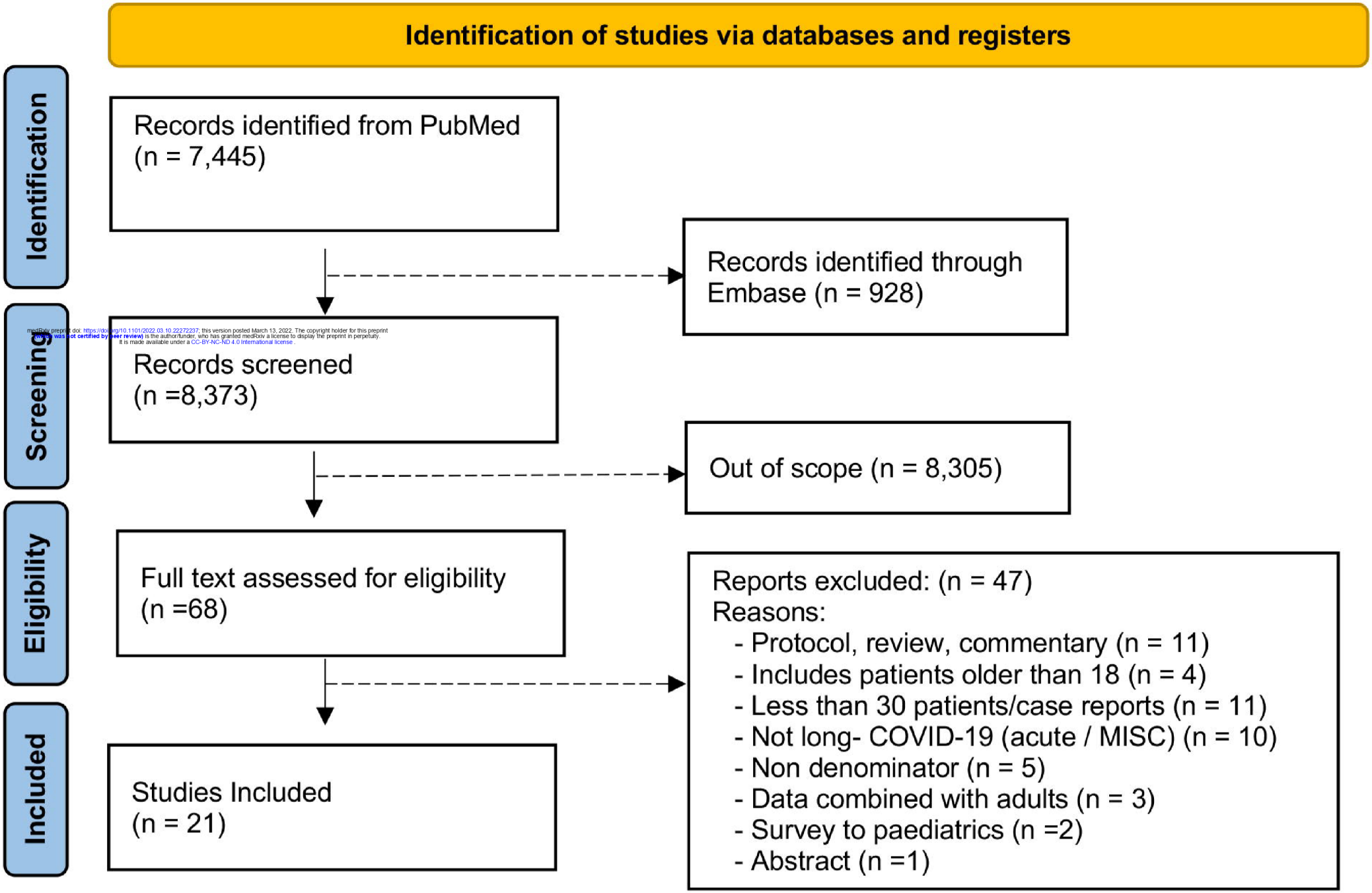
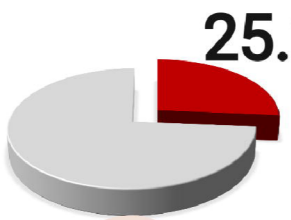


