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Robustness of reported postacute health outcomes in children with SARS-CoV-2 infection: a systematic review

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2022-324455).

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Received 24 May 2022
Accepted 31 July 2022

ABSTRACT

Objective To systematically assess the robustness of reported postacute SARS-CoV-2 infection health outcomes in children.

Methods A search on PubMed and Web of Science was conducted to identify studies published up to 22 January 2022 that reported on postacute SARS-CoV-2 infection health outcomes in children (<18 years) with follow-up of ≥2 months since detection of infection or ≥1 month since recovery from acute illness. We assessed the consideration of confounding bias and causality, as well as the risk of bias.

Results 21 studies including 81 896 children reported up to 97 symptoms with follow-up periods of 2.0–11.5 months. Fifteen studies had no control group. The reported proportion of children with post-COVID syndrome was between 0% and 66.5% in children with SARS-CoV-2 infection (n=16 986) and between 2.0% and 53.3% in children without SARS-CoV-2 infection (n=64 910). Only two studies made a clear causal interpretation of an association between SARS-CoV-2 infection and the main outcome of 'post-COVID syndrome' and provided recommendations regarding prevention measures. The robustness of all 21 studies was seriously limited due to an overall critical risk of bias.

Conclusions The robustness of reported postacute SARS-CoV-2 infection health outcomes in children is seriously limited, at least in all the published articles we could identify. None of the studies provided evidence with reasonable certainty on whether SARS-CoV-2 infection has an impact on postacute health outcomes, let alone to what extent. Children and their families urgently need much more reliable and methodologically robust evidence to address their concerns and improve care.

To cite: Hirt J, Janiaud P, Gloy VL, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2022-324455

INTRODUCTION

Children usually have mild or no symptoms of SARS-CoV-2 infection[1 2] and are rarely hospitalised with extremely rare fatal events.[3] However, symptoms persisting beyond the acute stage have been observed not only in adults[4] but also in children.[3]

Such persistent symptoms or postacute health outcomes are often referred to as long-COVID or post-COVID syndrome, but there is no consensus on how to define it.[5] The term long-COVID may encompass both ongoing symptomatic COVID-19 (4–12 weeks after the initial infection) and post-COVID-19 syndrome (≥12 weeks after the initial infection)[6] or defined as post-COVID-19 condition occurring 3 months from the onset of COVID-19 with symptoms that last for at least 2 months.[7]

Evidence syntheses aiming to assess postacute SARS-CoV-2 infection health outcomes in children are difficult, given the highly heterogenic study designs and complex limitations. There are methodological concerns about the validity of reported causal effects of infection on long-term outcomes,[3 4] including the absence of a control group, missing outcome data, and detection and misclassification biases.[4] Moreover, there is serious heterogeneity in study populations (diverse settings, eligibility criteria and sampling strategies) and lack of standardisation of cases and outcomes[3 4] that limits the interpretation of estimates for absolute risks and post-COVID-19 syndrome prevalence. The validity of relative risk estimates critically depends on the risk of confounding bias resulting from systematic differences between the compared groups. However, confounding is often ignored when interpreting epidemiological studies,[8 9] and their authors rarely call for cautious interpretation.[9]

Given the potential impact on child health worldwide, we would expect that studies assessing these risks are conducted with the greatest possible care and the intention to meet the highest available standards in reporting and transparency to deal with confounding, other biases and causal claims.

Here, we systematically assessed the robustness of reported outcomes of studies that aimed to determine the effect of SARS-CoV-2 infection on post-COVID syndrome in children.

METHODS

We used a similar search strategy and study selection as a previous related analysis.[10] Our study protocol is published[10] and no major deviations occurred. We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020.[11]

Eligibility criteria

Eligible studies included a cohort of children (<18 years) defined by the presence of SARS-CoV-2 infection; reported frequency of health outcomes (ie, any symptoms) for this cohort

(accepting subgroup analyses); had a clearly defined follow-up of ≥2 months since detection of SARS-CoV-2 infection, onset of symptoms, COVID-19 diagnosis and/or hospital admission, or a clearly defined follow-up of ≥1 month since recovery from acute illness and/or hospital discharge (follow-up defined as in previous related analysis[10]; and were published as preprint or peer-reviewed journal article in English.

We considered studies regardless of the severity of the acute infection or the setting (eg, outpatient, hospitalised or intensive care), and regardless of whether the investigation included a comparator group of participants without SARS-CoV-2 infection. We excluded meta-analyses, evidence syntheses, abstract-only publications and conference proceedings.

Information sources and search strategy

We adapted an existing search strategy[4] (online supplemental eMethods) and searched PubMed and Web of Science Core Collection since 1 January 2020; the living systematic COVID-19 map provided by the EPPI-Centre (using paediatric keywords)[11] and the L·OVE platform (for preprints).[12] The last searches were on 22 January (PubMed and Web of Science) and 25 January (L·OVE and EPPI-Centre) 2022. We contacted investigators of registered systematic reviews on long-COVID in children to cross-check eligible studies[13–15] (last search in the International Prospective Register of Systematic Reviews (PROSPERO) on 5 November 2021, authors' request 23 November 2021) and screened citations of further relevant reviews.[3 16 17]

Study selection

One researcher screened titles and abstracts (JH, PJ or LGH). Two researchers independently screened full texts (two of JH, PJ, SS, TVP or VLG). Disagreements were resolved by discussion or third-party arbitration (LGH).

Data extraction and methodological appraisal

Two researchers (two of JH, PJ, SS, TVP or VG) independently extracted study characteristics, assessed the consideration of confounding bias and causality, and the risk of bias.[8 9 18 19] Details on extracted items and algorithms for assessments were prespecified.[10] Disagreements were resolved by discussion or third-party arbitration (LGH).

Targeted outcomes

We considered symptoms and quality of life outcomes or other patient-relevant outcomes reflecting how children feel, function (or survive).[20] Imaging or laboratory measures were not considered. We determined the most frequent symptoms assessed among all studies.

We recorded the proportions of children presenting the main outcome. The main outcome was defined as stated by the authors or, if not available, the most inclusive one (eg, any symptoms).[10] We also assessed if the main outcome was analysed in relation to specific participant characteristics (eg, comorbidities) or infection-related factors (eg, severity acute disease). Full details are provided in online supplementary eMethods.

Consideration of confounding bias and causality, and risk of bias assessment

We assessed the consideration of confounding using a previously developed approach[8 9] based on prespecified questions focusing on reporting of confounders and bias in the abstract and discussion, and on what the findings mean and what the limitations are. For the analysis of limitations in the conclusion, we used clearly stated conclusion paragraphs (ie, conclusion subheading or paragraph starting with a phrase such as 'In summary' or 'In conclusion').We assessed three aspects related to consideration of causality, following a similar but simplified approach as Haber *et al*.[18] We determined whether an association of SARS-CoV-2 infection and the main outcome was interpreted causally and if any recommendations were made based on such causal implications; whether a conceptual causal model describing causal mechanisms (eg, a directed acyclic graph[21 22]) was used; and whether any explicit causal disclaimer was made.

We assessed the risk of bias for an estimated effect of SARS-CoV-2 infection on the main postacute symptom outcome using "Risk Of Bias In Non-randomised Studies of Interventions" (ROBINS-I),[19 23] replacing the notion of 'intervention' by 'infection' (see protocol for full details).[10] The ROBINS-I categories are 'low', 'moderate', 'serious' and 'critical' risk of bias.[10]

Statistical analysis

We used R V.4.1 for all analyses. We report medians and IQRs and calculated proportions with 95% CIs using the 'metaprop' function from the 'meta' package V.5.1–1.[24]

RESULTS

Twenty-one studies were eligible (table 1 and online supplemental eFigure1). Six studies had a control group[25–30] and 15 were uncontrolled.[31–45]

Study populations

Overall, the 21 studies included 81 896 children (range 14–71 700, median 58, IQR 25–151).[25–45] Nine studies included >100 children (including controls).[26–30 36 38 42 45] Children were analysed as a subgroup in four studies.[25 26 33 37]

Four studies, all controlled, primarily recruited children from the general population (ie, random sample from schools in Switzerland[27]; consecutive sample of home-isolated children in Norway[25]; based on large health insurance databases in Germany[26]; and based on a national health system database in the UK.[28] Seventeen studies recruited only hospitalised children,[30–32 34 37–44] only children attending the hospital as outpatient[35] or both.[29 33 36 45] Five of these 17 studies included children with multisystem inflammatory syndrome.[30 39 40 44 45]

Positive SARS-CoV-2 infection status was confirmed using RT-PCR only,[28 31–38 41 43] a mix of tests (RT-PCR, antigen test or serology)[25 29 30 39 40 44 45] or serology only.[27]

Negative infection status in the six controlled studies was defined as no diagnosis or symptoms of acute COVID-19,[26 29 30] determined by serology testing[25 27] or by RT-PCR[28] (table 1).

Outcome data collection methods and outcome ascertainment

Outcome data were collected over 2–7 months (median 5.3, IQR 3–6) in the 12 studies starting follow-up at infection or onset[25–30 35 40 42–45] and over 2.0–11.5 months (median 5, IQR 3.5–8) in the nine studies starting follow-up at recovery[31–34 36–39 41] (table 2 and online supplemental eTable1). Outcome data were collected by phone,[29 31 33 34 36 38 41 43] per clinical visit,[32 35 39 42 44] routinely collected,[26 30 40 45] online,[27 28] by personal interview,[25] or by a mix of case reports, medical records and self-reports.[40]

Eight studies considered data on symptom duration.[27 29 33 35 38 40–42] Symptom trend (n=3),[36 38 40] severity (n=3)[31 41 43], and frequency (n=2)[31 38] were uncommonly considered. The main outcome was analysed in relation to

Table 1 Characteristics of cohort studies reporting postacute health outcomes in children with SARS-CoV-2 infection

