How does post COVID differ from other post-viral conditions in childhood and adolescence (0–20 years old)? A systematic review

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Summary

Background Post Coronavirus disease (COVID) and other post-viral infection syndromes present an overlap of pathogenesis, onset, progression, and symptom profile. We aimed to systematically describe studies on post-viral conditions and determine the entity of post COVID compared to other post-viral conditions in children.

Methods We conducted a systematic search of the Embase, MEDLINE, Cochrane Library, and GoogleScholar databases (January 1946–3 November 2023), according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The main outcomes were differences in condition duration, symptom type, and development of chronic symptoms. This systematic review was registered on PROSPERO (CRD42023401789).

Findings 35/5051 studies were included, with 42,934 children, adolescents and young adults (0–20 years old) overall. Twenty-eight studies focused on post COVID symptoms, followed by five papers on Respiratory Syncytial Virus (RSV) and Rhinovirus, one study on Epstein–Barr Virus (EBV), and one on gastrointestinal viruses. Studies on post COVID mainly reported data on older children/adolescents, describing long-lasting symptoms, including fatigue, neurologic, cardiorespiratory, musculoskeletal, mental health, and gastrointestinal symptoms. The maximum described symptoms duration was eighteen months, with an average follow-up of seven months. The development of chronic symptoms was reported by 30 studies (93.8%) for 10,473/28,474 patients (36.8%). Recovery was achieved in 18,001/28,474 cases (63.2%). The study on EBV reported persistent fatigue in adolescents for a similar duration (6 months, 46% chronic). Studies on RSV and Rhinovirus were mainly done in children under three years, with development of recurrent wheezing (up to 3 years).

Interpretation Post-viral fatigue was a shared feature between post COVID and post EBV conditions. A better understanding of post COVID as a unique condition, sharing features with other post-viral syndromes, is needed. The healthcare burden and socio-economic consequences for children and their families warrant further investigation and development of appropriate healthcare management plans. The foremost requirement is the establishment of consistent and shareable definitions, as well as a consensus on outcomes, to effectively evaluate follow-up and quantify the burden of different viral infections.

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Keywords: Post-viral condition; Long COVID; Children; Adolescents; EBV; Chronic symptoms

Introduction

The impact and prevalence of post Coronavirus disease (COVID-19) condition, known as "Long/post COVID", in children are unclear due to the lack of high-quality studies and a clear clinical case definition.[1] There may be an increased risk in children older than ten years and those with certain underlying medical conditions. However, severe COVID-19 is generally uncommon in

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Research in context

Evidence before this study

The overlap between the clinical presentation and course of post Coronavirus disease (COVID) and other post-viral conditions highlights the need to review the clinical characteristics, duration of symptoms, and possible healthcare burden in the pediatric population of both entities. We conducted a systematic search of the Embase, MEDLINE, Cochrane Library databases and GoogleScholar, including citations from January 1946 to 3 November 2023, obtained combining Medical Subject Heading (MeSH) e and free-text terms for "post-viral" AND "condition" AND "children", according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were considered eligible if they included data on post-viral conditions in children up to 18 years and adolescents until 20 years of age. Randomized controlled trials (RCTs), observational, cohort, cross-sectional, and case–control studies were considered for inclusion.

Added value of this study

The results of the present systematic review confirm an overlap between post-viral infection symptoms following acute COVID and other viral infections, with some shared clinical features, duration of symptoms, and affected age subgroups. Potential risk factors for post COVID development, such as gender prevalence, socio-economic status, or comorbidities, did not emerge, or were not identified with certainty. Symptom duration was similar for post COVID and post Epstein–Barr Virus (EBV)/post gastrointestinal virus syndromes. However, recovery was achieved in more than half of the children with post COVID and post EBV condition, with a smaller proportion of children developing chronic symptoms. The timing for symptoms resolution for post COVID was similar to what has been reported so far by previously published studies.

Implications of all the available evidence

A better understanding of Long/post COVID as a unique condition, sharing features with other post-viral syndromes, is needed and implicates a multidisciplinary approach and international awareness in children and adolescents. The experience of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with the surge of post COVID-19 conditions also in pediatric patients, should be adopted as a model for preparedness for future pandemics and to better comprehend the true post-acute burden of other viral infections. The foremost requirement is the establishment of consistent and shareable definitions, as well as a consensus on outcomes, to effectively evaluate patient follow-up and quantify the burden.

children, so it is not known if post COVID symptoms are as frequent in the pediatric population as they are in adults and with the same clinical phenotype.[2] Furthermore, it is unclear whether post COVID differs from chronic conditions after other viruses in children, adolescents, and young adults. Different definitions for Long/post COVID have been formulated by the major international organizations, and therefore the term is often being used in a generally comprehensive manner by researchers, indicating the persistence of symptoms after Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3–5]

Some viral infections are known to cause post-acute infection syndromes,[6–10] and may represent a considerable healthcare burden, with social and economic consequences for children, adolescents, and their families.[7] The clinical presentation is heterogeneous and includes both physical and psychological symptoms,[6,7,11] usually without any specific clinical findings or laboratory abnormalities.[8] The features may vary according to the etiology of the viral infection, individual patient response (complete recovery, relapse, or remitting pattern), and age (younger children being more prone to respiratory symptoms and older children often presenting with chronic fatigue).[7] It can be argued that post-viral syndromes often share a similar symptom profile, irrespective of the involved pathogen.[6] This suggests the potential existence of a common etiopathogenesis.[7,12–14] Post-viral fatigue syndrome, also referred to as myalgic encephalomyelitis or chronic fatigue syndrome, presents symptoms of fatigue, muscle weakness, and variable neurological abnormalities.[6,9,12,15–19] Many viruses have been thought to be associated with post-acute infection syndromes, most commonly Coxsackie viruses, but also Influenza, Varicella, Epstein–Barr, Ebola, and tick-borne encephalitis viruses.[6,9,12,17,20,21] Similarly, SARS-CoV-2 infection may be followed by a comparable post-acute, long-lasting multi-organ syndrome.[13] The most commonly reported symptoms of Long/post COVID conditions include fatigue, headache, attention disorder, hair loss, cough, chest pain and dyspnea[22–24]; however, with a lower prevalence in children to young adults as compared to adults.[24] Fatigue is a dominant feature of Long/post COVID, potentially lasting for weeks to months.[22,24–26] According to adult data, prolonged illness duration and persistent symptoms after SARS-CoV-2 infection will generally resolve within six months or less,[25,27] except for severe fatigue or post-exertional malaise.[25]

Post COVID-19 conditions became a global concern after the initial acute phase of the pandemic, however little is known about the pathogenesis and long-term clinical course both in adults as well as in children, adolescents and young adults. The overlap between the clinical presentation and course of post COVID and other post-viral conditions highlights the need to review

the clinical characteristics, duration of symptoms, and possible healthcare burden in the pediatric population of both entities.

This review aims to systematically describe the available evidence on symptoms persisting beyond acute COVID infection, as compared to other viral infections; to evaluate clinical characteristics, duration, and healthcare burden.

Methods

Study design, data source, and search strategy

We conducted a systematic search of the Embase, MEDLINE (567 retrieved titles and abstracts), Cochrane Library databases (3625 retrieved titles and abstracts), and GoogleScholar (833 retrieved titles and abstracts), including citations from January 1946 to 3 November 2023, obtained combining Medical Subject Heading (MeSH) e and free-text terms for "post-viral" AND "condition" AND "children". The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[28] The full search strategy is available in the Supplementary Material. This systematic review was registered on PROSPERO (n. CRD42023401789).

Inclusion criteria

Studies were considered eligible for full-text review if they included data on post-viral conditions (not mandatorily following strict Long COVID definition criteria for SARS-CoV-2) in children and adolescents up to 18 years and young adults until 20 years of age according to the World Health Organization (WHO) definition. Randomized controlled trials (RCTs), observational, cohort, cross-sectional, and case–control studies were considered for inclusion, and included if reporting granular data on at least one of the primary outcomes in the population of interest.

Exclusion criteria

All studies on adults, Human Immunodeficiency Virus (HIV), hepatitis viruses (as both causing chronic infections), and Multisystem Inflammatory Syndrome in Children (MIS-C) were excluded. Studies evaluating the effects of pharmacological interventions on post-viral conditions (i.e., steroids, epinephrine, and palivizumab on post-Respiratory Syncytial Virus, RSV, wheezing) were excluded. Systematic and narrative reviews, case reports, case series, commentaries, editorials, book chapters, and conference abstracts were excluded. Papers with mixed study populations of adults and children, where extraction of pediatric data was not possible, were also excluded.

Study selection and risk of bias assessment (RoB)

Four investigators (CMcK, GS, CB, ID) independently assessed titles, abstracts, and full texts. Discussion with a fifth reviewer (CM) resolved disagreements regarding study selection. The risk of bias for non-randomized studies of interventions was assessed according to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[29] For each criterion, the included studies were classified by quality rating as good, fair, or poor by three reviewers (CMcK, CB, and CM), and disagreements were resolved by discussion.

Data collection

Data extraction was conducted using a standardized data collection form, which included information about authors, year and country of publication, study design, and setting, population, number of patients, patient age, duration of follow-up, virus type, post-viral symptoms, outcomes (duration of symptoms, recovery/remission, lost days of school, development of chronic symptoms/syndrome, number of Emergency Department, ED, evaluations).

Strategy for data synthesis

A narrative (descriptive) synthesis of data was performed. Continuous variables were expressed in mean, median, or range, if applicable. Categorical variables were presented as "number" (%), listed in the text or tabulated.

Outcome measures

The primary outcomes were the duration of symptoms including the difference in symptom type and duration in post COVID and other post-viral conditions; the number of children, adolescents and young adults developing chronic symptoms, including the difference between post COVID and other post-viral conditions, and the number of fully recovered children, adolescents, and young adults, including the difference between post COVID and other post-viral conditions (recovery was described as prolonged symptoms with resolution within the follow-up period, as reported in the studies).

The secondary outcomes for both post COVID and other post-viral conditions, if available, were the number of children, adolescents and young adults unable to attend school, the number of children, adolescents and young adults with difficulty in doing everyday tasks and the number of children, adolescents and young adults undergoing ED evaluations.