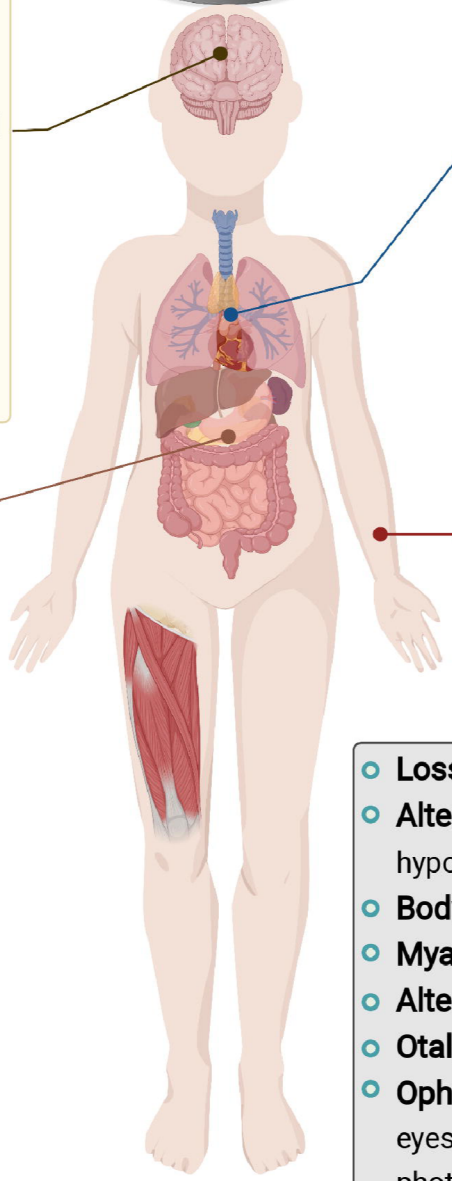
Long COVID in children and adolescents

8.00 - 17.00%
4.00 - 7.99%
2.00 - 3.99 %
0.00 - 1.99%

Neuropsychiatric (%)

- **Mood** 16.50 (sad, tense, angry, anxiety, depression)
- **Fatigue** 9.66
- **Sleep disorder** 8.42 (insomnia, hypersomnia, poor sleep quality)
- **Headache** 7.84
- **Cognition** 6.27 (confusion, impaired concentration, learning difficulties, memory loss)
- **Dizziness** 4.40
- **Neurological abnormalities** 0.86 (pins and needles, tremor, numbness)
- **Balance problems** 0.54





Cardiorespiratory (%)