	Total N (%)	Controlled n (%)	Uncontrolled n (%)
Total	21 (100)	6 (28.6)	15 (71.4)
Region			
Europe	12 (57.1)	5 (83.3)	7 (46.7)
Asia*	6 (28.6)	0 (0)	6 (40)
North America	2 (9.5)	1 (16.7)	1 (6.7)
Oceania	1 (4.8)	0 (0)	1 (6.7)
Population			
Hospitalised only	12 (57.1)	1 (16.7)	11 (73.3)
Hospitalised and outpatient	4 (19.0)	1 (16.7)	3 (20)
General population	4 (19.0)	4 (66.7)	0 (0)
Emergency department only	1 (4.8)	0 (0)	1 (6.7)
Sample size			
<100	12 (57.1)	1 (16.7)	11 (73.3)
100–500	4 (19.0)	1 (16.7)	3 (20.0)
501–1000	2 (9.5)	1 (16.7)	1 (6.7)
>1000	3 (14.3)	3 (50.0)	–
Definition of exposure (SARS-CoV-2 infection)			
Using RT-PCR only	11 (52.4)	1 (16.7)	10 (66.7)
Using RT-PCR or serology	5 (23.8)	2 (33.3)	3 (20.0)
Using RT-PCR, antigen or serology	2 (9.5)	1 (16.7)	1 (6.7)
Unclear†	2 (9.5)	1 (16.7)	1 (6.7)
Using serology only	1 (4.8)	1 (16.7)	0 (0)
Definition of no-exposure (control group)			
No diagnosis or symptoms	–	3 (50.0)	–
Using serology	–	2 (33.3)	–
Using RT-PCR	–	1 (16.7)	–
Study registration			
Mentioned	2 (9.5)	2 (33.3)	0 (0)
Not mentioned	19 (90.5)	4 (66.7)	15 (100)
Study protocol			
Mentioned	2 (9.5)	2 (33.3)	0 (0)
Not mentioned	19 (90.5)	4 (66.7)	15 (100)
Ethical approval			
Yes	19 (90.5)	6 (100)	13 (86.7)
No full review†	1 (4.8)	0 (0)	1 (6.7)
Unclear†	1 (4.8)	0 (0)	1 (6.7)

*Including Russia.
†Two studies did not provide information on the methods used[26 42] As the data analysis was retrospective and no additional data were collected beyond those required for standard medical care, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was not required.
‡One study did not report on ethical approval.[34]
No., number.

participant characteristics or infection-related factors in eight studies.[26 28 29 31 36 38 41 43]

Outcome definition and outcome types

Only two studies provided clear background information on how they defined postacute symptoms (ie, questionnaire based on international working group[31]), expert opinion and published literature[26] (table 2 and online supplemental eTable1).

Thirteen studies focused only on symptoms,[26–29 31 36–39 41–44] while the others also reported numerous laboratory parameters.[25 30 32–35 40 45] Reported symptoms ranged from 1 to 97 per study (median 9, IQR 1–20); however, for 11 of the 21 studies, the total number of assessed outcomes was unclear.[27 29 30 32–36 39 44 45]

The main outcome was a composite of any symptom in 16 studies[25–29 31 33–39 42 43 45]; the main outcomes in the remaining studies were fatigue[44]; respiratory,[32] gastrointestinal[40] and cardiac symptoms[30]; and olfactory symptoms.[41] The three symptoms most frequently assessed across studies were headache (n=13),[25–29 31 33 36–38 42 43 45] fatigue or tiredness (n=12),[26–28 30 31 33 37 38 42–45] and cough (n=10).[25–29 31 33 37 38 42]

Outcome results

The reported proportion of children with post-COVID syndrome (main postacute health outcomes) was between 0% and 66.5% in children with SARS-CoV-2 infection (median 13%, IQR 0–22%, 17 studies; figure 1). Between 2.0% and 53.3% of children without SARS-CoV-2 infection also had such symptoms (control groups of six studies; figure 1).

Only one study described a formal statistical comparison between SARS-CoV-2 infected children and controls, reporting an incidence rate ratio of 1.30 (95% CI 1.25 to 1.35) for all health outcomes combined.[26]

Consideration of confounding

Sixteen of the 21 studies did not allude to or mention confounding bias at all somewhere in the abstract or discussion section.[25 27 31–44]

Three studies alluded to confounding bias[29 30] or acknowledged specific non-adjusted confounders,[30 45] with one of them presenting a statement on residual confounding.[29]

Two studies statistically considered confounding[26 28] (matching on age, sex and geographical area[28]; matching on age, sex and comorbidities[26]). Only one study clearly discussed confounding: 'We cannot exclude that our results may be affected by unmeasured confounding, although we minimised differences between COVID-19 and control cohort via matching'.[26]

Ten studies clearly discussed other biases, for example, as information, referral, detection, response or recall bias, or alluded to other potential biases affecting, for example, missing data.[26–31 38 40 44 45]

Potential limitations were mentioned in the conclusion of the main text of one study[26] (five studies had no clearly stated conclusion section or paragraph,[25 27 40 42 43] while no study mentioned any limitations nor made a clear statement for cautious interpretation in the abstract (four studies had no abstract.[27 36 42 43]

Consideration of causality

A clear causal interpretation of an association between SARS-CoV-2 infection and the main outcome was made in 2 of the 21 studies; both were controlled studies and recommended actions regarding prevention measures[25 26] (online supplemental eBox1). Only one of them had a statement that the results may be impacted by confounders.[26] This was also the only study providing a clear causal disclaimer in the discussion, stating 'Due to the observational nature of our study, a main limitation is that its design does not induce a causal interpretation of results'.[26] No studies used a conceptual causal model.

Risk of bias

All 21 studies had an overall critical risk of bias with critical risk in at least one domain (figure 2 and online supplemental

Table 2 Details on reported postacute health outcomes

Study	Follow-up (months)*	Main outcome	Outcomes (n, reported/total assessed)	Outcome data collection method	Symptom duration reported	Symptom frequency reported	Symptom trend reported	Symptom severity reported	Subgroup analyses related to main outcome
Controlled studies									
Bergia *et al*[29]	4 (infection)	Any symptoms	20/n.r.	Structured questionnaire by phone led by physicians	Yes	–	–	–	Yes
Blomberg *et al*[25]	6 (infection)	Any symptoms	11/11	Personal interview led by medical staff	–	–	–	–	–
Matsubara *et al*[30]	3 (infection)	Cardiac symptoms	3/n.r.	Routinely collected data (medical records and structured clinical assessment)	–	–	–	–	–
Radtke *et al*[27]	6 (infection)	Any symptoms	11 /n.r.	Structured online questionnaire	Yes	–	–	–	–
Roessler *et al*[26]	3 (infection)	Health outcomes combined	97 (grouped)/97	Routinely collected data (administrative claims, unclear how symptoms were assessed)	–	–	–	–	Yes
Stephenson *et al*[28]	3 (infection)	Any symptoms	25/25	Structured online questionnaire	–	–	–	–	Yes
Uncontrolled studies									
Asadi-Pooya *et al* 2021[31]	8 (recovery)	Any symptoms	28/28	Structured questionnaire by phone (unclear who led by)	–	Yes	–	Yes	Yes
Bottino *et al*[32]	2 (recovery)	Respiratory symptoms	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	–	–	–	–	–
Capone *et al*[44]	6 (infection)	Fatigue	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	–	–	–	–	–
Chowdhury *et al*[33]	5 (recovery)	Any symptoms	16/n.r.	Phone call (unclear who led by and which symptoms were assessed)	Yes	–	–	–	–
Denina *et al*[34]	4 (recovery)	Any symptoms	1 /n.r.	Phone call (unclear who led by and which symptoms were assessed)	–	–	–	–	–
Isoldi *et al*[35]	6 (infection)	Any symptoms	1 /n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	Yes	–	–	–	–
Kahn *et al*[45]	2 (infection)	Any symptoms	9 /n.r.	Routinely collected data (registry, structured clinical assessment)	–	–	–	–	–

Continued

Table 2 Continued

Study	Follow-up (months)*	Main outcome	Outcomes (n, reported/total assessed)	Outcome data collection method	Symptom duration reported	Symptom frequency reported	Symptom trend reported	Symptom severity reported	Subgroup analyses related to main outcome
Matteudi *et al*[36]	11.5 (recovery)	Any symptoms	6/n.r.	Phone call led by a paediatric team (unclear which symptoms were assessed)	–	–	Yes	–	Yes
Mei *et al*[37]	5 (recovery)	Any symptoms	1/48	Case reports, medical records, self-reports (unclear who led by and how symptoms were assessed)	–	–	–	–	–
Osmanov *et al*[38]	8.5 (recovery)	Any symptoms	44/44	Structured questionnaire by phone led by medical students	Yes	Yes	Yes	–	Yes
Patnaik *et al*[39]	3.5 (recovery)	Any symptoms	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	–	–	–	–	–
Penner *et al*[40]	6 (infection)	Gastrointestinal symptoms	9/9	Routinely collected data (medical records, structured clinical assessment)	Yes	–	Yes	–	–
Rusetsky *et al*[41]	2 (recovery)	Olfactory disorder	1/1	Structured questionnaire by phone led by the investigators	Yes	–	–	Yes	Yes
Say *et al*[42]	4.5 (infection)	Any symptoms	24/24	Clinical visit using a structured clinical assessment (unclear who led by)	Yes	–	–	–	–
Sterky *et al*[43]	7 (infection)	Any symptoms	18/18	Structured questionnaire by phone (unclear who conducted)	–	–	–	Yes	Yes

*Follow-up started at detection of infection, onset of symptoms, COVID-19 diagnosis and/or hospital admission (described as infection) or at recovery from the acute illness and/or hospital discharge (described as recovery).
n.r., not reported.

eTable2). Risk of bias due to confounding was critical in all studies.[25–45]

Risk of bias due to selection of participants was serious or critical in all studies except for two controlled studies that recruited from electronic health databases regardless of acute symptoms and hospitalisation.[26 28]

Risk in classification of infection status/exposure was low for 14 uncontrolled studies that identified patients based on RT-PCR tests during acute COVID-19.[26 28 31–40 43–45] Risk of bias due to missing data was serious in 14 studies, because loss-to-follow-up was either >20%[25 27–30 33 35 36 38 39 44 45] or the information provided was unclear.[31 34] One study[37] reported following all participants but used multiple data sources without providing further details and was deemed to be of moderate risk of bias.