Ethics

The present study did not require informed consent or approval by the local Ethics Committees, due to the nature of the research.

Role of the funding source

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

Results

Of 5051 retrieved titles and abstracts, 35 studies, with data on 42,934 children, adolescents, and young adults with long-lasting, post-viral infection symptoms, were eligible for inclusion. Fig. 1 shows a flow diagram of the study selection process for this review according to PRISMA guidelines. Retrieved articles with authors, country, publication year, study design, control group, inclusion criteria (from virus positivity to symptoms/from outcome link back to disease), setting, median follow-up duration, method of outcome reporting, definition of Long/post COVID or other post-viral condition, number of patients with post-viral condition, post-viral symptoms by main area, and outcomes have been organized by pathogen and age sub-group, as summarized in Tables 1–5. The definition of Long COVID, as reported in the included studies if provided, was not univocal (Table 1) for symptoms duration and reference source.

The included studies were published between 1997 and 2023 (Fig. 2), mainly in the United Kingdom (six studies), Italy (four studies), Denmark, Germany, Norway and the United States of America (three studies each), followed by Russia, with two studies, and last, Australia, Brazil, Canada, Finland, Japan, Latvia, The Netherlands, Spain, Sweden, Switzerland and Thailand (one study each), without data from African countries. Most studies focused on SARS-CoV-2 and post COVID (28 studies), followed by five papers on other respiratory viruses (mostly RSV and Rhinovirus). The last two studies were respectively on EBV and gastrointestinal viruses (Torovirus and Adenovirus). Regarding age subgroups, 11/35 studies (31.4%) provided granular data exclusively on older children and adolescents/young adults, with further 18 studies (51.4%) including older children and adolescents/young adults along with younger children. Symptoms of the following areas were reported: neurologic, mental health, cardio-respiratory, general (including fatigue), dermatologic, musculoskeletal, gastrointestinal, and ear-nose-throat (ENT).

The main findings according to our primary outcomes are reported in detail by causative organism below. Overall, symptoms duration was similar for post-COVID-19 and post EBV/post gastrointestinal virus syndromes, ranging from 10 days to 18 months. A longer duration, with a median of three years, was described for post-acute syndromes after RSV/Rhinovirus infection, with recurrent wheezing after respiratory virus infections. Concerning the development of chronic symptoms versus recovery, 36.8% of patients had post COVID chronic symptoms within follow-up time, according to the available follow-up data, as compared with 63.2% that achieved recovery.

Data on the secondary outcomes (lost school days, activity limitation, and ED evaluations) were available only for some of the studies on SARS-CoV-2.

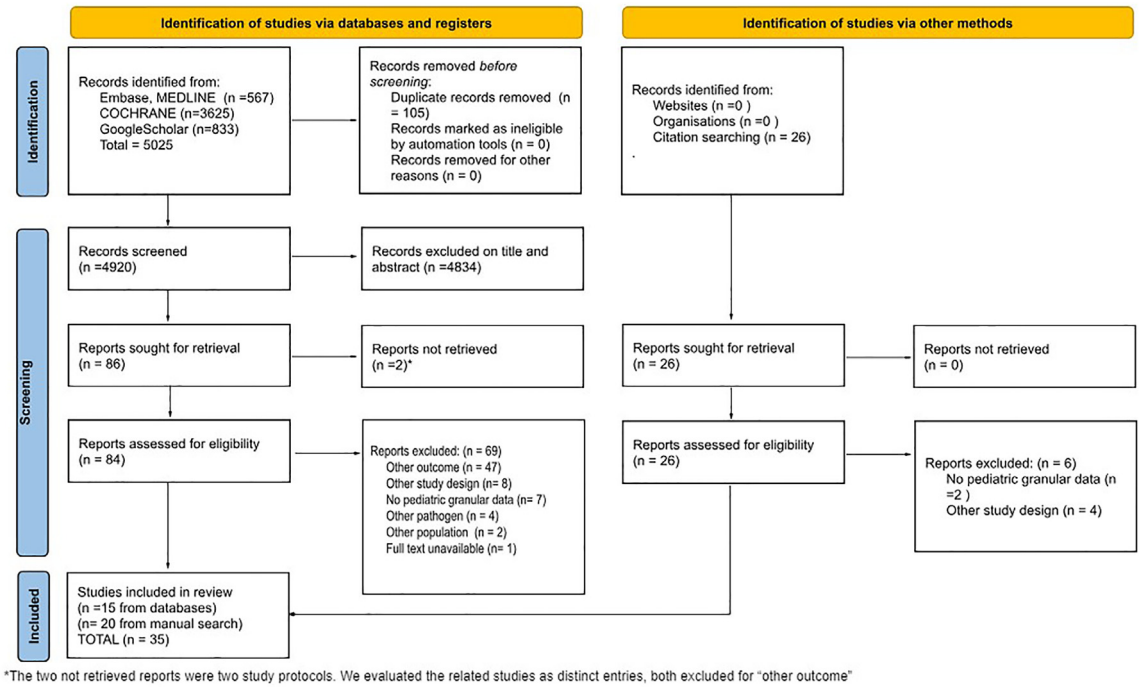

Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
Smane et al.,[30]	Latvia, 2020	Retrospective, cohort	No	Long/post COVID not mentioned (referred to COVID-19 persistent symptoms after recovery).	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients, of which some previously admitted	101	Interview/ questionnaire filled by medical staff
Sterky et al.,[31]	Sweden, 2021	Prospective, cohort	No	Long/post COVID mentioned, not defined (referred to persistent symptoms).	From virus positivity/ disease to symptoms —SARS-CoV-2	In-patients	219	Self-reported, then reviewed by assessors (interview for extent, and type, of persistent Symptoms)
Roessler et al.,[32]	Germany, 2022	Retrospective matched cohort	Yes, 1:5 matching negative controls	Long/post COVID defined according to NICE guidelines	From virus positivity/ disease to symptoms —SARS-CoV-2	In- and out-patients	236	Routine data from German statutory health insurance organizations, with incident morbidity outcomes documented in the second quarter after index date or later
Borch et al.,[33]	Denmark, 2022	Prospective, cohort	Yes, negative controls	Long/post COVID defined as symptoms lasting >4 weeks after being diagnosed with SARS-CoV-2 infection	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	211	Online questionnaire (completed by proxy under 15 yo, otherwise self-reported)
Di Gennaro et al.,[34]	Italy, 2022	Prospective, cohort	Yes, controls with previous SARS-CoV-2 infection, fully recovered	Long/post COVID condition defined as: PCC8/12 group (children with persisting symptoms for at least 8/12 weeks after SARS-CoV-2 infection, that cannot be explained by an alternative diagnosis) PCC ≥3 group (children experiencing at least three persisting symptoms for at least 8 weeks).	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	84	Pediatric Long Covid International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) survey (self/proxy-reported)
Gonzalez-Aumatell et al.,[35]	Spain, 2022	Longitudinal, cohort	No	Long/post COVID defined as three or more compatible symptoms lasting longer than twelve weeks after SARS-	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	365	Out-patient assessment and self/ parent-proxy completed questionnaires (pediatric Functional

(Table 1 continues on next page)

Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
				CoV-2 infection, not present before infection				Assessment of Chronic Illness Therapy—Fatigue (pedsFACIT-F) scale and "Pediatric Symptom Checklist" (PSC) for mental health
Morello et al.,[36]	Italy, 2023	Prospective, cohort	No	Long/post COVID Condition was persistence of symptoms for at least three months after initial infection, which had a negative impact on daily life, and other possible diagnoses excluded.	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	547	In-clinic follow-up assesment, with standardized COVID-19 follow-up protocol, t serial intervals (3-, 6-, 12- and 18-months post-onset).
Kikkenborg Berg et al.,[37]	Denmark, 2022	Cross-sectional	Yes, 1:4 matched negative controls	Long/post COVID according to WHO definition as new symptoms that presented after SARS-CoV-2 infection and were present for 8 weeks after the positive SARS-CoV-2 test	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	531	Survey conducted by parent proxy report
Say et al.,[38]	Australia, 2021	Prospective, cohort	No	Long/post COVID mentioned, not defined (referred to persistent symptoms).	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	182	Standardized clinic proforma
Molteni et al.,[27]	UK, 2021	Prospective, cohort	Yes, symptomatic children testing negative for SARS-CoV-2, matched 1:1 for age, gender, and week of testing	Long/post COVID defined as prolonged illness duration after acute infection.	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	365	Reported by an adult proxy (caregiver) through mobile application
Brackel et al.,[39]	Netherlands, 2021	Cross-sectional	No	Long/post COVID defined as cases where symptoms such as persistent tiredness, headaches, dyspnea, concentration	From symptoms to disease—SARS-CoV-2	Out-patients	84	Survey filled by hospital pediatricians (given a definition of long-COVID as well as a list of predominant symptoms in adults, and able to consult

(Table 1 continues on next page)

Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
				problems, depression, skin lesions, and gastro-intestinal complaints persisted months after initial COVID-19 infection.				their patient records)
Buonsenso et al.,[40]	Italy, 2021	Cross-sectional	No	Long/post COVID, defined according to the Long COVID ISARIC study group protocol and survey.	From virus positivity/ disease to symptoms —SARS-CoV-2	In- and out-patients	163	Reported by an adult proxy (caregiver) through questionnaire
Zavala et al.,[41]	UK, 2021	Case-control	Yes, matched PCR-negative SARS-CoV-2 symptomatic controls	Long/post COVID, defined as on-going symptoms (not specified)	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	28	Reported by an adult proxy (caregiver) through questionnaire
Radtke et al.,[42]	Switzerland, 2021	Prospective, cohort	Yes, SARS-CoV-2 seronegative controls	Long/post COVID mentioned, not defined (considered symptoms beyond 4 and 12 weeks).	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	182	Reported by an adult proxy (caregiver) through questionnaire
Di Sante et al.,[43]	Italy, 2021	Cross-sectional	Yes, patients that completely recovered after acute infection	Long/post COVID: patients having persisting symptoms for more than five weeks and 67 involvement of two systems or more.	From symptoms to disease—SARS-CoV-2	Out-patients	98	Survey (not specified)
Buonsenso et al.,[44]	UK, 2022	Cross-sectional	No	Long/post COVID as presence of persistent symptoms in children with previous COVID-19, defined according to WHO definition	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	28	Reported by an adult proxy (caregiver) on online platform
Knoke et al.,[45]	Germany, 2022	Cross-sectional	Yes, SARS-CoV-2 seronegative controls	Long/post COVID not mentioned, the study focused on long term respiratory symptoms	From virus positivity/ disease to symptoms —SARS-CoV-2	In- and out-patients	79	Interview
Osmanov et al.,[46]	Russia, 2022	Prospective, cohort	No	Long/post COVID defined as ongoing symptoms including fatigue and muscle weakness, breathlessness, and neurological problems more than 6 months after the acute phase of coronavirus disease 2019 (COVID-19)	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients (previously admitted for acute disease and discharged)	268	Telephone interview