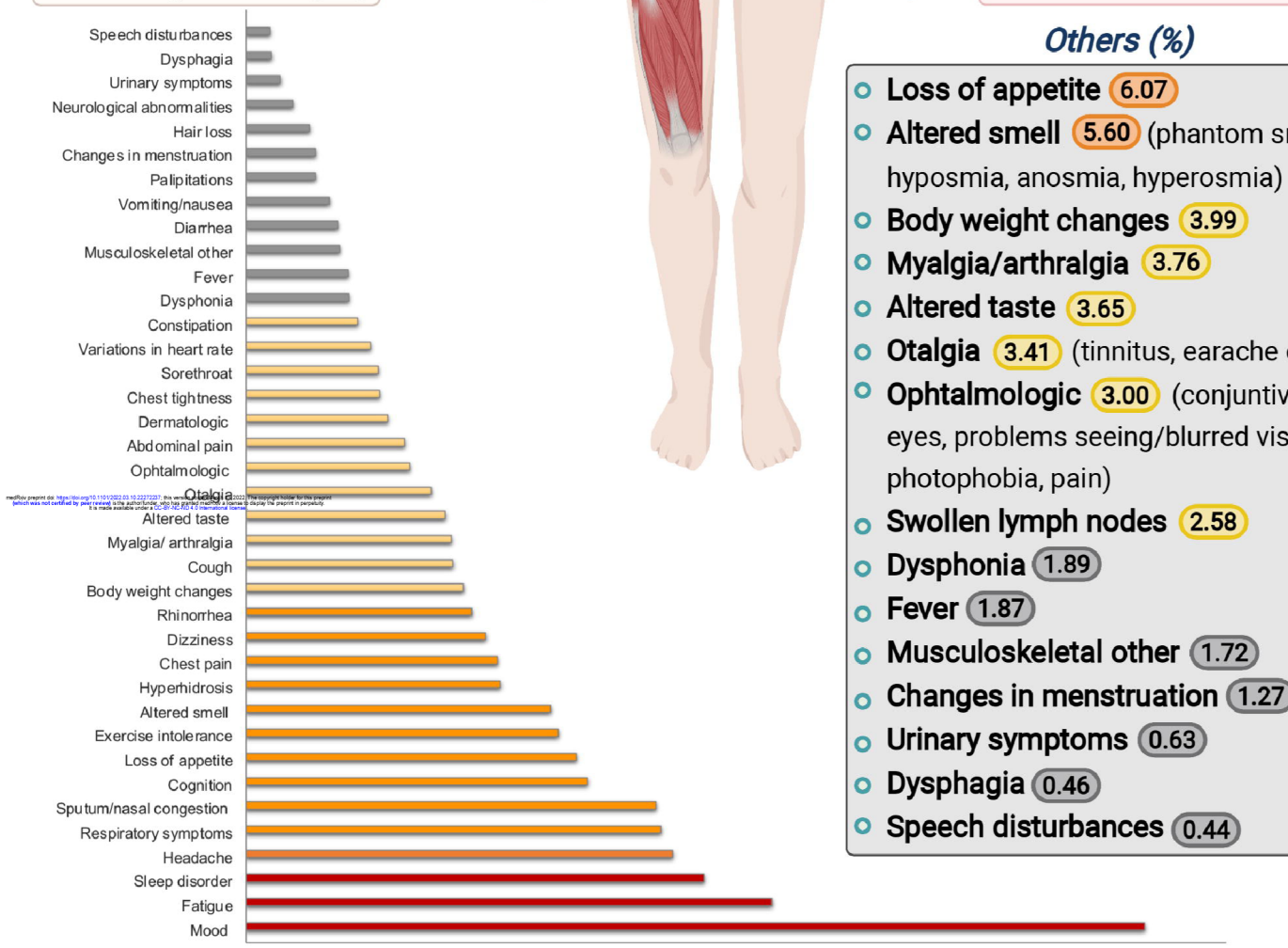
- **Respiratory symptoms** 7.62
- **Sputum/nasal congestion** 7.53
- **Orthostatic intolerance** 6.92
- **Exercise intolerance** 5.73
- **Chest pain** 4.62
- **Rhinorrhea** 4.15
- **Cough** 3.80
- **Chest tightness** 2.45
- **Variations in heart rate** 2.29
- **Palpitations** 1.27

Gastrointestinal (%)

- **Abdominal pain** 2.91
- **Constipation** 2.05
- **Diarrhea** 1.68
- **Vomiting/nausea** 1.53