Risk of bias in outcome measurement was serious for 12 studies that used self-report methods[28–32 34 36 37 39 41 44 46]; we assumed that participants who knew they were infected were more likely to report symptoms.[46 47]

Risk of bias in selection of reported outcome was critical in 16 studies either because they did not provide a protocol and/or the questionnaire used, failed to clearly define outcomes, and/or did not report all outcomes assessed.[25 27–31 33–37 39 40 42 44 45]

DISCUSSION

This systematic review of 21 studies found critically limited robustness of reported SARS-CoV-2 infection health outcomes in children that may be perceived as post-COVID syndrome. There was huge heterogeneity in the definition, assessment and reported frequency of symptoms with frequently missing important information. Overall, none of the studies provided evidence with reasonable certainty on whether SARS-CoV-2

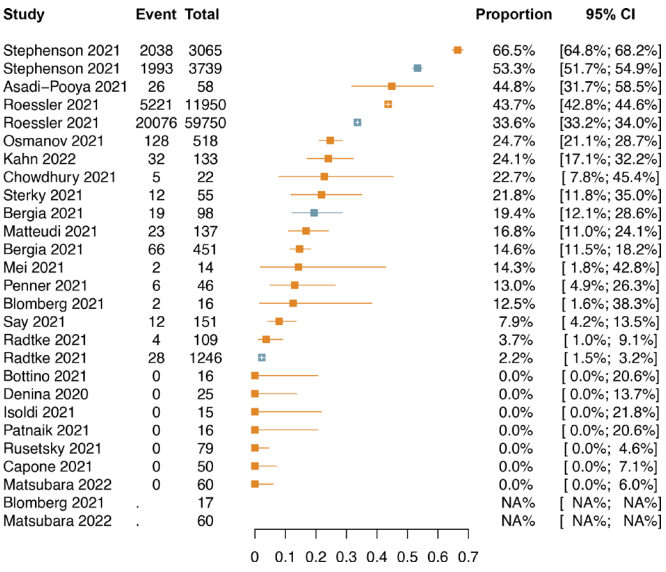

Figure 1 Proportions of children with reported main postacute health outcomes. Orange-coloured: estimates and 95% CIs for children with SARS-CoV-2 infection; blue-coloured: estimates and CIs for children without SARS-CoV-2 infection in the six controlled studies.[25–30] No data reported for children without SARS-CoV-2 infection.[25 30]

infection has an impact on postacute health outcomes, let alone to what extent.

There are two ongoing systematic reviews aiming to determine the prevalence of persistence of symptoms associated with SARS-CoV-2 infection in children,[13–15] and two have been published.[16 48] However, none specifically assessed the robustness of reported postacute symptoms with a focus on an integrative assessment of confounding, other biases and causal claims.

We avoided any quantitative synthesis of risk estimates, given the biases and heterogeneity in these studies; any combined estimate would most likely be misleading for patients, parents, clinicians, the general public and policymakers. Children in the control groups of the two largest studies[26 28] very often had symptoms of post-COVID syndrome without infection (affecting 34% and 53% of children, respectively). This is much higher than any estimate for children with infections in the uncontrolled studies (except for one small study[31]), although these children were mostly hospitalised. This underscores that a control group is essential for a meaningful interpretation.

The exact relationships and inter-relationships of the various factors that influence both the risk of infection and the risk of symptomatic disease need to be understood. These may include age; social factors (eg, housing conditions, education level of children but also of parents and guardians, and family situation); psychological and mental factors (eg, mental illness or impairment, at least of the children themselves); and economic factors (eg, financial situation and additional financial burden on the family due to the pandemic). This may also include information on the parents as they most likely have serious impact on the

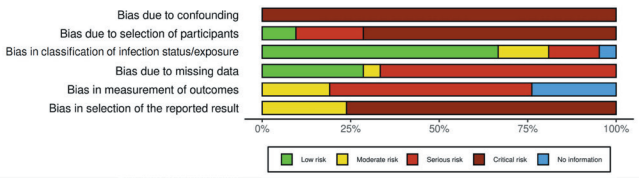

Figure 2 Summary of risk of bias assessment.

children's risk to be infected and becoming aware of symptoms. Of 21 studies, only 6 used control groups, and only 2 adjusted for some confounders, but their results were likely at risk of unmeasured or residual confounding. Hence, for all studies, the risk of confounding was critical.

Another level of complexity is the detection of outcomes due to the inconsistently used and non-standardised definition of 'long COVID-19', but also, and above all, the recording of the outcomes themselves, which are often self-reported and subjectively assessed in an unstructured, non-standardised way. A strong association between risk of infection (eg, being a close contact of a family member) and recognition of an outcome (ie, recognition of symptoms) can be assumed in this situation. It is conceivable that great concern about long COVID-19 leads to more cautious behaviour and more contact restrictions (possibly leading to a lower risk of infection but also higher psychological and mental distress), and to greater attention to symptoms and more frequent contacts with the healthcare system, increasing the probability of receiving such a diagnosis. Structured prospective data collection with a parallel control group would help to avoid such issues. However, given that most infections are unrecognised, a control group would need to be defined based on a strategy with high sensitivity (eg, both negative PCR and negative serology). Test-negative designs may help to address biases resulting from awareness of exposure (ie, infection).[49]

Overall, the 21 studies had mostly serious risk of bias for the outcome measurement; most studies had missing data for more than 20% of the participants and had a critical risk of selective reporting without clear prespecification of analyses, without protocols and with unclear definitions of results.

We did not consider studies reporting only surrogate outcomes (such as laboratory markers or healthcare use) unless we found information on pertinent patient-relevant outcomes.[20] Studies were also not eligible if they reported only cumulative incidences of outcomes not allowing to differentiate the acute situation from the longer follow-up and acute symptoms from those persistent over time.

Overall, authors have mostly refrained from causally classifying their results or making exaggerated interpretations of their findings; most study groups have been cautious in their interpretations. While this restraint is commendable, none of the studies communicated the limitations of this evidence clearly or called for caution in their conclusions.

We encourage authors of future studies to report more granular details. Previous work has outlined recommendations that can help improve the design, conduct and reporting of such studies.[4] For studies in children, specific issues require special attention. This includes consideration of confounding due to factors not related to the patient but to parents, guardians and the family that may be associated with both, infection risk and outcome (eg, educational level, housing situation, financial situation and additional financial burden on the family due to the pandemic). Other critical factors relate to schooling, for example, remote learning or school closure. All these factors are typically complex and not included in routinely collected data sources, requiring specific and very granular active data collection and careful consideration in the analyses.

Overall, studies on the effect of SARS-CoV-2 infection on post-COVID syndrome in children would at least require (1) to compare two groups of children with and without SARS-CoV-2-infection with parallel follow-up, (2) to avoid (or control for) any systematic differences of prognostic factors between the comparison groups and (3) to avoid any systematic differences

in data collection and classification between the comparison groups.

Limitations

Since we included only articles published in English, we may have missed reports from authorities or published in other languages. However, a comparison with related reviews did not reveal such studies.

Our assessment of risk of bias and study characteristics involves a degree of subjectivism. However, given that many extracted items related to existence of reported information (eg, availability of study protocols), this left little room for inconsistency. For the risk of bias assessment, vital items were clear and unambiguous, and these alone determined the overall risk of bias assessment (eg, the critical risk of confounding bias that affects all studies). Here it needs to be highlighted that the tool we used has been designed for observational studies of interventions, but we felt it is the best available choice and it is important to note the underlying logic determining causal effects is the same for interventions (eg, drugs and vaccines) or exposures (eg, infections from viruses). Due to the often-limited reporting quality, isolated misinterpretations cannot be ruled out despite our predefined processes, but this would not change the overall interpretation.

CONCLUSIONS

Clarifying the frequency and severity of post-COVID syndrome remains an important research aim. The best possible research is needed to clarify the current conundrum. Children and their families need reliable and methodologically robust evidence to address their concerns and improve care.

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Contributors The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design, critical revision of the manuscript for important intellectual content: all authors; acquisition, analysis or interpretation of data: JH, PJ, VLG, SS, TVP and LGH; drafting of the manuscript: JH, PJ and LGH; statistical analysis: JH and PJ; obtained funding: TVP (Chevening Scholarship Programme); supervision: LGH.

Funding TVP is funded by the Chevening Scholarship Programme (Foreign and Commonwealth Office, UK).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data generated or analysed during this study are included in this publication and supplement content.

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REFERENCES

1 Dong Y, Mo X, Hu Y, *et al*. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020;145:e20200702.
2 Mantovani A, Rinaldi E, Zusi C, *et al*. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res* 2021;89:733–7.
3 Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents? *Pediatr Infect Dis J* 2021;40:e482–7.
4 Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. *JAMA Netw Open* 2021;4:e2111417.
5 Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, *et al*. Defining Post-COVID symptoms (post-acute COVID, long COVID, persistent Post-COVID): an integrative classification. *Int J Environ Res Public Health* 2021;18:2621.
6 National Institute for Care Excellence. The prevalence of long COVID symptoms and COVID-19 complications. Available: https://www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications [Accessed 25 Nov 2021].
7 World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. Available: https://apps.who.int/iris/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf [Accessed 17 Nov 2021].
8 Hemkens LG, Ewald H, Naudet F, *et al*. Interpretation of epidemiologic studies very often lacked adequate consideration of confounding. *J Clin Epidemiol* 2018;93:94–102.
9 Munkholm K, Faurholt-Jepsen M, Ioannidis JPA, *et al*. Consideration of confounding was suboptimal in the reporting of observational studies in psychiatry: a meta-epidemiological study. *J Clin Epidemiol* 2020;119:75–84.
10 Hirt J, Janiaud P, Gloy V, *et al*. Long-COVID in children: validity of reported post-acute health outcomes in children with SARS-CoV2 infection: project outline. Available: https://osf.io/pemxr/
11 EPPI-Centre. About the COVID-19 MAP. Available: https://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews(bydate)/COVID-19Livingsystematicmapoftheevidence/AbouttheCOVID-19map/tabid/3796/Default.aspx [Accessed 16 Nov 2021].
12 Epistemonikos Foundation. Living overview of evidence. Available: https://iloveevidence.com/ [Accessed 20 Dec 2021].
13 et alAyuzo-del-Valle C, Lopez-Leon S, Wegman-Ostrosky T. Long-term efects of COVID-19 in Children : A systematic review and meta-analysis: PROSPERO CRD42021275408, 2021. Available: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=275408
14 et alWelsh V, Corp N, Burton C. Long term COVID-19 (long COVID) in children and young people: a living systematic review: prospero CRD42020226624, 2020. Available: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=226624