(Table 1 continues on next page)

Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
Atchison et al.,[47]	UK, 2023	Cross-sectional	No	Long/post COVID defined as persistent symptoms lasting ≥3 months post-COVID-19.	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	365	Online questionnaire (parent/guardian completed by proxy for those aged 5–12 years old)
Hahn et al.,[48]	Canada, 2023	Prospective, cohort	No	Long/post COVID was defined as continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with symptoms lasting for at least 2 months with no other explanation, according to WHO definition	From symptoms to disease—SARS-CoV-2	Out-patients	532	Parent-proxy symptom reporting
Blankenburg et al.,[49]	Germany, 2021	Retrospective, cohort	Yes, seronegative patients reporting symptoms	Long/post COVID defined as persisting symptoms 4–12 weeks and more than 12 weeks after an acute SARS-CoV-2 infection	From symptoms to disease—SARS-CoV-2	Out-patients	NR	Self-completed survey
Leftin Dobkin et al.,[50]	USA, 2021	Retrospective, cohort	No	Study focused on prolonged symptoms following acute COVID-19 infection. Long/post COVID mentioned (persistence of symptoms or development of sequelae beyond 3 or 4 weeks from the onset of acute symptoms of COVID-19).	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	97	Retrospective chart review (spirometry and plethysmogtraphy data)
Rusetsky et al.,[51]	Russia, 2021	Cross-sectional	No	Study focused on smell assessment, Long COVID not mentioned/defined.	From virus positivity/ disease to symptoms —SARS-CoV-2	In-patients	60	Telephone survey (twice) and physical examination; questionnaire and odor identification test were used for smell assessment
Stephenson et al.,[52]	UK, 2022	Cross-sectional	Yes, seronegative patients reporting symptoms	Long/post COVID Defined as symptoms 3 months after a	From symptoms to disease—SARS-CoV-2	Out-patients	104	Self-reported symptoms (online questionnaire;

(Table 1 continues on next page)

Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
				positive SARS-CoV-2 test.				patients who could report, without recall bias, symptoms 3 months after testing)
Kikkenborg Berg et al.,[53]	Denmark, 2022	Cross-sectional	Yes, 1:4 matched controls (never had SARS-CoV-2 positivity/never tested)	Long/post COVID according to WHO definition as new symptoms that presented after SARS-CoV-2 infection and were present for 8 weeks after the positive SARS-CoV-2 test	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	531	Self-reported symptoms (online questionnaire)
Selvakumar et al.,[54]	Norway, 2023	Prospective, cohort	Yes, seronegative patients	Long/post COVID reported according to WHO definition	From virus positivity/ disease to symptoms —SARS-CoV-2	Out-patients	182	Clinical examination, functional testing and questionnaire
Sakurada et al.,[55]	Japan, 2023	Retrospective, cohort	Yes, adults with Long COVID	Long/post COVID defined as symptoms that persist for more than four weeks after the onset of COVID-19	From symptoms to disease—SARS-CoV-2	Out-patients	75	Complete face-to-face medical interview and examination by a physician
Miller et al.,[56]	UK, 2022	Prospective, cohort	No	Long/post COVID mentioned as "persistent, post-acute symptoms after acute infection".	From symptoms to disease—SARS-CoV-2	Out-patients	334	Self-reported/reported by an adult proxy (caregiver) through monthly surveys, after recruitment of households via social media, postal service and text messages.
Pedersen et al.,[57]	Norway, 2018	Prospective, cohort	Yes, healthy controls (comparison data not reported)	Chronic fatigue defined as substantial fatigue lasting for more than six months after acute EBV infection	From virus positivity/ disease to symptoms —EBV	Out-patients	182	Investigational program including clinical evaluation, cognitive testing and a questionnaire
Teeratakulpisarn et al.,[58]	Thailand, 2015	Prospective, cohort	No	Recurrent wheezing defined as children with a history of healthcare visits with wheezing or having received beta2 agonist nebulization to relieve respiratory symptoms.	From symptoms to disease—RSV; Rhinovirus; Influenzavirus; hMPV; mixed viruses	Out-patients (previously admitted)	1825	Clinical evaluations
Lukkarinnen et al.[59]	Finland, 2017	Retrospective, cohort	No	Recurrent wheezing/ asthma at age 8 years if met 1 or more of	From symptoms to disease—RSV; Rhinovirus	Out-patients	2482	Clinical evaluations and telephonic interview

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Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
				the subsequent criteria during the preceding 12 months: reports from patient charts of doctor-diagnosed asthma; need for regular use of doctor-prescribed asthma therapy with ICSs for more than a month, use of OCSs for asthma exacerbations, acute asthma attack relieved by repeated use of bronchodilator, and/ or hyperreactivity in spirometry defined as reversible airflow obstruction with an increase of 12% or greater in FEV1 in the broncho-dilatation test or a decrease of 15% or greater in the exercise challenge.				
Dumas et al.,[60]	USA, 2019	Prospective, cohort	No	Recurrent wheezing by age 3 defined as parental report of at least 2 corticosteroid-requiring breathing problems in 6 months or at least 4 breathing problem episodes in one year that last at least one day and affect sleep.	From symptoms to disease—RSV; Rhinovirus; mixed viruses	Out-patients (previously admitted)	1095	Telephonic interviews with families/parental report
Lemanske et al.,[61]	USA 2005	Prospective, cohort	No	Recurrent wheezing defined as (1) physician diagnosed wheezing at an office visit; (2) an illness for which the child was prescribed short-acting or long-acting b-agonists and/or long-term controller medications; or (3) an illness given the	From symptoms to disease—RSV; Rhinovirus	Out-patients	1095	Caregiver notification ± clinical evaluation

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Author	Country, year of publication	Study design	Control group (yes/no; kind)	Post-viral condition definition (if provided)	Inclusion criteria (from virus positivity/ disease to symptoms/from symptoms to disease)	Setting	Follow-up duration (days, median)	Method of outcome reporting
(Continued from previous page)								
				following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation.				
Hunderi et al.,[62]	Norway, 2019	Prospective, cohort	No	Recurrent bronchial obstruction (wheeze) defined as number of episodes of wheezing and/or chest tightness from birth to enrolment (first assessment) and from enrolment to the two-year assessment.	From symptoms to disease—RSV; Rhinovirus; mixed viruses	In- and out-patients	730	Structured interviews of caregivers during clinical evaluation
Koopmans et al.,[63]	Brazil, 1997	Case-control	Yes, controls without diarrhea	Persistent diarrhea defined as lasting >2 weeks.	From symptoms to disease—Torovirus, Adenovirus	Out-patients	NR	Caregiver report/ clinical evaluation

COVID, Coronavirus disease; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; yo, years old; UK, United Kingdom; USA, United States of America; EBV, Epstein–Barr Virus; RSV, Respiratory Syncytial Virus.

Table 1: **General characteristics of the included studies.**

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
Children < 3 yo; Children > 3 yo, < 10 yo; Children over 10 yo/adolescents/young adults																
Smane et al., Latvia, 2020[30]	Retrospective, cohort	30	yes headache 1 (3.3)	NR	NR	NR	yes myalgia/arthralgia 1 (3.3)	NR	yes fever/chills 2 (6.7)	yes Microhematuria 1 (3.3)	yes altered smell 1 (3.3); altered taste 1 (3.3)	101 days (mean)	**1**: 9 (30) **0**: 21 (70)	NR	NR	NR
Sterky et al., Sweden, 2021[31]	Prospective, cohort	55	yes headache 4 (7.3%)	yes difficulty concentrating 3 (5.5); depression 3 (5.5)	NR	yes non-specific respiratory 3 (5.5)	yes myalgia	yes non-specific 3 (5.5)	NR	NR	yes altered smell and taste 2 (3.6%)	>4 months	**1**: 12 (22) **0**: 43 (78)	NR	NR	NR
Roessler et al., Germany, 2022[32]	Retrospective matched cohort	11,950	yes, headache incidence rate ratio 1.58 (CI 95% 1.35–1.84), p < 0.01	yes, adjustment disorder incidence rate ratio 1.71 (CI 95% 1.42–2.06), p < 0.01; Somatization disorder incidence rate ratio 1.62 (CI 95% 1.30–2.02), p < 0.01; anxiety disorder incidence rate ratio 1.54 (CI 95% 1.23–1.92) p < 0.01; depression incidence rate ration 1.45 (CI 95% 1.12–1.87), p < 0.01	NR	yes, cough incidence rate ratio 1.74 (CI 95% 1.48–2.04), p < 0.01; chest pain incidence rate ratio 1.72 (CI 95% 1.39–2.12), p < 0.01	NR	yes, abdominal pain incidence ratio 1.45 (CI 95% 1.27–1.64), p < 0.01	yes, malaise/ **fatigue**/ exhaustion incidence rate ratio 2.28 (95% CI 1.71–3.06), p < 0.01; fever incidence rate ratio 1.56 (CI 95% 1.30–1.87), p < 0.01	NR	NR	>3 months	NR	NR	NR	NR
Borch et al., Denmark, 2022[33]	Prospective cohort	3813 (439 pre-schoolers vs 3374 school aged)	yes, headache, dizziness	NR	NR	yes, chest pain, cough	yes, myalgia/ arthralgia, muscle weakness (risk difference in pre-schoolers 0.01 (CI 0.0–0.01))	yes, diarrhea, nausea	yes, fever, **fatigue** (risk difference in pre-schoolers 0.05 (CI 0.04–0.06); in school children 0.05 (CI 0.05–0.06)).	NR	yes, loss of smell (risk difference in pre-schoolers 0.01 (CI 0.01–0.01); in school children 0.12 (CI 0.12–0.13)); loss of taste (risk difference in pre-schoolers RD 0.01 (CI 0.01–0.02), in school children 0.10 (CI 0.09–0.10)).	At least >4 weeks (maximum: still symptoms after 13 months)	**1:** 3813 (100) at 4 weeks; 954 (25) within 5 months **0:** 0 (0) at 4 weeks; 2859 (75) within 5 months	NR	NR	NR