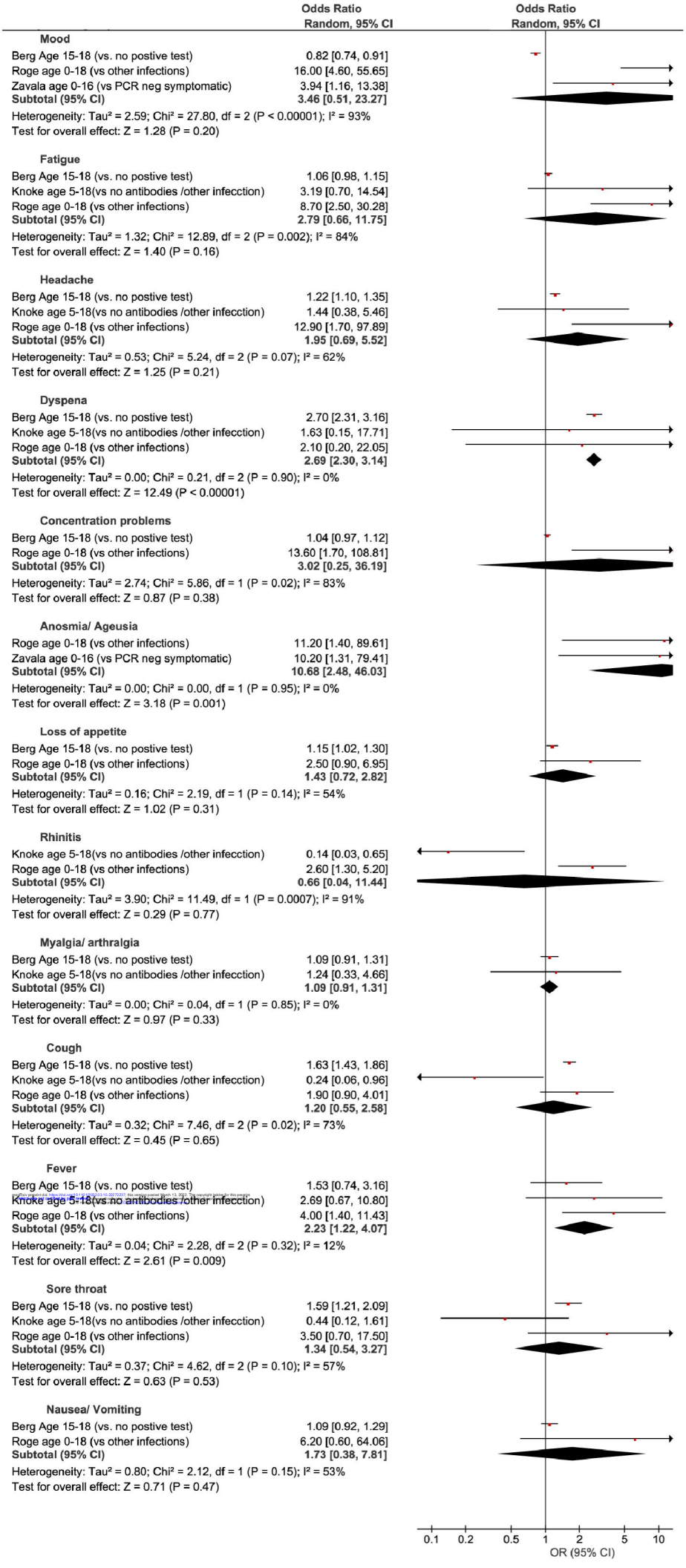
Dermatologic/Teguments (%)

- **Hyperhidrosis** 4.66
- **Dermatologic** 2.61 (dry skin, itchy skin, rashes, hives)
- **Hair loss** 1.17



Others (%)

- **Loss of appetite** 6.07
- **Altered smell** 5.60 (phantom smell, hyposmia, anosmia, hyperosmia)
- **Body weight changes** 3.99
- **Myalgia/arthralgia** 3.76
- **Altered taste** 3.65
- **Otalgia** 3.41 (tinnitus, earache or vertigo)
- **Ophtalmologic** 3.00 (conjuntivitis, dry eyes, problems seeing/blurred vision, photophobia, pain)
- **Swollen lymph nodes** 2.58
- **Dysphonia** 1.89
- **Fever** 1.87
- **Musculoskeletal other** 1.72
- **Changes in menstruation** 1.27
- **Urinary symptoms** 0.63
- **Dysphagia** 0.46
- **Speech disturbances** 0.44