15 Behnood S, Swann O. A systematic review of the prevalence and duration of symptoms of COVID-19 among children infected with SARS-CoV-2 following acute illness: prospero CRD42021233153, 2021. Available: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=233153
16 Behnood SA, Shafran R, Bennett SD, *et al*. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. *J Infect* 2022;84:158–70.
17 Saniasiaya J, Kulasegarah J, Narayanan P. Olfactory dysfunction amongst children and adolescents with laboratory confirmed coronavirus disease 2019: a systematic review. *J Laryngol Otol* 2021;135:953–7.
18 Haber NA, Wieten SE, Rohrer JM, *et al*. *Causal and Associational language in observational health research: a systematic evaluation: Preprint*, 2021.
19 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
20 Biomarkers Definitions Working Group.. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
21 Foraita R, Spallek J, Zeeb H. Directed Acyclic Graphs. In: Ahrens W, Pigeot I, eds. *Handbook of epidemiology*. 2nd ed. New York: Springer, 2014: 1481–517.
22 Nilsson A, Bonander C, Strömberg U, *et al*. A directed acyclic graph for interactions. *Int J Epidemiol* 2021;50:613–9.
23 McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web APP for visualizing risk-of-bias assessments. *Res Synth Methods* 2021;12:55–61.
24 RDocumentation. functions in meta (5.1-1). Available: https://www.rdocumentation.org/packages/meta/versions/5.1-1 [Accessed 10 Feb 2022].
25 Blomberg B, Mohn KG-I, Brokstad KA, *et al*. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021;27:1607–13.
26 Roessler M, Tesch F, Batram M, *et al*. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19: Preprint. *medRxiv* 2021.
27 Radtke T, Ulyte A, Puhan MA, *et al*. Long-Term symptoms after SARS-CoV-2 infection in children and adolescents. *JAMA* 2021;326:869–71.
28 Stephenson T, Pereira SP, Shafran R, *et al*. Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study: Preprint. *ResearchSquare* 2021.
29 Bergia M, Sanchez-Marcos E, Gonzalez-Haba B, *et al*. Study of prevalence and characteristics of long Covid in Spanish children: Preprint. *ResearchSquare* 2021.
30 Matsubara D, Chang J, Kauffman HL, *et al*. Longitudinal assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated with COVID-19 infections. *J Am Heart Assoc* 2022;11:e023251.
31 Asadi-Pooya AA, Nemati H, Shahisavandi M, *et al*. Long COVID in children and adolescents. *World J Pediatr* 2021;17:495–9.
32 Bottino I, Patria MF, Milani GP, *et al*. Can asymptomatic or Non-Severe SARS-CoV-2 infection cause medium-term pulmonary sequelae in children? *Front Pediatr* 2021;9:621019.
33 Mohiuddin Chowdhury ATM, Karim MR, Ali MA, *et al*. Clinical characteristics and the long-term Post-recovery manifestations of the COVID-19 Patients-A prospective multicenter cross-sectional study. *Front Med* 2021;8:663670.
34 Denina M, Pruccoli G, Scolfaro C, *et al*. Sequelae of COVID-19 in hospitalized children: a 4-Months follow-up. *Pediatr Infect Dis J* 2020;39:e458–9.
35 Isoldi S, Mallardo S, Marcellino A, *et al*. The comprehensive clinic, laboratory, and instrumental evaluation of children with COVID-19: a 6-months prospective study. *J Med Virol* 2021;93:3122–32.
36 Matteudi T, Luciani L, Fabre A, *et al*. Clinical characteristics of paediatric COVID-19 patients followed for up to 13 months. *Acta Paediatr* 2021;110:3331–3.
37 Mei Q, Wang F, Yang Y, *et al*. Health Issues and Immunological Assessment Related to Wuhan's COVID-19 Survivors: A Multicenter Follow-Up Study. *Front Med* 2021:617689.
38 Osmanov IM, Spiridonova E, Bobkova P, *et al*. Risk factors for long covid in previously hospitalised children using the ISARIC global follow-up protocol: a prospective cohort study. *Eur Respir J* 2021.
39 Patnaik S, Jain MK, Ahmed S, *et al*. Short-Term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Rheumatol Int* 2021;41:1957–62.
40 Penner J, Abdel-Mannan O, Grant K, *et al*. 6-Month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric Hospital: a retrospective cohort study. *Lancet Child Adolesc Health* 2021;5:473–82.
41 Rusetsky Y, Meytel I, Mokoyan Z, *et al*. Smell status in children infected with SARS-CoV-2. *Laryngoscope* 2021;131:E2475–80.
42 Say D, Crawford N, McNab S, *et al*. Post-Acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health* 2021;5:e22–3.
43 Sterky E, Olsson-Åkefeldt S, Hertting O, *et al*. Persistent symptoms in Swedish children after hospitalisation due to COVID-19. *Acta Paediatr* 2021;110:2578–80.
44 Capone CA, Misra N, Ganigara M, *et al*. Six month follow-up of patients with multi-system inflammatory syndrome in children. *Pediatrics* 2021;148:e2021050973.
45 Kahn R, Berg S, Berntson L, *et al*. Population-based study of multisystem inflammatory syndrome associated with COVID-19 found that 36% of children had persistent symptoms. *Acta Paediatr* 2022;111:354–62.
46 Spencer EA, Brassey J, Mahtani K, Catalogue of Bias Collaboration,. Recall bias. Catalogue of bias, 2017. Available: https://catalogofbias.org/biases/recall-bias/ [Accessed 08 Jun 2022].
47 Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol* 1990;43:87–91.
48 Lopez-Leon S, Wegman-Ostrosky T, Ayuzo del Valle NC, *et al*. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep* 2022;12.
49 Chua H, Feng S, Lewnard JA, *et al*. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. *Epidemiology* 2020;31:43–64.

Robustness of reported post-acute health outcomes in children with SARS-CoV-2 infection: a systematic review

Supplement content

Hirt J, *et al. Arch Dis Child* 2022;0:1–8. doi: 10.1136/archdischild-2022-324455

eMethods: Search strategies and documentation

PubMed (last search: January 22, 2022)

#	Entry	Hits
1	((COVID-19) OR (SARS-CoV-2) OR (coronavirus) OR (2019-nCoV))	235,644
2	((long-term) OR ("long term") OR ("long haul*") OR (“after recovery”) OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*”) OR (post-covid*) OR ("post covid*") OR (post-acute*) OR (“post acute*”))	1,754,935
3	((outcome*) OR (symptom*) OR (disease*) OR (illness*))	10,045,993
4	((cohort) OR (follow up) OR (longitudinal))	3,433,478
5	#1 AND #2 AND #3 AND #4	3,782
6	#5 AND Filters: from 2020/1/1 - 3000/12/12	3,726

Web of Science Core Collection (last search: January 22, 2022)

#	Entry	Hits
1	TS=((COVID-19) OR (SARS-CoV-2) OR (coronavirus) OR (2019-nCoV))	255,865
2	TS=((long-term) OR ("long term") OR ("long haul*") OR (“after recovery”) OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*”) OR (post-covid*) OR ("post covid*") OR (post-acute*) OR (“post acute*”))	2,403,177
3	TS=((outcome*) OR (symptom*) OR (disease*) OR (illness*))	7,633,107
4	TS=((cohort) OR (follow up) OR (longitudinal))	2,481,606
5	#1 AND #2 AND #3 AND #4	2,554
6	#5 AND Publication Date from 2021-01-01 to 2021-12-31	2,511

L·OVE (last search: January 25, 2022)

#	Entry	Hits
1	((long-term) OR ("long term") OR ("long haul*") OR ("after recovery") OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*") OR (post-covid*) OR ("post-covid*") OR (“post-acute*”)) AND ((match*) OR (control*) OR (propensity) OR (seropositive*) OR (seronegativ*))	3,633
2	Filter “Children & adolescents”	285
3	Manually picking preprints from medRxiv, ResearchSquare, and Social Science Research Network (SSRN)	75

EPPI-Centre (last search January 25, 2022)

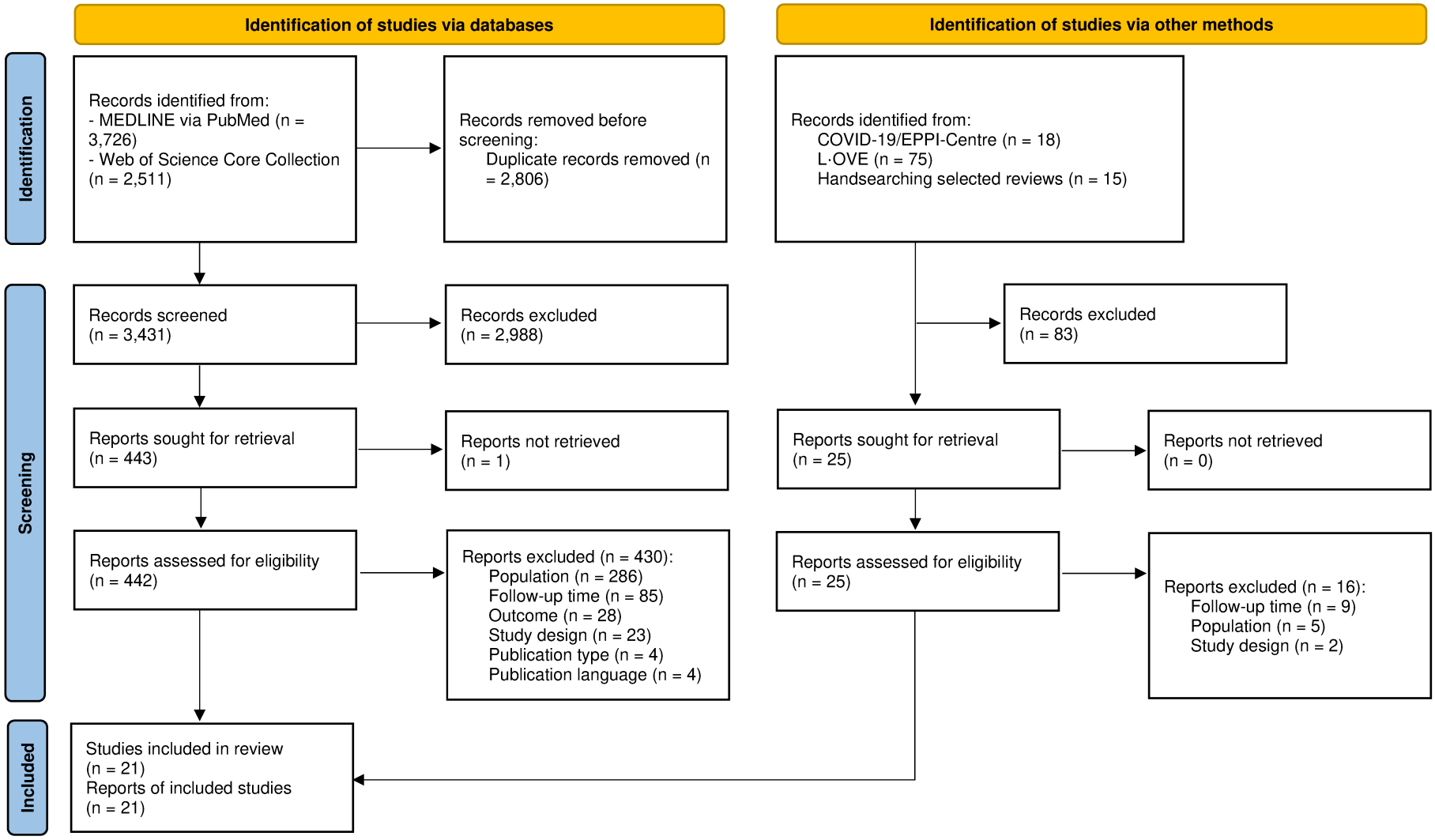
Separated all field searches in the “Long COVID Segment” using the keywords "children", "adolescents", "paediatric", "pediatric", and "kids" retrieved 18 hits.