(Table 2 continues on next page)

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
(Continued from previous page)																
Di Gennaro et al., Italy, 2022[34]	Prospective, cohort	46	yes, headache; amnesia; paresthesias; dizziness	yes, difficulty concentrating	yes, rash	yes, cough; dyspnea at rest/under exertion; asthma; chest pain; tachycardia	yes, arthralgia; myalgia;	yes, gastrointestinal disorders	yes, fever; asthenia	NR	yes, anosmia; dysgeusia	8–12 weeks	**1:** 46 at 8 weeks follow-up (PCC8), 39 at 12 weeks (PCC12); 15 had at least three persisting symptoms (PCC ≥ 3) at 12 weeks. **0:** 7 (15.2) at 12 weeks	NR	NR	NR
Gonzalez-Aumatell, Spain, 2022[35]	Longitudinal cohort	50	yes, neurocognitive disorders 37 (74); headaches 36 (72); insomnia 27 (54); tinnitus 21 (42); paresthesia 17 (34); photophobia 17 (34); dizziness 15 (30)	NR	yes, skin signs 13 (26)	yes, dyspnea 33 (66); chest pain 24 (48); palpitations/ tachycardia 18 (36); cough 14 (28);	yes, myalgia/ arthralgias 32 (64)	yes, hyporexia/anorexia 21 (42); abdominal pain 18 (36); diarrhea 12 (24); dyspepsia 6 (12); dysphagia 4 (8)	yes, asthenia/ **fatigue** 50 (100); weakness 37 (74); orthostatic hypotension 22 (46)	NR	yes, anosmia 18 (36); ageusia/ dysgeusia 18 (36); weight loss 10 (20); dysphonia 2 (4)	At least >12 weeks;	**1:** 50 (100) >12 weeks; 18 (36) > 6 months **0:** 32 (64) > 6 months	Not able to attend to regular school schedule 17 (34); School dropout 9 (18)	Stopped sport activities 36 (72)	NR
Morello et al., Italy, 2023[36]	Prospective, cohort	1234	yes, headache 69 (5.6);	yes, concentration problems 31 (2.5)	yes, rash 14 (1.1)	yes, cough 16 (1.3); dyspnea at rest 7 (0.6); dyspnea after exercise 77 (6.2); asthma 10 (0.8); chest pain 29 (2.4); tachycardia 20 (1.6)	yes, arthralgia 31 (2.5); myalgia 53 (4.3)	yes, diarrhea and/ or other gastrointestinal symptoms 56 (4.5)	yes, fever 10 (0.8); weakness 162 (13.1); **fatigue** under exertion 15 (1.2)	NR	yes, rhinitis 8 (0.6); lost or altered smell 11 (0.9); lost or altered taste 11 (0.9);	>3 months–18 months	**1:** 294 (23.8) at 3 months; 143 (11.6) at 6 months; 38 (3) at 12 months; 15 (1.2) at 18 months. **0:** 1219 (98.8) at 18 months	NR	NR	NR
Children 0–3 years																
[a]**Kikkenborg Berg** et al., Denmark, 2022[37] (A)	Cross-sectional	1194	NR	yes, mood swings 73 (6.1), OR 1.63 (1.22–2.19), p = 0.0011	yes, rashes 53 (4.4) OR 1.57 (1.11–2.22), p = 0.01; cold extremities 14 (1.2%), OR 3.94 (1.81–8.56), p = 0.0005	yes, trouble breathing 18 (1.5) OR 4.40 (2.13–9.11), p < 0.0001; cough 77 (6.4), OR 4.65 (3.27–6.64), p < 0.0001	yes, pain in muscles or joints 5 (0.4), OR 1.84 (0.54–6.30), p = 0.33	yes, stomach aches 40 (3.4), OR 248 (1.63–3.77), p < 0.0001; nausea 5 (0.4), OR 8.30 (1.61–42.91), p = 0.011	yes, **fatigue** 41 (3.4), OR 3.50 (2·0.21–5.55), p < 0.0001; fever 22 (1.8), OR 5.89 (2.95–11.77), p < 0.0001; loss of appetite 49 (4.1), OR 3.72 (2.44–5.67), p < 0.0001; dark circles under eyes 17 (14), OR 6.15 (2.60–14.55), p < 0.0001; extreme paleness 6 (0.5); OR 3.25 (094–11.24), p = 0.063	NR	NR	At least 2 months, maximum 12 months	**1:** 427 (35.7) Long COVID **0:** 767 (64.3)	Of 391 patients 13 months–3 years: 0–5 days 116 (29.7); 6–10 days 84 (21.5); 11–15 days 50 (12.8); 16 days –1 month 110 (28.1); more than 1 month 31 (7.9).	PedsQL social functioning scores lower in cases.	NR
Children > 3 yo, < 10 yo																
Say et al., Australia, 2021[38]	Prospective, cohort	12	NR	NR	NR	yes, cough 6 (50)	NR	NR	yes, **fatigue** 3 (25)	NR	NR	14.6 days (mean)	**1:** 0 (0) **0:** 12 (100)	NR	NR	NR

(Table 2 continues on next page)

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
(Continued from previous page)																
[b]**Molteni** et al., UK, 2021 (A)[27]	Prospective, cohort	588	yes headache 324 (55.1), dizziness/ vertigo 84 (14.3) eye soreness/ redness 89 (15.1)	yes, difficulty concentrating 15 (2.6)	NR	yes, cough 145 (24.7), thoracic pain 37 (6.3) dyspnea 24 (4)	yes, myalgia/ arthralgia 54 (9.2)	yes, diarrhea 48 (8.2), stomach pain 163 (27.7) nausea 95 (16.2),	yes, **fatigue** 258 (43.9), fever/chills 257 (43.7) loss of appetite 120 (20.4)	NR	yes, sore throat 213 (36.2), hoarse voice 63 (10.7) altered smell 132 (22.4)	<28 days (570 patients, 96.9%), ≥ 28 days (18 patients, 3.1%)	**1**: 18 (3.1) **0**: 570 (96.9)	NR	NR	16 (2.7)
Children > 3 yo, < 10 yo; Children over 10 yo/adolescents/young adults																
Brackel et al., Netherlands, 2021[39]	Cross-sectional	89	yes headache 34 (38); dizziness 3 (3); memory loss 12 (13)	yes difficulty concentrating 40 (45)	yes Rash 6 (7)	yes Thoracic pain 31 (35); palpitations 16 (18); dyspnea 49 (55)	yes myalgia/arthralgia 25 (28); not specified 50 (56)	NR	yes **fatigue** 77 (87) fever/ chills 2 (2)	NR	NR	28–252 days (range)	**1**:89 (100) **0**: 0 (0)	32 (36)	75 (84.2) mild 43 (48), severe 32 (36)	16 (18)
Buonsenso et al., Italy, 2021[40]	Cross-sectional	129	yes, headache 13 (10.1), insomnia 24 (18.6)	yes, difficulty concentrating 13 (10.1)	yes Rash/skin irritation 9 (6.9), swollen extremities 9 (6.9)	yes, cough 7 (5.4), thoracic pain 4 (3.1), palpitations 5 (3.8)	yes, myalgia/ arthralgia 13 (10.1)	yes, diarrhea 2 (1.5), stomach pain 3 (2.39)	yes, **fatigue** 14 (10.9), weight loss 10 (7.7)	NR	yes altered smell 6 (4.6) altered taste 4 (3.1)	>120 days	**1:** 75 (58.1) 46 (35.6) had 1-2 persisting symptoms, 29 (22.5) 3 or more **0:** 54 (41.9)	NR	NR	NR
Zavala et al., UK, 2021,[41]	case control	472	yes, headache 20 (4.2), insomnia 33 (6.9) dizziness/ vertigo 16 (3.4) memory loss 10 (2.1) slurred speech 8 (1.7) ringing in ears 6 (1.2) blurred vision 5 (0.7) flashes of light 3 (0.6)	yes, difficulty concentrating 19 (4), sadness 27 (5.7), depression 18 (3.8) mood swings 31 (6.6) anxiety 33 (6.9)	yes, hair loss 1 (0.2), itchy skin 12 (2.5), rash 9 (1.9), peeling skin on extremities 18 (3.8), swollen extremities 2 (0.4)	yes, cough 40 (8.4) thoracic pain 4 (0.84) dyspnea 9 (1.9)	yes, myalgia/ arthralgia 6 (1.2) tingling 8 (1.7)	yes, constipation 4 (0.8), diarrhea 4 (0.8) stomach pain 11 (2.3) nausea 4 (0.8)	yes, post-exertion malaise 16 (3.3), **fatigue** 33 (7) malaise 5 (1), fever/ chills 2 (0.4) loss of appetite 16 (3.4)	NR	yes, sore throat 8 (1.7), otalgia 7 (1.5) altered smell 22 (4.6), altered taste 23 (4.8)	>30 days	**NR**	NR	NR	NR
Radtke et al., Switzerland, 2021[42]	Prospective, cohort	109	yes, headache 5 (5) insomnia 3 (3)	yes, difficulty concentrating 2 (2)	NR	yes cough 2 (2) thoracic pain 1 (1)	NR	yes stomach pain 1 (1)	yes, **fatigue** 3 (3) Increased need for sleep 2 (2)	NR	yes congested/ runny nose 1 (1)	≥12 weeks (4 patients, 4%), ≥ 4 weeks (10 patients, 9%)	**1:** 4 (3.7) **0:** 105 (96.3)	NR	NR	NR
Di Sante et al., Italy, 2021[43]	cross-sectional	12	yes, headache 4 (33.3), insomnia 1 (8.3)	NR	NR	yes, cough 2 (16.6), thoracic pain 3 (25.0), palpitations 1 (8.3)	yes, myalgia/ arthralgia 3 (25)	yes, gastrointestinal disturbances 4 (33.3)	yes, post-exertion malaise 3 (25.0), **fatigue** 5 (41.6) fever/ chills 2 (16.6)	NR	NR	>5 weeks	**1**: 12 (100) **0**: 0 (0)	NR	NR	NR
Buonsenso et al., UK, 2022[44]	cross-sectional	510	yes, headache 401 (78.6), dizziness/ vertigo 245 (48) memory loss 167 (51.4)	yes, difficulty concentrating 309 (60.6)	yes, rash 267 (52.4), red and cracked lips 201 (39.4) peeling skin on extremities 143 (28) swollen extremities 107 (21) ulcers 79 (15.5)	yes, cough 151 (29.6), palpitations 205 (40.2)	yes, myalgia/ arthralgia 349 (68.4)	yes, diarrhea 216 (42.4), stomach pain 387 (75.9) nausea 233 (45.7)	yes, post-exertion malaise 274 (53.7), **fatigue** 410 (80.4) fever/chills 151 (29.6), limitations in daily functioning 444 (87.1)	NR	NR	8.2 months (standard deviation: 3.9)	**1**: 129 (25.3); 97 (19%) had a prolonged period of wellness followed by symptoms. **0**: 381 (74.7)	NR	240 (40)	NR
Knoke et al., Germany, 2022[45]	cross-sectional	70	yes, headache 3 (4.2)	NR	NR	yes, cough 2 (2.9), dyspnea 6 (8.3) recurrent wheezing 12 (16.4)	NR	NR	yes, **fatigue** 10 (14.3)	NR	yes, altered smell 7 (10)	6 months	**1**: 19 (27.2) **0**: 51 (72.8)	NR	NR	NR