Odds Ratio
Random, 95% CI
Odds Ratio
Random, 95% CI
Mood
Berg Age 15-18 (vs. no postive test) 0.82 [0.74, 0.91]
Roge age 0-18 (vs other infections) 16.00 [4.60, 55.65]
Zavala age 0-16 (vs PCR neg symptomatic) 3.94 [1.16, 13.38]
Subtotal (95% CI) 3.46 [0.51, 23.27]
Heterogeneity: Tau² = 2.59; Chi² = 27.80, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.28 (P = 0.20)
Fatigue
Berg Age 15-18 (vs. no postive test) 1.06 [0.98, 1.15]
Knoke age 5-18(vs no antibodies /other infecction) 3.19 [0.70, 14.54]
Roge age 0-18 (vs other infections) 8.70 [2.50, 30.28]
Subtotal (95% CI) 2.79 [0.66, 11.75]
Heterogeneity: Tau² = 1.32; Chi² = 12.89, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 1.40 (P = 0.16)
Headache
Berg Age 15-18 (vs. no postive test) 1.22 [1.10, 1.35]
Knoke age 5-18(vs no antibodies /other infecction) 1.44 [0.38, 5.46]
Roge age 0-18 (vs other infections) 12.90 [1.70, 97.89]
Subtotal (95% CI) 1.95 [0.69, 5.52]
Heterogeneity: Tau² = 0.53; Chi² = 5.24, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 1.25 (P = 0.21)
Dyspena
Berg Age 15-18 (vs. no postive test) 2.70 [2.31, 3.16]
Knoke age 5-18(vs no antibodies /other infecction) 1.63 [0.15, 17.71]
Roge age 0-18 (vs other infections) 2.10 [0.20, 22.05]
Subtotal (95% CI) 2.69 [2.30, 3.14]
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 12.49 (P < 0.00001)
Concentration problems
Berg Age 15-18 (vs. no postive test) 1.04 [0.97, 1.12]
Roge age 0-18 (vs other infections) 13.60 [1.70, 108.81]
Subtotal (95% CI) 3.02 [0.25, 36.19]
Heterogeneity: Tau² = 2.74; Chi² = 5.86, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.87 (P = 0.38)
Anosmia/ Ageusia
Roge age 0-18 (vs other infections) 11.20 [1.40, 89.61]
Zavala age 0-16 (vs PCR neg symptomatic) 10.20 [1.31, 79.41]
Subtotal (95% CI) 10.68 [2.48, 46.03]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.18 (P = 0.001)
Loss of appetite
Berg Age 15-18 (vs. no postive test) 1.15 [1.02, 1.30]
Roge age 0-18 (vs other infections) 2.50 [0.90, 6.95]
Subtotal (95% CI) 1.43 [0.72, 2.82]
Heterogeneity: Tau² = 0.16; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.02 (P = 0.31)
Rhinitis
Knoke age 5-18(vs no antibodies /other infecction) 0.14 [0.03, 0.65]
Roge age 0-18 (vs other infections) 2.60 [1.30, 5.20]
Subtotal (95% CI) 0.66 [0.04, 11.44]
Heterogeneity: Tau² = 3.90; Chi² = 11.49, df = 1 (P = 0.0007); I² = 91%
Test for overall effect: Z = 0.29 (P = 0.77)
Myalgia/ arthralgia
Berg Age 15-18 (vs. no postive test) 1.09 [0.91, 1.31]
Knoke age 5-18(vs no antibodies /other infecction) 1.24 [0.33, 4.66]
Subtotal (95% CI) 1.09 [0.91, 1.31]
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)
Cough
Berg Age 15-18 (vs. no postive test) 1.63 [1.43, 1.86]
Knoke age 5-18(vs no antibodies /other infecction) 0.24 [0.06, 0.96]
Roge age 0-18 (vs other infections) 1.90 [0.90, 4.01]
Subtotal (95% CI) 1.20 [0.55, 2.58]
Heterogeneity: Tau² = 0.32; Chi² = 7.46, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 0.45 (P = 0.65)
Fever
Berg Age 15-18 (vs. no postive test) 1.53 [0.74, 3.16]
Knoke age 5-18(vs no antibodies /other infecction) 2.69 [0.67, 10.80]
Roge age 0-18 (vs other infections) 4.00 [1.40, 11.43]
Subtotal (95% CI) 2.23 [1.22, 4.07]
Heterogeneity: Tau² = 0.04; Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 2.61 (P = 0.009)
Sore throat
Berg Age 15-18 (vs. no postive test) 1.59 [1.21, 2.09]
Knoke age 5-18(vs no antibodies /other infecction) 0.44 [0.12, 1.61]
Roge age 0-18 (vs other infections) 3.50 [0.70, 17.50]
Subtotal (95% CI) 1.34 [0.54, 3.27]
Heterogeneity: Tau² = 0.37; Chi² = 4.62, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.63 (P = 0.53)
Nausea/ Vomiting
Berg Age 15-18 (vs. no postive test) 1.09 [0.92, 1.29]
Roge age 0-18 (vs other infections) 6.20 [0.60, 64.06]
Subtotal (95% CI) 1.73 [0.38, 7.81]
Heterogeneity: Tau² = 0.80; Chi² = 2.12, df = 1 (P = 0.15); I² = 53%
Test for overall effect: Z = 0.71 (P = 0.47)
0.1
0.2
0.5
1
2
5
10
OR (95% CI)