Hirt J, *et al. Arch Dis Child* 2022;0:1–8. doi: 10.1136/archdischild-2022-324455

eMethods: Data extraction of targeted outcomes

We recorded the number of reported and total assessed (i.e., as reported in the protocol, registry, or methods section) outcomes; source of outcome definition (e.g., expert opinion, literature-based questionnaire); outcome data collection method (e.g., phone, online, clinical visit); length of follow-up (median or mean, as reported; in studies where only a range was reported, we used the midpoint); reported duration of symptoms (i.e., persistent, episodic, or single event); reported frequency of symptoms (e.g., several times daily, once per day or week); reported trend of persistent symptoms (i.e., improving or worsening); reported severity of symptoms.

eFigure1: Literature search and study retrieval process



eTable1: Details on reported post-acute health outcomes (expanded table 2)

Study	Follow-up (months) *	Outcomes (main outcome)	Number of outcomes (reported/total assessed)	Outcome data collection method	Symptom duration reported	Symptom frequency reported	Symptom trend reported	Symptom severity reported	Subgroup analyses related to main outcome
Controlled studies									
Bergia 2021[1]	4 (infection)	any symptoms; rhinorrhoea; fever; cough; dyspnoea; diarrhoea; vomits; abdominal pain; loss of appetite; headache; anosmia/ageusia; myalgia; asthenia; concentration problems; insomnia; apathy, sad feeling; anxiety; palpitations/tachycardia; dizziness; others	20/n.r.	Structured questionnaire by phone led by physicians	Yes	-	-	-	Yes ** (gender; hospital stay; days of admission; covid severity; comorbidity; another family member with long COVID; relative long-covid symptoms; age)
Blomberg 2021[2]	6 (infection)	any symptoms; fever; cough; dyspnoea; palpitations; stomach upset; disturbed taste/smell; sleep problems; headache; dizziness; tingling in fingers	11/11	Personal interview led by medical staff	-	-	-	-	-
Matsubara 2022[3]	3 (infection)	cardiac symptoms; fatigue; others	3/n.r.	Routinely collected data (medical records, structured clinical assessment)	-	-	-	-	-
Radtke 2021[4]	6 (infection)	any symptoms; tiredness; difficulty concentrating; increased need for sleep; congested or runny nose; stomachache; chest tightness; headache; sleep disturbances; cough; health status	11/n.r.	Structured online questionnaire	Yes	-	-	-	-
Roessler 2021[5]	3 (infection)	health outcomes combined; abdominal pain; acute pain; adjustment disorder; anuria/oliguria; anxiety disorder; arthritides; ascites; behavioral symptoms; cachexia; carditis due to viruses; changes in bowel habits; chronic fatigue syndrome; cognitive function impairment; concentration impairment/concentration deficit; cough; covid toe; depression; developmental delay; disorientation; dysgeusia; dyslexia; dysmenorrhea; dysphagia; dyspnea; dysuria; emotional and behavioral disorder; epistaxis; eye pain; facial nerve paralysis; fever; flatulence; gangrene; general symptoms; hair loss; headache; hearing loss/tinnitus; heart failure; heart murmurs; heartburn; hemorrhage; hepatomegaly and splenomegaly; hoarseness; hyperhidrosis; hypotension; impaired balance; joint pain; loss of appetite; lymphadenopathy; malaise/fatigue/exhaustion; memory impairment; meningism; mood disorder; mood disorder; movement disorders; myalgia; myocardial infarction; myocarditis; nausea; neurasthenia; neurological manifestation of post-covid; obsessive-compulsive disorder; oedema; other cardiac arrhythmias; other coordination disorders/ataxia; other symptoms of the urinary system; pain, not elsewhere classified; paresis; paresthesia of skin; pathological findings from male genital tract; pathological lung findings; pathological reflexes; pericarditis; polyuria; post-covid; pulmonary embolism; rash; respiratory insufficiency; seizures; sensation and perception disorder; shock; sinus vein thrombosis; sleep disorders; somatization disorder; somnolence; sopor/coma; speech and language disorders; stroke; subcutaneous nodules; syncope; tetany; throat/chest pain; thrombosis; urethral discharge; urinary retention; vertigo; visual disturbances; weight gain/loss, eating disorders	97 (grouped)/97	Routinely collected data (administrative claims; unclear how symptoms were assessed)	-	-	-	-	Yes (severity of COVID-19 (hospitalized, intensive care unit, outpatient) stratified by age group; diagnosis/symptom complex stratified by age group)
Stephenson 2021[6]	3 (infection)	any symptoms; fever; chills; persistent cough; tiredness; shortness of breath; loss of smell; unusually hoarse voice; unusual chest pain; unusual abdominal pain; diarrhoea; headaches; confusion, disorientation or drowsiness; unusual eye-soreness; skipping meals; dizziness or light-headedness; sore throat; unusual strong muscle pains; earache or ringing in ears; raised welts on skin or swelling; red/purple sores/blisters on feet; other; quality of life/functioning; fatigue; mental health and wellbeing	25/25	Structured online questionnaire	-	-	-	-	Yes (age group)
Uncontrolled studies									
Asadi-Pooya 2021[7]	8 (recovery)	any symptoms; muscle weakness; muscle pain; joint pain; fatigue; sleep difficulty; anxiety; depression; shortness of breath; chest pain; palpitation; cough; excess septum; decreased sense of smell; decreased sense of taste; sore throat; headache; dizziness; concentration difficulty; excess sweating; exercise difficulty; walking difficulty; diarrhoea; abdominal pain/stomachache; loss of appetite; skin lesions; other; chronic medical illness/problem	28/28	Structured questionnaire by phone (unclear who led by)	-	Yes	-	Yes	Yes (sex; age; length of hospital stay; symptoms at presentation (fever, respiratory distress, cough, muscle pain, diarrhoea, intensive care unit admission)
Bottino 2021[8]	2 (recovery)	respiratory symptoms	1/n.r.	Clinical visit (unclear who led by and how	-	-	-	-	-

				symptoms were assessed)					
Capone 2021[9]	6 (infection)	fatigue	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	-	-	-	-	-
Chowdhury 2021[10]	5 (recovery)	any symptoms; lethargy; cough; chest discomfort and pain; fatigue; breathlessness on activity; anxiety, lack of concentration, and occasional amnesia; headache; fever (persisting fever); joint pain; mild body ache; chill; enteric fever; back pain; type 2 diabetes mellitus (following covid-19); hypertension (following covid-19)	16/n.r.	Phone call (unclear who led by and which symptoms were assessed)	Yes	-	-	-	-
Denina 2020[11]	4 (recovery)	any symptoms	1/n.r.	Phone call (unclear who led by and which symptoms were assessed)	-	-	-	-	-
Isoldi 2021[12]	6 (infection)	any symptoms	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	Yes	-	-	-	-
Kahn 2022[13]	2 (infection)	any symptoms; fatigue; muscle/joint weakness/pain; skin manifestations; gastrointestinal symptoms; reduced exercise capacity; psychiatric or neuropsychiatric problems; headache; others	9/n.r.	Routinely collected data (registry; structured clinical assessment)	-	-	-	-	-
Matteudi 2021[14]	11.5 (recovery)	any symptoms; late-onset symptoms; recovery from symptoms; asthenia; learning difficulties; headache	6/n.r.	Phone call led by a paediatric team (unclear which symptoms were assessed)	-	-	Yes	-	Yes (age group; symptomatic/asymptomatic during the acute phase; hospitalization)
Mei 2021[15]	5 (recovery)	any symptoms; shortness of breath; cough/sputum; pharyngitis/foreign body feeling; dyspnoea; pulmonary fibrosis; lung damage; bronchitis; copd; haemoptysis; chest pain/tightness; palpitation; cardiac disease; tachycardia; angina pectoris; heart attack; insomnia; joint pain/back pain/lumbago; fatigue; headache/dizziness/poor memory; change of taste and smell; myalgia; impaired vision; leg numbness/finger stiffness; neuralgia; paralysis; tinnitus; confusion; coma; cerebral infarction; hair loss; bitter/dryness in mouth; high blood sugar; diabetes; gastrointestinal complaints/poor appetite; diarrhoea; constipation; emesis; hidrosis; erythron; allergy; hepatic insufficiency; enema; antiadoncus; hypertension; kidney insufficiency; reduction of physical strength; dryness/excessive secretion	1/48	Case reports, medical records, self-reports (unclear who led by and how symptoms were assessed)	-	-	-	-	-
Osmanov 2021[16]	8.5 (recovery)	any symptoms; fatigue; nasal congestion/rhinorrhoea; insomnia; disturbed smell; headache; disturbed taste; hyperhidrosis; persistent cough; hypersomnia; poor appetite; skin rash; diarrhea; stomach/abdominal pain; problems seeing/blurred vision; hair loss; dizziness/light headedness; joint pain or swelling; variations in heart rate; constipation; loss of smell; difficulty breathing/chest tightness; palpitations; feeling nauseous; chest pain; persistent muscle pain; problems with balance; urination problems; vomiting; confusion/lack of concentration; pain on breathing; cannot fully move or control movement; tremor/shakiness; bleeding; changes in menstruation; loss of taste; tingling feeling/"pins and needles"; weight loss; problems swallowing or chewing; bilateral conjunctivitis; seizures/fits; lumps or rashes (purple/pink) on toes; problems speaking or communicating; fainting/blackouts	44/44	Structured questionnaire by phone led by medical students	Yes	Yes	Yes	-	Yes (age group; sex; neurological conditions; allergic diseases; gastrointestinal problems; excessive weight and obesity; COVID severity)
Patnaik 2021[17]	3.5 (recovery)	any symptoms	1/n.r.	Clinical visit (unclear who led by and how	-	-	-	-	-

				symptoms were assessed)					
Penner 2021[18]	6 (infection)	gastrointestinal symptoms; persistent abdominal pain; persistent diarrhoea; new-onset nausea and vomiting; new-onset diarrhoea; dysphonia; anosmia or dysgeusia; dysphagia; rashes	9/9	Routinely collected data (medical records; structured clinical assessment)	Yes	-	Yes	-	-
Rusetsky 2021[19]	2 (recovery)	olfactory disorder	1/1	Structured questionnaire by phone led by the investigators	Yes	-	-	Yes	Yes (age group; gender)
Say 2021[20]	4.5 (infection)	any symptoms; fever >38; sore throat; cough; runny nose; shortness of breath; loss of taste; loss of smell; poor appetite; vomiting; low energy or tiredness; headaches; muscle aches and pains; abdominal pain; diarrhoea; other; shortness of breath; fatigue; rash; fever; abdominal pain; conjunctivitis; wellbeing; immunisation reaction	24/24	Clinical visit using a structured clinical assessment (unclear who led by)	Yes	-	-	-	-
Sterky 2021[21]	7 (infection)	any symptoms; fever; elevated pulse; palpitations; difficulties breathing; headache; fatigue; increased need of sleep; decreased activity level; decreased physical strength; concentration difficulties; reduced/changed taste; loss of appetite; affected memory; difficulties managing school; depressive symptoms; recurrent body pains; other diagnosed illness	18/18	Structured questionnaire by phone (unclear who conducted)	-	-	-	Yes	Yes (age group; symptoms at onset; treatment received; days of hospitalization; c-reactive protein; days since discharge; chronic illness)