(Table 2 continues on next page)

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Symptoms yes/no/NR n (%)								Outcomes				
			Neurologic	Mental health	Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
(Continued from previous page)																
Osmanov et al., Russia, 2022[46]	Prospective, cohort	514	yes, headache, insomnia, dizziness/ vertigo, blurred vision	yes, difficulty concentrating	yes, hair loss, rash, swollen extremities,	yes, cough, thoracic pain, palpitations, dyspnea,	yes, myalgia/arthralgia, tingling	yes, constipation, diarrhea, stomach pain, nausea, vomiting	yes, **fatigue**, loss of appetite	yes, changes in menstruation	yes, altered smell, altered taste	1–7 months from discharge	**1**: 128 (24.9) Multiple symptoms were experienced by 44 (8.4%) participants. **0**: 386 (75.1)	29 (5.7)	27 (5.2)	NR
[a]**Kikkenborg Berg** et al., Denmark, 2022[37] (B)	Cross-sectional	5023 (4–11 yo)	yes, headache 126 (2.5), OR 1.66 (1.34–2.05), p < 0.0001; dizziness 12 (0.2), OR 4.07 (1.82–9.10), p = 0.0006; light sensitivity 48 (1.0), OR 1.18 (0.85–1.64), p = 0.31	yes, mood swings 263 (5.2), OR 0.72 (0.63–0.83), p < 0.0001; difficulty remembering and concentrating 176 (35%), OR 0.86 (0.73–1.02), p = 0.081	yes, rashes 94 (1.9), OR 0.64 (0.51–0.80), p < 0.0001; dark circles under eyes 87 (1.7), OR 1.53 (1.19–1.97), p = 0.0009; cold extremities 32 (0.6), OR 1.23 (0.82–1.83), p = 0.31; chapped lips 57 (1.1), OR 1.17 (0.87–1.58), p = 0.30; extreme paleness 17 (0.3), OR 1.17 (0.68–2.01), p = 0.58	yes, chest pain 10 (0.2), OR 266 (1.18–6.00), p = 0.018; dyspnea 31 (0.6), OR 2.61 (1.65–4.14), p < 0.0001; palpitations 12 (0.2), OR 2.31 (1.13–4.73), p = 0.022; cough 61 (1.2), OR 1.83 (1.34–2.49), p = 0·0001	yes, myalgia/arthralgia 72 (1.4%), OR 1.38 (1.05–1.81), p = 0.021	yes, stomach aches 125 (2.5), OR 0·95 (0.78–1.17) p = 0.67: nausea 39 (0.8), OR 1.33 (0.92–1.93), p = 0.13	yes, **fatigue** 194 (3.9), OR 1.80 (1.51–2.14), p < 0.0001; fever 9 (0.2), OR 3.21 (1.24–8.34) p = 0.016; loss of appetite 105 (2.1), OR 1.44 (1.15–1.81), p = 0.0018	NR	yes, sore throat 29 (0.6%), OR 4.56 (2.65–7.85), p < 0.00 01	At least 2 months, maximum 12 months	**1:** 1505 (29.9) Long COVID **0:** 3518 (70.1)	0–5 days 589 (52.6); 6–10 days 260 (23.2): 11–15 days 135 (12.1); 16 days-1 month 120 (10.7), more than 1 month16 (1.4)	PedsQL social functioning scores lower in cases.	NR
[c]**Atchison** et al., UK, 2023[47] (A)	Cross-sectional	138	yes, headache (25.4); insomnia, dizziness/ vertigo, itchy/ sore/red eyes/ conjunctivitis, vision issues, numbness, tingling	yes, confusion	yes, scaly skin, itch, redness, hair loss, blisters on extremities, face/lips swelling	yes, cough (27.4); dyspnea, wheezing, chest pain, palpitationss	yes, myalgia/ arthralgia	yes, stomach aches, diarrhea, nausea, vomiting	yes, **fatigue**, loss of appetite, weight los, fever, tinnitus	NR	yes, loss or change to sense of taste/smell, sore throat or hoarse voice, sneezing, runny/ blocked nose	≥3 months	**1:** 138 (100) **0:** 0 (0)	NR	18 (13.5) (95% CI 8.4–20.9)	NR
Hahn et al., Canada, 2023[48]	Prospective, cohort	1026	yes, headache 533 (52)	NR	NR	yes, cough 430 (42)	NR	NR	yes, fever 420 (41); **fatigue** 359 (35)	NR	yes, rhinitis 636 (62); sore throat 697 (68)	minimum 8 weeks (4 reporting periods)	**1:** 1 (0.1) **0:** 1025 (99.0)	NR	NR	NR
Children over 10 yo/adolescents/young adults																
Blankenburg et al., Germany, 2021[49]	Retrospective, cohort	188	yes headache 109 (57.9); insomnia 112 (59.6); memory loss 91 (48.4)	yes difficulty concentrating 144 (76.5)	NR	NR	yes myalgia/arthralgia 62 (32.9) not specified 82 (43.6)	NR	yes **fatigue** 71 (37.7) malaise 139 (73.9)	NR	NR	at least 28 days	**1**: 188 (100) **0**: 0 (0)	NR	NR	NR
Leftin Dobkin et al., USA, 2021[50]	Retrospective, cohort	29	no 0 (0)	no 0 (0)	no 0 (0)	yes, cough 15 (51.7), dyspnea 28 (96.6)	no 0 (0)	no 0 (0)	yes, post-exertion malaise 14 (48.3), **fatigue** 4 (13.8)	no 0 (0)	no 0 (0)	3.2 ± 1.5 months [range 1.3–6.7 months]	**1**: 28 (96.6) **0**: 1 (3.4)	NR	NR	NR

(Table 2 continues on next page)

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
(Continued from previous page)																
[b]**Molteni** et al., UK, 2021 (B)[27]	Prospective, cohort	1146	yes, headache 755 (65.9), dizziness/ vertigo 300 (26.2), eye soreness 248 (21.6)	yes difficulty concentrating 81 (7)	no 0 (0)	yes, cough 298 (26), thoracic pain 143 (6.2), dyspnea 143 (12.5)	yes myalgia/ arthralgia 231 (20.2)	yes, diarrhea 79 (6.9), stomach pain 194 (16.9), nausea 193 (16.9)	yes, **fatigue** 696 (60.7), fever/chills 396 (34.5), loss of appetite 254 (22.2)	no 0 (0)	yes, sore throat 585 (51), hoarse voice 166 (14.5), altered smell 554 (48.3)	<28 days (1087 patients); ≥ 28 days (59 patients)	**1**: 59 (5.1) **0**: 1087 (94.9)	NR	NR	21 (1.8)
Rusetsky et al., Russia, 2021[51]	Cross sectional	52	NR	NR	NR	NR	NR	NR	NR	NR	yes, altered smell	10 days–in 37 patients (71.2%), 11–29 days–in 12 patients (23.1%), and more than 30 days–in 3 children (5.7%)	**1**: 0 (0) **0**: 52 (100) after 2 months	NR	NR	NR
Stephenson et al., UK, 2022[52]	Cross-sectional	3065	yes, headache 710 (23.2); dizziness 419 (13.7); ringing in ears 191 (6.2); eye soreness/ redness 182 (5.9)	yes, difficulty concentrating	yes, rash 35 (1.1); swollen extremities 48 (1.6)	yes, cough 98 (3.2); thoracic pain 216 (7); dyspnea 717 (23.4);	yes, myalgia/ arthralgia 165 (5.4)	yes, diarrhea 92 (3); stomach pain 119 (3.9);	yes, **fatigue** 1196 (39); fever/chills 319 (10.4); loss of appetite 296 (9.7)	NR	yes, sore throat 291 (9.5); hoarse voice 56 (1.8); otalgia 191 (6.2); altered smell 414 (13.5);	3 months	**1:** 2038 (66.5) **0**: 1027 (33.5)	NR	NR	NR
[a]**Kikkenborg Berg** et al., Denmark, 2022[37] (C)	Cross-sectional	2857 (12–14 yo)	yes, headache 142 (5%), OR 1.55 (1.27–1.90), p < 0.0001; dizziness 50 (1.8), OR 2.32 (1.63–3.31), p < 0.0001, light sensitivity 29 (1.0), OR 0.74 (0.49–1.11), p = 0.14	yes, mood swings 230 (8.1), OR 0.75 (0.65–0.88), p = 0·0002. difficulty memorizing and concentrating 170 (6.0%); OR 0.91 (0.76–108), p = 0.29	yes, rashes 81 (2.8), OR 1.03 (0.81–1.33), p = 0.79; dark circles under eyes 63 (2.2), OR 1.24 (0.93–1.65), p = 0.15, cold extremities 79 (2.8); OR 1.12 (0.87–1.44), p = 0.40; chapped lips 59 (2.1), OR, 1.26 (0.94–1.70), p = 0.12	yes, chest pain 23 (0.8%), OR 3.53 (2.00–6.24), p < 0.0001; travel breathing 37 (1.3), OR 2.94 (1.91–4.53), p < 0.0001; palpitations 19 (0.7), OR 1.66 (0.95–2.90), p = 0.073; cough 22 (0.8), OR 2.39 (1.38–4.15), p = 0.0018	yes, myalgia/ arthralgia 82 (2.9), OR 1.47 (1.13–1.90), p = 0.0036	yes, stomach aches 60 (2.1%), OR 0.91 (0.68–1.22), p = 0.54 nausea 38 (1.3), OR 1.25 (0.86–1.81), p = 0.24	yes, **fatigue** 285 (10), OR 1.39 (1.21–1.60), p < 0.0001, loss of appetite 93 (3.3), OR 1.22 (0.96–1.54), p = 0.11; extreme paleness 17 (0.6) OR 0.82 (0.48–1.38), p = 0.45	NR	yes, sore throat 30 (1.1), OR 5.32 (2.99–9.46), p < 0.0001	At least 2 months, maximum 12 months	**1:** 1077 (37.7) Long COVID **0:** 1780 (62.3)	0–5 days 516 (47.9), 6–10 days 273 (25.4), 11–15 days 148 (13.7), 16 days-1 month 111 (10.3), more than 1 month 29 (2.7)	PedsQL social functioning scores lower in controls.	NR
Kikkenborg Berg et al., Denmark, 2022[53]	Cross-sectional	5106, of which 3159 at least one symptom >2 months (15–18 yo)	yes, headache, OR 1.22 (1.10–1.34), <0.0001; dizziness, OR 1.36 (1.16–1.59), p = 0.001; light sensitivity 0.94 (0.84–1.06), p = 0.40	yes, mood swings, OR 0.82 (0.74–0.91), p = 0.0002, difficulty memorizing and concentrating, OR 1.04 (0.97–1.12), p = 0.17	yes, rashes, OR 0.72 (0.60–0.87), p = 0.0009; dark circles under eyes, OR 0.72 (0.65–0.80), p < 0.0001; cold extremities, OR 0.89 (0.81–0.97), p = 0.015; chapped lips, OR 0.82 (0.74–0.90), p = 0·0001; discolored fingers or toes, OR 0.48 (0.32–0.70), p = 0·0002	yes, chest pain, OR 1.38 (1.12–1.69), p = 0.0021; dyspnea, OR 2.70 (2.31–3.15), p < 0.0001; palpitations, OR 1.22 (1.10–1.36), p = 0·0001; cough, OR 1·63 (1·43–1·85), p < 0.0001	yes, myalgia/ arthralgia, OR 1.09 (0.91–1.30), p = 0.31	yes, stomach aches, OR 0.79 (0.65–0.97), p = 0.029, nausea, OR 1.09 (0.92–1.29), p = 0.27,	yes, **fatigue**, OR 1.06 (0.98–1.14), p = 0.086; fever, OR 1.53 (0.74–3.16), p = 0.22; loss of appetite, OR 1.15 (1.02–1.29), p = 0.015; extreme paleness, OR 0.64 (0.51–0.82), p = 0.0004	NR	yes, sore throat, OR 1.59 (1.21–2.10), p = 0.0007	At least 2 months, maximum 12 months	**1:** 2297 (44.9) Long COVID **0:** 2809 (55.1)	0–5 days 1601 (53.4); 6–10 days 745 (24.7); 11–15 days 386 (12.9); 16 days-1 month 210 (7.0); more than 1 month 55 (1.8)	Significantly better quality of life on social functioning at PedsQL.	NR

(Table 2 continues on next page)

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
(Continued from previous page)																
[c]**Atchison** et al., UK, 2023[47] (A)	Cross-sectional	913 (12–17 yo)	yes, headache, insomnia, dizziness, vision issues, numbness/ tinting, tinnitus, itchy/ sore/red eyes/ conjunctivitis	yes, confusion	yes, hair loss, itch, scaly skin, redness, blisters on extremities, face of lips swelling	yes, dyspnea, wheezing, chest pain, palpitations, cough	yes, myalgia, arthralgia	yes, stomach aches, diarrhea, nausea, vomiting	yes, **fatigue**, loss of appetite, weight loss, fever	NR	yes, loss or change of sense of smell (52.2) and taste (40.7), runny/ blocked nose, sore throat or hoarse voice, sneezing	≥3 months	**1:** 913 (100) **0:** 0 (0)	NR	99 (10.9) (95% CI 9.0–13.2)	NR
Selvakumar et al., Norway, 2023[54]	Prospective cohort	379	yes, sleep disturbances; memory, dizziness; headache	yes, depression; anxiety; decision making and concentrating problems	NR	yes, dyspnea; chest pain; palpitations; cough;	yes, myalgia	NR	yes, **fatigue** 53 (13.9), post-exertional malaise, pain; fever/chills;	NR	yes, altered smell and/or taste	6 months	**1:** 184 (48.5) **0:** 195 (51.5)	NR	Quality of life (0–100, a score ≤80 corresponds to a chronic disease of "mild" severity): median 78.3 (IQR 66.3–88.0)	NR
Sakurada et al., Japan, 2023[55]	Retrospective, cohort	54	yes, headache 27 (35.2); insomnia; memory problems; dizziness	yes, depression; anxiety	yes, hair loss	yes, dyspnea; cough; palpitations; chest pain; hyperventilation	yes, arthralgia	yes, diarrhea	yes, **fatigue** 30 (55.6); low-grade fever	NR	yes, dysosmia; dygeusia	>4 weeks (maximum 90 days)	**1:** 54 (100) **0:**0 (0)	28 (56) (most frequent causes for missing school: fatigue 85.7%; headache 42.9% and insomnia 32.1%)	NR	NR
Children age category not reported																
Miller et al.[56]	Prospective, cohort	43	NR	NR	NR	yes, non-specific respiratory 6/43 (14)	NR	NR	yes, general symptoms 13/ 43 (30.2)	NR	yes, non-specific ENT 6/43 (14)	33 days median (IQR 30–74)	**1:** 43 (100) **0:** 0 (0)	NR	18 (41.8)	NR

NR, not reported; COVID, Coronavirus disease; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; USA, United States of America; CI, confidence interval; ED, Emergency Department; yo, years old, IQR, interquartile range; PedsQL, Pediatric Quality of Life Inventory. [a]The study by Kikkenborg Berg et al.[37] was divided according to age category into **A (Children 0–3 yo), B (Children > 3 yo, < 10 yo; Children over 10 yo/adolescents)** and **C (Children over 10 yo/adolescents/young adults)**. [b]The study by Molteni et al. was divided according to age category into **A (Children > 3 yo, < 10 yo)** and **B (Children over 10 yo/adolescents/young adults)**. [c]The study by Atchison et al. was divided according to age category into **A (Children > 3 yo, < 10 yo; Children over 10 yo/adolescents)** and **B (Children over 10 yo/adolescents/young adults)**.

***Table 2*: Studies on SARS-CoV-2 and post COVID: symptoms and outcomes.**

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
Children over 10 yo/adolescents/young adults																
Pedersen et al., Norway, 2018[57]	Prospective, cohort	195	NR	NR	NR	NR	NR	NR	yes, **fatigue** 91 (46.6)	NR	NR	6 months	**1**: 91 (46.6) **0**: 104 (53.4)	NR	NR	NR

EBV, Epstein–Barr virus, NR, not reported; ED, Emergency Department; yo, years old.

***Table 3*: Study on post-EBV condition: symptoms and outcomes.**

Retrieved articles by pathogen/post-viral condition

SARS-CoV-2 and post COVID

Twenty-eight studies on post COVID (Tables 1 and 2)[27,30–56] reported data for at least one of the outcomes of interest on 40,896 patients overall. Control groups were present in half of the studies (14, 50%) and mostly consisted of seronegative symptomatic children (eleven studies), showing that sometimes seronegative patients also had persistent and burdensome illness. In particular, the two studies by Kikkenborg-Berg et al. reported that long-lasting symptoms, with a duration of at least two months, occurred frequently in the study population, regardless of whether or not they had had COVID-19. Moreover, there was a tendency towards better quality-of-life scores related to emotional and social functioning in cases than in controls in older children.

Selvakumar et al. reported a prevalence of Long COVID six months after acute infection of approximately 50%, equally high in a control group of comparable SARS-CoV2–negative individuals. Knoke et al. reported no significant differences were detected in frequency of abnormal pulmonary function between cases and controls. Di Sante et al. described control patients that completely recovered after acute infection showing immunological differences as compared with cases.

The median follow-up duration was 182 days. The children were almost universally outpatients (26 studies, 82.1%), sometimes previously admitted. The outcome was measured in heterogeneous ways (see Table 1 for details) and in most cases through the report (questionnaire/survey/online or mobile platform/interview) of an adult proxy (caregiver) at fixed follow up points, through self-reporting of pediatric patients, or clinical evaluations with interviews. In 21 studies (75%) children were included following the criterium "from virus positivity/disease to symptoms", while in the remaining seven studies (25%) according to the criterium "from symptoms to disease".

Studies providing granular data for age subgroups were tabulated as sub-studies (Kikkenborg Berg et al., Molteni et al., Atchison et al., Table 2) Thus, because of treating these studies effectively, we considered the denominator to be 32 for the evaluation of symptoms and outcomes.

Different age categories were represented, especially older children and adolescents/young adults. Seven studies (21.9%) included patients younger than three years to adolescents. One study considered children under three years of age (3.1%); two (6.2%) included children aged 3–10 years; 11 (34.4%) included patients from 3 years to adolescents, and ten (31.3%) considered children older than 10 to young adults only. One study (3.1%) did not report data relative to age subgroups.