* Follow-up started at detection of infection, onset of symptoms, COVID-19 diagnosis and/or hospital admission (described as infection) or at recovery from the acute illness and/or hospital discharge (described as recovery). Median follow-up length if reported by the authors, we converted weeks and days to months[3,8,15,16,21] (4 weeks/30 days = 1 month); if the median follow-up was not available, we assumed the half of the range[2,7,14,17,20] or the interquartile range[11] to be the median; if both median and range were not available, the fixed follow-up length as reported by the authors has been chosen for our analysis[1,4-6,9,12,18,19]; one study reported outcome data for multiple follow-up lengths between 1 and 5 months, here, we report on 5 months follow-up[10]; one study reported outcome data for multiple follow-up lengths between 2 and 6 months, here, we report on 6 months follow-up[13].

** Data for subgroups only reported for children with SARS-CoV-2 infection.

Abbreviations: n.r. = not reported.

eBox1: Reported action recommendations for children based on causal interpretations of their findings

- "Considering the millions of young people infected during the ongoing pandemic, our findings are a strong impetus for comprehensive infection control and population-wide mass vaccination." [2]
- "To the extent that these results reflect a higher long-run morbidity related to SARS-CoV-2 infections, they may indicate an important public health challenge that should be considered in discussions about adequate preventive measures." [5]

eTable2: Details and justification on risk of bias assessment (ROBINS-I)

	Asadi-Pooya 2021	Bergia 2021	Blomberg 2021	Bottino 2021	Capone 2021	Chowdhury 2021	Denina 2020	Isoldi 2021	Kahn 2022	Matsubara 2022	Matteudi 2021	Mei 2021	Osmanov 2021	Patnaik 2021	Penner 2021	Radtke 2021	Roessler 2021	Rusetsky 2021	Say 2021	Stephenson 2021	Sterky 2021
Bias due to confounding	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Bias due to selection of participants	C	C	C	C	C	C	C	S	C	C	C	S	C	C	S	S	L	C	C	L	C
Bias in classification of infection status/exposure	L	S	M	L	L	L	L	L	L	S	L	L	L	L	L	M	S	L	NI	M	L
Bias due to missing data	S	S	S	L	S	S	S	S	S	S	S	M	S	S	L	S	L	L	L	S	L
Bias in measurement of outcomes	S	S	S	NI	NI	S	S	NI	M	M	S	NI	S	NI	M	S	S	S	M	S	S
Bias in selection of the reported result	C	C	C	M	C	C	C	C	C	C	C	C	M	C	C	C	M	M	C	C	M

C: Critical risk of bias; S: Serious risk of bias; M: Moderate risk of bias; L: Low risk of bias; NI: No information to assess respective risk of bias.

BIAS DUE TO CONFOUNDING

All uncontrolled studies by design cannot adjust for confounders and are thus at a critical risk of confounding bias.

Roessler 2021 and **Stephenson 2021** used a matched case-control design. However, none of them adjusted the analysis for potential confounders such as housing and family setting and socioeconomic status that we assume to be likely associated with the risk of being exposed to SARS-CoV-2 and of reporting long COVID symptoms.

Radtke 2021 used a control group but did not make any formal comparison between the cases and controls nor mentioned the issue of confounders.

Blomberg 2021 used a control group but did not make any formal comparison between the pediatric cases and control nor mentioned the issue of confounders.

Although **Bergia 2021** and **Matsubara 2022** used a control group and alluded to confounding in the discussion and **Bergia 2021** mentioned that findings may be affected by residual confounding, and **Matsubara 2022** acknowledged specific non-adjusted confounders, both studies did not make any formal comparison between the pediatric cases and control.

BIAS DUE TO SELECTION OF PARTICIPANTS

Studies were deemed as having critical risk of bias if they included only hospitalized participants and/or participants who were aware of their COVID-19 status and/or children with multisystem inflammatory syndrome and were more likely to participate to the study if they had persistent symptoms due to self-selection.

Blomberg 2021 included outpatient and hospitalized patients; however the selection of the infection-negative was made from the same households as the cases and some cases were defined on serology with no clear indication if the timing of the infection. It was thus assessed at critical risk of bias.

Isoldi 2021, **Mei 2021,** and **Penner 2021** were deemed as having serious risk of bias as they included hospitalized participants but followed all participants until the end and there was no risk of self-selection.

Roessler 2021 and **Stephenson 2021** were deemed as having low risk of bias as cases and controls were selected from public health databases with hospitalized, non-hospitalized, symptomatic, and asymptomatic patients. In addition, in **Roessler 2021** outcome data were collected from electronic health records and in **Stephenson 2021** outcome data were collected through an online questionnaire with similar response rates in both groups; thus both studies were deemed at low risk of self-selection.

BIAS IN CLASSIFICATION OF INFECTION STATUS/EXPOSURE

Uncontrolled studies were assessed as having low risk of bias, if the infection status classification was based on RT-PCR, antigen or serology testing during the acute phase of COVID-19.

Say 2021 did not provide information on the type of test/diagnosis and could not be assessed.

Radtke 2021 used serology for infection status classification with no clear indication of the timing of the infection for the positive SARS-CoV-2 infection status.

Blomberg 2021 defined positive SARS-CoV-2 infection status using RT-PCR test and in some cases serology testing while all negative SARS-CoV-2 infection status was defined using serology.

Stephenson 2021 SARS-CoV-2 infection status was defined using RT-PCR; however, it cannot be excluded that participants identified as SARS-CoV-2 negative had been infected in the past.

Roessler 2021 did not provide information on the type of testing, but positive SARS-CoV-2 infection status was defined as documented COVID-19 diagnosis with confirmed laboratory virus detection in the health insurance database while negative SARS-CoV-2 infection status was defined as lack of a documented COVID-19 diagnosis regardless of there was a record of laboratory virus detection.

Matsubara 2022 and **Bergia 2021** defined positive SARS-CoV-2 infection status using PCR test or serology, but controls were defined as pre-pandemic (**Matsubara 2022**) or as having no COVID-19 symptoms (**Matsubara 2022 and Bergia 2021),** testing was not required for controls.

BIAS DUE TO MISSING DATA

Bottino 2021, Penner 2021, Rusetsky 2021, Say 2021, and **Sterky 2021** were assessed as having low risk of bias as authors reported no or minimal loss to follow-up (≤ 20%). **Roessler 2021** was also assessed as having low risk of bias as data were collected using systematically routinely collected data.

Mei 2021 was assessed as having a moderate risk of bias as, although report following all eligible participants, data were collected from multiple data sources without further details (i.e., case reports, medical records, and self-reports).

Matsubara 2022 was assessed as having a serious risk of bias with >20% loss to follow-up in children with positive SARS-CoV-2 infection status and unclear loss to follow-up in controls.

All other studies were assessed as having a serious risk of bias and had >20% loss to follow-up except for **Asadi-Pooya 2021** and **Denina 2020** who report unclear information regarding missing data.

BIAS IN MEASUREMENT OF OUTCOMES

Studies deemed as having serious risk of bias if the outcomes were reported by the participants who had knowledge of their COVID-19 status; thus, cases were more likely to report subjective symptoms.

Roessler 2021 deemed as having serious risk of bias since they used routinely collected data but did not provide sufficient information on how the symptoms were assessed.

Say 2021 deemed as having moderate risk of bias since the outcomes were assessed during a clinical visit using structure clinical assessments but the outcome assessor was likely to be more attentive as aware of the COVID-19 status of participants.

Matsubara 2022, Penner 2021, and **Kahn 2022** deemed as having moderate risk of bias since they used routinely collected data based on structured clinical assessment.

For **Isoldi 2021, Bottino 2021, Patnaik 2021, Mei 2021,** and **Capone 2021**, no detailed information is provided for the outcome measurement and the risk of bias could not be assessed.

BIAS IN SELECTION OF THE REPORTED RESULT

Studies deemed as having critical risk of bias if they did not provide a protocol, did not clearly define their outcomes in the method section, did not provide the questionnaire as supplement and/or clearly did not report all outcomes.

Studies deemed as having moderate risk of bias if they did not provide a protocol (or the protocol was not freely available **Osmanov 2021**) but either defined their outcome in the methods section (**Bottino 2021** and **Rusetsky 2021**) or provided the questionnaire used as supplement (**Sterky 2021, Roessler 2021,** and **Osmanov 2021**) and reported on all outcomes.