Long-lasting symptoms of all areas were described, mostly general symptoms, including post-exertional

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Neurologic	Mental health	Symptoms yes/no/NR n (%)							Outcomes				
					Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/ weeks/ months/ years	Chronic symptoms development **1**; n (%); recovery/ remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
Children < 3 yo																
Teeratakulpisarn et al., Thailand, 2015[58]	Prospective, cohort (long-term follow up of RCT)	170, of which **RSV** 110 (64.7) **Rhinovirus** 31 (18.2) **Influenzavirus** 30 (17.6) **hMPV** 6 (3.5) **mixed viruses** 49 (28.8)	NR	NR	NR	yes, 94/152 (61.8) recurrent wheezing/ asthma	NR	NR	NR	NR	NR	5.4 ± 7.2 months (mean ± SD) duration after 1st episode	**1:** 15/94 (16) had persistent wheeze >60 months **0:** 79/94 (84) **NR:** 76/170 (44.7)	NR	NR	NR
Lukkarinnen et al., Finland, 2017[59]	Retrospective, cohort	127, of which **RSV** 35 (28) **Rhinovirus** 65 (51)	NR	NR	NR	yes, recurrent wheezing/ asthma	NR	NR	NR	NR	NR	NR	**1:** 37/67 (55.2) **0:** 30/67 (44.8) **NR:** 60/127 (47.2)	NR	NR	NR
Dumas et al., USA, 2019[60]	Prospective, cohort	921, of which **RSV** 755 (82) **Rhinovirus** 193 (21) **mixed viruses** 332 (36%)	NR	NR	NR	yes, 251 (27.3%) recurrent wheezing/ asthma	NR	NR	NR	NR	NR	NR	**1:** 251 (27.3%) **NR:** 670 (72.7)	NR	NR	NR
Children > 3 yo, < 10 yo																
Lemanske et al., USA 2005[61]	Prospective, cohort	285 patients, 543 episodes of which **RSV** 99/ 543 episodes (10.1) **Rhinovirus** 258/ 534 episodes (47.5)	NR	NR	NR	yes, 76 (26.6) wheezing (118/ 543 wheezing illness episodes)	NR	NR	NR	NR	NR	>3 years	**1:** 63 (22.1) **NR:** 222 (77.9)	NR	NR	NR
Hunderi et al., Norway, 2019[62]	Prospective, cohort	266 patients, of which **RSV** 219 (82.3) **Rhinovirus** 93 (34.9) **Mixed viruses** 170 (63.9)	NR	NR	NR	yes, recurrent wheezing 129 (48.4)	NR	NR	NR	NR	NR	730 days	**1**: 129 (48.4) **0:** 137 (51.6)	NR	NR	NR

NR, not reported; ED, Emergency Department; yo, years old; RCT, randomized controlled trial; RSV, Respiratory Syncytial Virus, hMPV, human Metapneumovirus.

Table 4: **Studies on post-viral conditions after respiratory viruses' infection: symptoms and outcomes.**

Author, country, year	Study design and setting	Patients with post-acute symptoms (n)	Symptoms yes/no/NR n (%)							Outcomes				
			Neurologic	Mental health	Dermatologic	Cardiorespiratory	Musculoskeletal	Gastrointestinal	General	Genitourinary	ENT	Duration of symptom(s) in days/weeks/months/years	Chronic symptoms development **1**; n (%); recovery/remission **0**; n (%); NR	Can't go to school n (%)	Difficulty in everyday tasks n, (%)	Patients undergoing ED evaluations n (%)
Children < 3 yo																
Koopmans et al., Brazil, 1997[63]	Case-control	74	NR	NR	NR	NR	NR	yes, diarrhea 74 (100)	NR	NR	NR	>14 days	**1**:41 (55.5) of which 1/41 (2.4) had persistent adenovirus, 11/41 (27) torovirus **0**: 33 (44.5)	NR	NR	NR

NR, not reported; ED, Emergency Department; yo, years old.

Table 5: Study on post-viral conditions after infection by gastrointestinal viruses: symptoms and outcomes.

malaise, fatigue, malaise/listlessness, fever/chills, weight loss, loss of appetite, increased need for sleep (30/32 studies, 93.8%), with fatigue alone being reported in 27/32 studies (84.4%). Further symptoms are reported in detail in Table 2. Notably, only one of the three studies including data on children younger than three years mentioned fatigue, and none mentioned wheezing.

Among the primary outcomes, symptom duration was reported by for a maximum of 18 months, most commonly for 3–4 months. The development of chronic symptoms was reported by 30 studies (93.8%) for 10,473/28,474 patients (36.8%). Recovery was achieved in 18,001/28,474 cases (63.2%).

Considering the secondary outcomes, eight studies reported the number of school-age patients losing school days, that is, 2937/14,887 children overall (19,7%), while 513/2257 (22.7%) children had difficulties completing everyday tasks, as described in seven studies. Three studies reported the number of patients that underwent ED evaluations, with 53/1823 (2.9%) children.

EBV

The only included study on EBV[57] reported persistent fatigue in 195 older children and adolescents followed for six months, especially males (71, 35.5%), becoming chronic in 91 (46.6%) patients (Table 3). Recovery was reported for the remaining 104 patients (53.4%). There was a control group of healthy patients, intended for cross-sectional comparison with the subgroup of fatigued EBV individuals at six months follow-up; the comparisons were however not reported in the paper. Children, all out-patients, were included from virus positivity/disease to symptoms. The outcome was measured through an investigational program including a clinical evaluation, a cognitive testing, and a questionnaire.

Respiratory viruses

Five studies on respiratory viruses[58–62] (Table 4) reported data on 1769 outpatients overall and mainly focused on children younger than three years (3 studies, 60%) and children aged 3–10 years (2 studies, 40%), with a median follow-up of 1095 days (3 years). All the studies included data on RSV and Rhinovirus. Three of them (Lukkarinnen et al., Teeratakulpisarn et al., and Dumas et al.) reported data on gender, with male predominance (ranging from 60 to 64%). The only described long-lasting symptom was recurrent wheezing with a duration ranging from 5 to 7 months to more than three years, when reported, becoming chronic in 495/741 patients (66.8%). Data on recovery were only available for three studies, reporting 246/741 patients (33.1) (single recovery rates of 84%, 44.8%, and 51.6%, respectively). The criterium for patient inclusion was "from symptoms to disease". The outcome was assessed

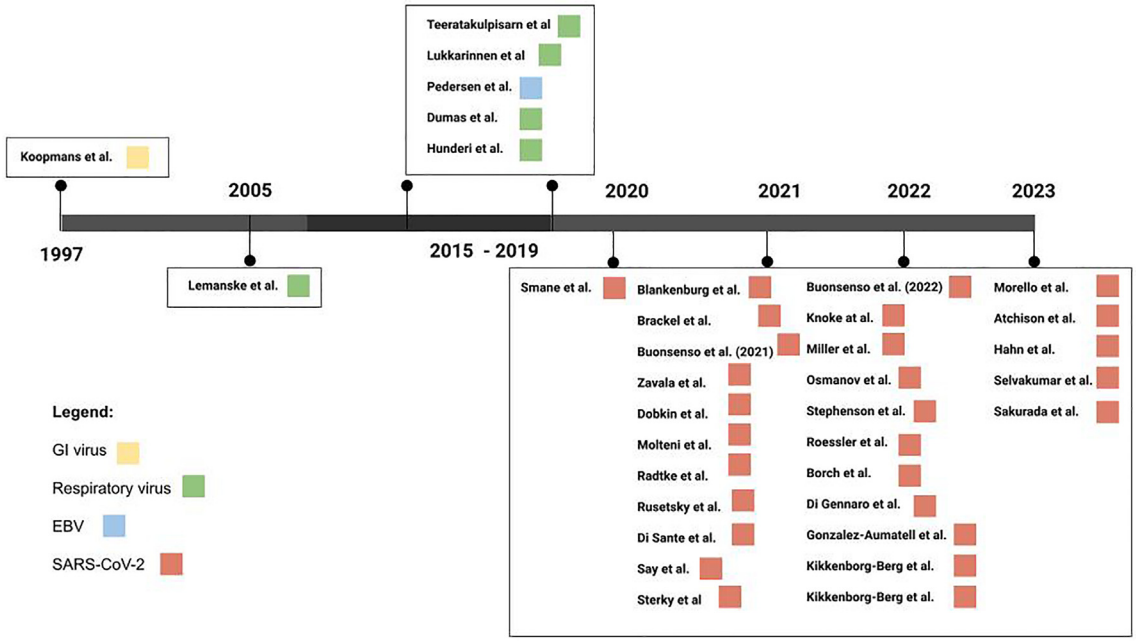

Fig. 2: Timeline of retrieved articles by publication year.

with clinical evaluations and/or telephonic interviews. None of these studies had a control group.

Other viruses–gastrointestinal

One study[63] (Table 5) reported data on 74 out-patients younger than three years with unspecified gender who developed persistent diarrhea (over 14 days since acute infection) after gastrointestinal viral infection (Adenovirus, Torovirus), becoming chronic in 41 (55.5%) and with recovery in 33 (44.5%). These patients, included according to a "from symptoms to disease" criterium, were compared to controls without diarrhea and the outcome was assessed by caregiver report and clinical evaluation. Torovirus antigen was detected in a small percentage of children with persistent diarrhea and none of the controls. Follow-up time was not reported.

Risk of bias assessment for non-randomized studies

The included studies were mainly prospective, cohort (17 studies), followed by cross-sectional (10 studies), retrospective cohort (6 studies), and case–control (2 studies). The overall risk of bias was high-moderate due to the study types and characteristics.

Among retrieved studies, one was rated as "good", 31 were rated as "fair" and three as "poor". The risk of bias assessment tool and results for the non-randomized studies are available in the Supplementary Material.

Discussion

The results of the present systematic review confirm an overlap between post-viral infection symptoms following acute COVID and other viral infections, with some shared clinical features, duration of symptoms, and affected age subgroups. Potential risk factors for post COVID development, such as gender prevalence, socio-economic status, or comorbidities, did not emerge, or were not identified with certainty. First, considering our primary outcomes, symptom duration was similar for post COVID and post EBV/post gastrointestinal virus syndromes. However, recovery was achieved in more than half of the children with post COVID and post EBV condition, with a smaller proportion of children developing chronic symptoms. The timing for symptoms resolution for post COVID was similar to what has been reported so far by previously published studies.[25–27] Nevertheless, post COVID symptoms, in terms of severity and duration, have not been compared to those occurring after other respiratory viruses in the literature.

The underlying pathophysiological mechanisms of post-viral conditions are still unclear, and multiple mechanisms have been proposed: the chronic activation of the immune system,[17] and the neuro-immuno-endocrinological pillars may be the critical points to understanding the complexity of the disease.[9,18,20] Viral persistence has also been postulated[8,9,11,13,19,21,64–67]; however, in most cases, no changes in viral antibody titers can be found, not surprisingly, as the symptoms usually appear long after the initial infection.[6] For Long COVID, the possible mechanisms for prolonged symptoms are similar and include the hypothesis of viral persistence in "sanctuary" organs (i.e., brain), direct organ damage, and an increased tendency to blood clotting. Other involved mechanisms may be a dysregulated immune response to the acute infection, possibly including mast

cell activation, autoimmunity, and/or changes in the autonomic nervous system.[68,69]

Our intended comparison between post-acute conditions in children in terms of type and duration of symptoms, development of chronic symptoms, and the number of patients with full recovery was limited due to the heterogeneity of study designs, all of which were non-randomized, and the discrepancy in many post-COVID studies as compared to much fewer on other post-viral conditions. A reasonable explanation lies within the surge in the production of papers on COVID-19, exponentially increasing since the beginning of the pandemic, representing an unprecedented phenomenon in the scientific literature, as documented by recent bibliometric analyses.[70–72] The COVID-19 pandemic was a unique situation, as the causative agent was known and an unprecedented number of people all over the world was repeatedly screened for it in a period in which virtually no other pathogen was circulating, being therefore ideal to demonstrate cause-effect relationships. This would have been impossible in the past, when patients manifesting long-lasting symptoms after an acute infection would have likely not been tested, with the responsible pathogen remaining unknown. On the other hand, billions of people were infected for the first time, with only a small proportion developing symptoms, not being always related to severity of disease. Many studies on adults in the literature confirm persistent symptoms after COVID-19, especially fatigue, dyspnea, myalgia/arthralgia, and post-exertional malaise, following the acute phase of the disease.[73] The pattern of long-lasting symptoms among children, including fatigue, cough, thoracic pain, dyspnea, palpitations, headache, altered smell/taste, myalgia/arthralgia, difficulty concentrating, diarrhea, and abdominal pain, was reproducible among the retrieved studies, and this may demonstrate these are defining symptoms of post COVID, similarly to studies on adults.[40,73]

Interestingly, the two studies by Kikkenborg Berg et al., respectively on children from 0 to 14 years and adolescents from 15 to 18 years denoted a considerable burden of symptoms not only among patients experiencing Long/post COVID, but also among seronegative controls.[37,53] Symptoms of any kind were slightly more frequent in cases, and there was a paradoxical tendency towards better quality-of-life scores related to emotional and social functioning in cases than in controls in older children. The fact that symptoms were almost as frequent in seronegative children underlines that a temporal association with an event, such the infection, does not necessarily imply causality.[74] Alongside the many studies providing insight on subjective symptoms, few studies reported data on objective measures, highlighting the absence of objective functional or structural abnormalities between cases and healthy controls (i.e., Knoke et al.,[45]). Other studies showed immunological differences between patients recovered after SARS-CoV-2 acute infection and those that developed chronic symptoms (Di Sante et al.,[43]) or even an extended coagulation profile (Di Gennaro et al.,[34] Such aspects deserve further in-depth analysis, that may help clarify similarities or differences observed in cases and controls.

Similarities between post-viral and post COVID specific symptoms were noted. For example, fatigue, a dominant feature of the post EBV condition, was also among the most frequently reported symptoms by studies on post COVID, especially in older children and adolescents. Fatigue may be long-lasting, up to several months after acute disease, and possibly exposes these young patients to limitations in everyday tasks and activities, including school attendance, with consequences for their families, as well. Moreover, as a subjective, self-reported, symptom, fatigue may be difficult to measure. Among the papers evaluated for inclusion, two studies on EBV were excluded for reporting data on a mixed population of adolescents, adults, and elderly, with no granular data on adolescents and young adults only,[75,76] mentioning fatigue and neuropsychiatric disorder persisting for 1–3 months, also with data for days in bed and out of school/role. Despite the post EBV infection condition being well-known and recognized, we found few studies reporting data on the pediatric population alone, perhaps because it is already a well-established entity, compared to the novelty of post COVID, which has not been completely understood yet.

Another feature shared by both post COVID and post-acute conditions after infection by viruses affecting the gastrointestinal tract was persistent diarrhea, especially related to younger children in the latter. It is now well-accepted that gastrointestinal symptoms may be a distinctive feature of SARS-CoV-2 acute infection, sometimes becoming long-lasting, up to 6 months after COVID-19 in 10–25% of patients according to recent studies, and being furthermore responsible for viral shedding.[77,78]

The included studies on respiratory viruses, namely RSV and Rhinovirus, targeted mostly children and infants younger than three years of age. Such pathogens are well-known to cause recurrent wheezing in this age subgroup, with an increased risk of subsequent asthma development. The sequelae following RSV infection in infants are caused by distal bronchiolar inflammation and obstruction, resulting in reduced airflow into the small airways and alteration in exhalation capacity, which eventually determine lung hyperexpansion and function alterations, increased mucus production, and wheezing, as a consequence of severe bronchiolitis.[79] The development of wheezing as a prolonged symptom was not observed in our study among the described cardiorespiratory symptoms in papers on post COVID and was reported only in a small proportion of patients older than three years. However, limited data was available especially in young children with COVID-19, which is the typical age group.

On the other hand, some symptoms appear to be specific to post COVID as a unique condition. This is the case of taste or smell alterations and of neurocognitive symptoms, such as the lack of concentration, all reported among adolescents, representing a separate category as compared to younger pediatric patients. Possible effects of SARS-CoV-2 on the nervous system and its consequences on neuro-sensory functions have been postulated, with mechanisms that are yet to be established.[80,81]

The impact of post-infectious conditions in general deserves special attention, to improve disease care beyond acute infections, but on a larger population scale, perhaps the impact of SARS-CoV-2 infection alone on children and adolescents may have been less significant that the effects of the pandemics itself. This differs from other post-infectious conditions with a different spectrum and prevalence and a high morbidity burden.[82]

Last, data relating to our secondary outcomes (lost school days, activity limitation, and ED evaluations) were only available from few studies, all on post COVID, indicating a gap in current knowledge about long-term effects of post-viral conditions on children, their families and quality of life. There was limited data available from Asia and South America and a complete lack of data from African countries, which was also highlighted in a 2021 bibliometric analysis.[83]

The study selection was narrowed by the exclusion of many reports according to their outcome, for evaluating the effects of pharmacological interventions (exclusion criteria). This choice was made to give our review consistency, and to avoid confounding factors, after running a search that was constructed to be as inclusive and broad as possible. The discrepancy in the number of studies on COVID-19 versus other viruses, their non-randomized nature, and heterogenous study design made comparisons on our primary outcomes difficult to make and did not allow further conclusions. Thus, we could not lead a meta-analysis with the available evidence. Post-viral conditions other than post COVID were clearly defined, while post COVID, which is still a less well-defined entity, was often described according to different definitions. Moreover, there was a lack of standardization in follow-up and how the outcomes were measured, and the frequent lack of control groups did not allow the identification of a certain cause-effect link between disease/infection and symptoms. Different organizations have formulated their individual terminology and explanations for Long/post COVID. For instance, the WHO established its definitions via an international Delphi consensus process, while the UK National Institute for Health and Care Excellence and the US Centers for Disease Control and Prevention also introduced their own terms and clarifications. Therefore, the term "long COVID" remains commonly employed among researchers encompassing persistent manifestations that emerge and endure subsequently to the acute SARS-CoV-2 infection, without a specific time frame. In contrast, certain alternative terms possess more stringent and precise definitions.

Except for fatigue, gastrointestinal and cardio-respiratory symptoms, no data were retrieved on persisting symptoms of other areas for post-viral conditions other than post COVID, and this represents another gap of knowledge. Moreover, it was not possible to estimate the prevalence of symptoms and evaluate the outcomes for definite age sub-groups for post COVID, as almost half of the studies included data on pre-schoolers to adolescents.

While a post-viral condition manifests across various viruses, it remains heterogeneous and further study is needed to better understand this entity. Post-viral fatigue syndrome was a shared feature between post COVID and post EBV conditions in older children and adolescents. Despite long-lasting symptoms, recovery appears to be achieved in more than half of the cases. A better understanding of post COVID as a unique condition, sharing features with other post-viral syndromes, is needed and implicates a multidisciplinary approach and international awareness in children and adolescents. Some interesting points for further investigation would be the eventual rate of recurrence of symptoms after recovery, considering more extended periods of follow-up; the evaluation of possible differences between children with pre-existing conditions before COVID-19 and previously healthy patients, as well as the comparison of the entity of persistent symptoms developed after an asymptomatic/pauci-symptomatic acute infection. Moreover, the healthcare burden and socio-economic consequences for children and their families urge further study.

Last, the experience of the SARS-CoV-2 pandemic, with the surge of post COVID conditions also in pediatric patients, should be adopted as a model for preparedness for future pandemics and to better comprehend the true post-acute burden of other viral infections. The foremost requirement is the establishment of consistent and shareable definitions, as well as a consensus on outcomes, to effectively evaluate patient follow-up and quantify the burden.

Contributors

Conceptualization, C.M., D.D., M.v.d.Z.; Methodology, C.M., D.D., M.v.d.Z.; Validation, D.D. M.v.d.Z., C.G.; Formal Analysis, C.M., CMcK; I.D.; C.B., De.D; G.S; Investigation, C.M., CMcK; I.D.; C.B., De.D; G.S; Data Curation, C.M., CMcK; I.D.; C.B., De.D; G.S; Writing—Original Draft Preparation, C.M., CMcK; I.D.; Writing—Review & Editing, C.M., D.D., M.v.d.Z.; Visualization, C.B., De.D; G.S; C.G.; Supervision, M. v.d.Z., C. G.

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The datasets generated during and/or analysed during the current study are available in the text and Supplementary material. Rough data supporting reported results are available from the corresponding author on reasonable request.

Declaration of interests
The Authors declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102436.

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