eReferences

1. Bergia M, Sanchez-Marcos E, Gonzalez-Haba B, et al. Study of Prevalence and Characteristics of Long Covid in Spanish Children: Preprint. *ResearchSquare*. 2021. doi:10.21203/rs.3.rs-1068678/v1.
2. Blomberg B, Mohn KG, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med*. 2021;9:1607-1613. doi:10.1038/s41591-021-01433-3.
3. Matsubara D, Chang J, Kauffman HL, et al. Longitudinal Assessment of Cardiac Outcomes of Multisystem Inflammatory Syndrome in Children Associated With COVID-19 Infections. *J Am Heart Assoc*. 2022;10:e023251. doi:10.1161/JAHA.121.023251.
4. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA*. 2021;326(9):869-871. doi:10.1001/jama.2021.11880.
5. Roessler M, Tesch F, Batram M, et al. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19: Preprint. *medRxiv*. 2021. doi:10.1101/2021.10.21.21265133.
6. Stephenson T, Pereira SP, Shafran R, et al. Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study: Preprint. *ResearchSquare*. 2021. doi:10.21203/rs.3.rs-798316/v1.
7. Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents. *World J Pediatr*. 2021;17(5):495-499. doi:10.1007/s12519-021-00457-6.
8. Bottino I, Patria MF, Milani GP, et al. Can Asymptomatic or Non-Severe SARS-CoV-2 Infection Cause Medium-Term Pulmonary Sequelae in Children? *Front Pediatr*. 2021;9:621019. doi:10.3389/fped.2021.621019.
9. Capone CA, Misra N, Ganigara M, et al. Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children. *Pediatrics*. 2021;148(4):e2021050973. doi:10.1542/peds.2021-050973.
10. Chowdhury ATMM, Karim R, Ali A, Islam J, Li Y, He S. Clinical Characteristics and the Long-Term Post-recovery Manifestations of the COVID-19 Patients-A Prospective Multicenter Cross-Sectional Study. *Front Med*. 2021;8:663670. doi:10.3389/fmed.2021.663670.
11. Denina M, Pruccoli G, Scolfaro C, et al. Sequelae of COVID-19 in Hospitalized Children: A 4-Months Follow-Up. *Pediatr Infect Dis J*. 2020;39(12):e458-e459. doi:10.1097/INF.0000000000002937.
12. Isoldi S, Mallardo S, Marcellino A, et al. The comprehensive clinic, laboratory, and instrumental evaluation of children with COVID-19: A 6-months prospective study. *J Med Virol*. 2021;93(5):3122-3132. doi:10.1002/jmv.26871.
13. Kahn R, Berg S, Berntson L, et al. Population-based study of multisystem inflammatory syndrome associated with COVID-19 found that 36% of children had persistent symptoms. *Acta Paediatr*. 2022;111(2):354-362. doi:10.1111/apa.16191.
14. Matteudi T, Luciani L, Fabre A, et al. Clinical characteristics of paediatric COVID-19 patients followed for up to 13 months. *Acta Paediatr*. 2021;110(12):3331-3333. doi:10.1111/apa.16071.

15. Mei Q, Wang F, Yang Y, et al. Health Issues and Immunological Assessment Related to Wuhan's COVID-19 Survivors: A Multicenter Follow-Up Study. *Front Med*. 2021;7/8:617689. doi:10.3389/fmed.2021.617689.
16. Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study. *Eur Respir J*. 2021;Article in Press. doi:10.1183/13993003.01341-2021.
17. Patnaik S, Jain MK, Ahmed S, et al. Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Rheumatol Int*. 2021;41(11):1957-1962. doi:10.1007/s00296-021-04932-1.
18. Penner J, Abdel-Mannan O, Grant K, et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health*. 2021;5(7):473-482. doi:10.1016/S2352-4642(21)00138-3.
19. Rusetsky Y, Meytel I, Mokoyan Z, Fisenko A, Babayan A, Malyavina U. Smell Status in Children Infected with SARS-CoV-2. *Laryngoscope*. 2021;131(8):E2475-E2480. doi:10.1002/lary.29403.
20. Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health*. 2021;5(6):e22-e23. doi:10.1016/S2352-4642(21)00124-3.
21. Sterky E, Olsson-Åkefeldt S, Hertting O, et al. Persistent symptoms in Swedish children after hospitalisation due to COVID-19. *Acta Paediatr*. 2021;110(9):2578-2580. doi:10.1111/apa.15999.

Robustness of reported post-acute health outcomes in children with SARS-CoV-2 infection: a systematic review

Supplement content

Hirt J, *et al. Arch Dis Child* 2022;0:1–8. doi: 10.1136/archdischild-2022-324455

eMethods: Search strategies and documentation

PubMed (last search: January 22, 2022)

#	Entry	Hits
1	((COVID-19) OR (SARS-CoV-2) OR (coronavirus) OR (2019-nCoV))	235,644
2	((long-term) OR ("long term") OR ("long haul*") OR (“after recovery”) OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*”) OR (post-covid*) OR ("post covid*") OR (post-acute*) OR (“post acute*”))	1,754,935
3	((outcome*) OR (symptom*) OR (disease*) OR (illness*))	10,045,993
4	((cohort) OR (follow up) OR (longitudinal))	3,433,478
5	#1 AND #2 AND #3 AND #4	3,782
6	#5 AND Filters: from 2020/1/1 - 3000/12/12	3,726

Web of Science Core Collection (last search: January 22, 2022)

#	Entry	Hits
1	TS=((COVID-19) OR (SARS-CoV-2) OR (coronavirus) OR (2019-nCoV))	255,865
2	TS=((long-term) OR ("long term") OR ("long haul*") OR (“after recovery”) OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*”) OR (post-covid*) OR ("post covid*") OR (post-acute*) OR (“post acute*”))	2,403,177
3	TS=((outcome*) OR (symptom*) OR (disease*) OR (illness*))	7,633,107
4	TS=((cohort) OR (follow up) OR (longitudinal))	2,481,606
5	#1 AND #2 AND #3 AND #4	2,554
6	#5 AND Publication Date from 2021-01-01 to 2021-12-31	2,511

L·OVE (last search: January 25, 2022)

#	Entry	Hits
1	((long-term) OR ("long term") OR ("long haul*") OR ("after recovery") OR (prolong*) OR (persist*) OR (long-covid*) OR ("long covid*") OR (post-covid*) OR ("post-covid*") OR (“post-acute*”)) AND ((match*) OR (control*) OR (propensity) OR (seropositive*) OR (seronegativ*))	3,633
2	Filter “Children & adolescents”	285
3	Manually picking preprints from medRxiv, ResearchSquare, and Social Science Research Network (SSRN)	75

EPPI-Centre (last search January 25, 2022)

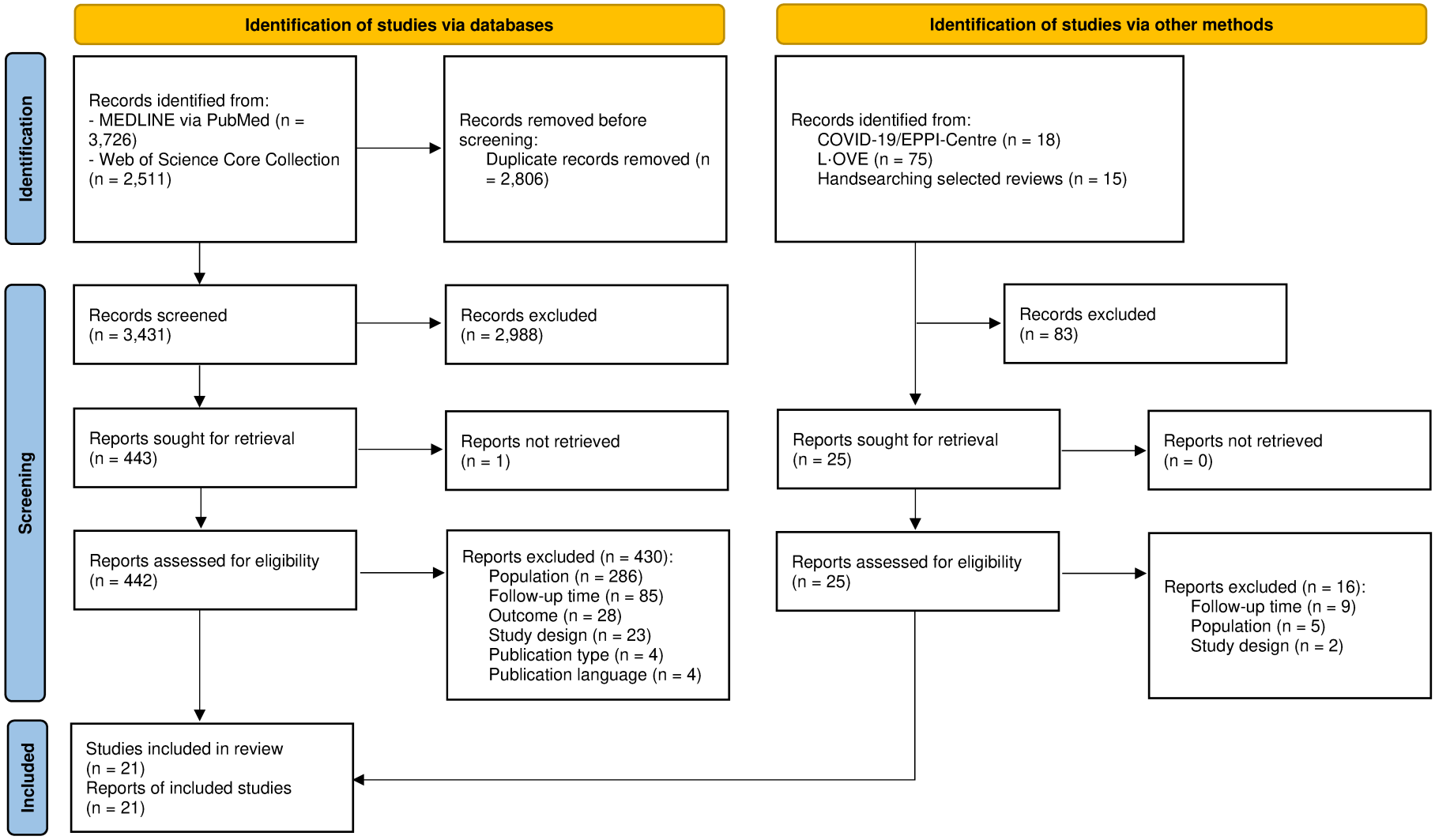
Separated all field searches in the “Long COVID Segment” using the keywords "children", "adolescents", "paediatric", "pediatric", and "kids" retrieved 18 hits.

Hirt J, *et al. Arch Dis Child* 2022;0:1–8. doi: 10.1136/archdischild-2022-324455

eMethods: Data extraction of targeted outcomes

We recorded the number of reported and total assessed (i.e., as reported in the protocol, registry, or methods section) outcomes; source of outcome definition (e.g., expert opinion, literature-based questionnaire); outcome data collection method (e.g., phone, online, clinical visit); length of follow-up (median or mean, as reported; in studies where only a range was reported, we used the midpoint); reported duration of symptoms (i.e., persistent, episodic, or single event); reported frequency of symptoms (e.g., several times daily, once per day or week); reported trend of persistent symptoms (i.e., improving or worsening); reported severity of symptoms.

eFigure1: Literature search and study retrieval process



eTable1: Details on reported post-acute health outcomes (expanded table 2)

Study	Follow-up (months) *	Outcomes (main outcome)	Number of outcomes (reported/total assessed)	Outcome data collection method	Symptom duration reported	Symptom frequency reported	Symptom trend reported	Symptom severity reported	Subgroup analyses related to main outcome
Controlled studies									
Bergia 2021[1]	4 (infection)	any symptoms; rhinorrhoea; fever; cough; dyspnoea; diarrhoea; vomits; abdominal pain; loss of appetite; headache; anosmia/ageusia; myalgia; asthenia; concentration problems; insomnia; apathy, sad feeling; anxiety; palpitations/tachycardia; dizziness; others	20/n.r.	Structured questionnaire by phone led by physicians	Yes	-	-	-	Yes ** (gender; hospital stay; days of admission; covid severity; comorbidity; another family member with long COVID; relative long-covid symptoms; age)
Blomberg 2021[2]	6 (infection)	any symptoms; fever; cough; dyspnoea; palpitations; stomach upset; disturbed taste/smell; sleep problems; headache; dizziness; tingling in fingers	11/11	Personal interview led by medical staff	-	-	-	-	-
Matsubara 2022[3]	3 (infection)	cardiac symptoms; fatigue; others	3/n.r.	Routinely collected data (medical records, structured clinical assessment)	-	-	-	-	-
Radtke 2021[4]	6 (infection)	any symptoms; tiredness; difficulty concentrating; increased need for sleep; congested or runny nose; stomachache; chest tightness; headache; sleep disturbances; cough; health status	11/n.r.	Structured online questionnaire	Yes	-	-	-	-
Roessler 2021[5]	3 (infection)	health outcomes combined; abdominal pain; acute pain; adjustment disorder; anuria/oliguria; anxiety disorder; arthritides; ascites; behavioral symptoms; cachexia; carditis due to viruses; changes in bowel habits; chronic fatigue syndrome; cognitive function impairment; concentration impairment/concentration deficit; cough; covid toe; depression; developmental delay; disorientation; dysgeusia; dyslexia; dysmenorrhea; dysphagia; dyspnea; dysuria; emotional and behavioral disorder; epistaxis; eye pain; facial nerve paralysis; fever; flatulence; gangrene; general symptoms; hair loss; headache; hearing loss/tinnitus; heart failure; heart murmurs; heartburn; hemorrhage; hepatomegaly and splenomegaly; hoarseness; hyperhidrosis; hypotension; impaired balance; joint pain; loss of appetite; lymphadenopathy; malaise/fatigue/exhaustion; memory impairment; meningism; mood disorder; mood disorder; movement disorders; myalgia; myocardial infarction; myocarditis; nausea; neurasthenia; neurological manifestation of post-covid; obsessive-compulsive disorder; oedema; other cardiac arrhythmias; other coordination disorders/ataxia; other symptoms of the urinary system; pain, not elsewhere classified; paresis; paresthesia of skin; pathological findings from male genital tract; pathological lung findings; pathological reflexes; pericarditis; polyuria; post-covid; pulmonary embolism; rash; respiratory insufficiency; seizures; sensation and perception disorder; shock; sinus vein thrombosis; sleep disorders; somatization disorder; somnolence; sopor/coma; speech and language disorders; stroke; subcutaneous nodules; syncope; tetany; throat/chest pain; thrombosis; urethral discharge; urinary retention; vertigo; visual disturbances; weight gain/loss, eating disorders	97 (grouped)/97	Routinely collected data (administrative claims; unclear how symptoms were assessed)	-	-	-	-	Yes (severity of COVID-19 (hospitalized, intensive care unit, outpatient) stratified by age group; diagnosis/symptom complex stratified by age group)
Stephenson 2021[6]	3 (infection)	any symptoms; fever; chills; persistent cough; tiredness; shortness of breath; loss of smell; unusually hoarse voice; unusual chest pain; unusual abdominal pain; diarrhoea; headaches; confusion, disorientation or drowsiness; unusual eye-soreness; skipping meals; dizziness or light-headedness; sore throat; unusual strong muscle pains; earache or ringing in ears; raised welts on skin or swelling; red/purple sores/blisters on feet; other; quality of life/functioning; fatigue; mental health and wellbeing	25/25	Structured online questionnaire	-	-	-	-	Yes (age group)
Uncontrolled studies									
Asadi-Pooya 2021[7]	8 (recovery)	any symptoms; muscle weakness; muscle pain; joint pain; fatigue; sleep difficulty; anxiety; depression; shortness of breath; chest pain; palpitation; cough; excess septum; decreased sense of smell; decreased sense of taste; sore throat; headache; dizziness; concentration difficulty; excess sweating; exercise difficulty; walking difficulty; diarrhoea; abdominal pain/stomachache; loss of appetite; skin lesions; other; chronic medical illness/problem	28/28	Structured questionnaire by phone (unclear who led by)	-	Yes	-	Yes	Yes (sex; age; length of hospital stay; symptoms at presentation (fever, respiratory distress, cough, muscle pain, diarrhoea, intensive care unit admission)
Bottino 2021[8]	2 (recovery)	respiratory symptoms	1/n.r.	Clinical visit (unclear who led by and how	-	-	-	-	-

				symptoms were assessed)					
Capone 2021[9]	6 (infection)	fatigue	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	-	-	-	-	-
Chowdhury 2021[10]	5 (recovery)	any symptoms; lethargy; cough; chest discomfort and pain; fatigue; breathlessness on activity; anxiety, lack of concentration, and occasional amnesia; headache; fever (persisting fever); joint pain; mild body ache; chill; enteric fever; back pain; type 2 diabetes mellitus (following covid-19); hypertension (following covid-19)	16/n.r.	Phone call (unclear who led by and which symptoms were assessed)	Yes	-	-	-	-
Denina 2020[11]	4 (recovery)	any symptoms	1/n.r.	Phone call (unclear who led by and which symptoms were assessed)	-	-	-	-	-
Isoldi 2021[12]	6 (infection)	any symptoms	1/n.r.	Clinical visit (unclear who led by and how symptoms were assessed)	Yes	-	-	-	-
Kahn 2022[13]	2 (infection)	any symptoms; fatigue; muscle/joint weakness/pain; skin manifestations; gastrointestinal symptoms; reduced exercise capacity; psychiatric or neuropsychiatric problems; headache; others	9/n.r.	Routinely collected data (registry; structured clinical assessment)	-	-	-	-	-
Matteudi 2021[14]	11.5 (recovery)	any symptoms; late-onset symptoms; recovery from symptoms; asthenia; learning difficulties; headache	6/n.r.	Phone call led by a paediatric team (unclear which symptoms were assessed)	-	-	Yes	-	Yes (age group; symptomatic/asymptomatic during the acute phase; hospitalization)
Mei 2021[15]	5 (recovery)	any symptoms; shortness of breath; cough/sputum; pharyngitis/foreign body feeling; dyspnoea; pulmonary fibrosis; lung damage; bronchitis; copd; haemoptysis; chest pain/tightness; palpitation; cardiac disease; tachycardia; angina pectoris; heart attack; insomnia; joint pain/back pain/lumbago; fatigue; headache/dizziness/poor memory; change of taste and smell; myalgia; impaired vision; leg numbness/finger stiffness; neuralgia; paralysis; tinnitus; confusion; coma; cerebral infarction; hair loss; bitter/dryness in mouth; high blood sugar; diabetes; gastrointestinal complaints/poor appetite; diarrhoea; constipation; emesis; hidrosis; erythron; allergy; hepatic insufficiency; enema; antiadoncus; hypertension; kidney insufficiency; reduction of physical strength; dryness/excessive secretion	1/48	Case reports, medical records, self-reports (unclear who led by and how symptoms were assessed)	-	-	-	-	-
Osmanov 2021[16]	8.5 (recovery)	any symptoms; fatigue; nasal congestion/rhinorrhoea; insomnia; disturbed smell; headache; disturbed taste; hyperhidrosis; persistent cough; hypersomnia; poor appetite; skin rash; diarrhea; stomach/abdominal pain; problems seeing/blurred vision; hair loss; dizziness/light headedness; joint pain or swelling; variations in heart rate; constipation; loss of smell; difficulty breathing/chest tightness; palpitations; feeling nauseous; chest pain; persistent muscle pain; problems with balance; urination problems; vomiting; confusion/lack of concentration; pain on breathing; cannot fully move or control movement; tremor/shakiness; bleeding; changes in menstruation; loss of taste; tingling feeling/"pins and needles"; weight loss; problems swallowing or chewing; bilateral conjunctivitis; seizures/fits; lumps or rashes (purple/pink) on toes; problems speaking or communicating; fainting/blackouts	44/44	Structured questionnaire by phone led by medical students	Yes	Yes	Yes	-	Yes (age group; sex; neurological conditions; allergic diseases; gastrointestinal problems; excessive weight and obesity; COVID severity)
Patnaik 2021[17]	3.5 (recovery)	any symptoms	1/n.r.	Clinical visit (unclear who led by and how	-	-	-	-	-

				symptoms were assessed)					
Penner 2021[18]	6 (infection)	gastrointestinal symptoms; persistent abdominal pain; persistent diarrhoea; new-onset nausea and vomiting; new-onset diarrhoea; dysphonia; anosmia or dysgeusia; dysphagia; rashes	9/9	Routinely collected data (medical records; structured clinical assessment)	Yes	-	Yes	-	-
Rusetsky 2021[19]	2 (recovery)	olfactory disorder	1/1	Structured questionnaire by phone led by the investigators	Yes	-	-	Yes	Yes (age group; gender)
Say 2021[20]	4.5 (infection)	any symptoms; fever >38; sore throat; cough; runny nose; shortness of breath; loss of taste; loss of smell; poor appetite; vomiting; low energy or tiredness; headaches; muscle aches and pains; abdominal pain; diarrhoea; other; shortness of breath; fatigue; rash; fever; abdominal pain; conjunctivitis; wellbeing; immunisation reaction	24/24	Clinical visit using a structured clinical assessment (unclear who led by)	Yes	-	-	-	-
Sterky 2021[21]	7 (infection)	any symptoms; fever; elevated pulse; palpitations; difficulties breathing; headache; fatigue; increased need of sleep; decreased activity level; decreased physical strength; concentration difficulties; reduced/changed taste; loss of appetite; affected memory; difficulties managing school; depressive symptoms; recurrent body pains; other diagnosed illness	18/18	Structured questionnaire by phone (unclear who conducted)	-	-	-	Yes	Yes (age group; symptoms at onset; treatment received; days of hospitalization; c-reactive protein; days since discharge; chronic illness)

* Follow-up started at detection of infection, onset of symptoms, COVID-19 diagnosis and/or hospital admission (described as infection) or at recovery from the acute illness and/or hospital discharge (described as recovery). Median follow-up length if reported by the authors, we converted weeks and days to months[3,8,15,16,21] (4 weeks/30 days = 1 month); if the median follow-up was not available, we assumed the half of the range[2,7,14,17,20] or the interquartile range[11] to be the median; if both median and range were not available, the fixed follow-up length as reported by the authors has been chosen for our analysis[1,4-6,9,12,18,19]; one study reported outcome data for multiple follow-up lengths between 1 and 5 months, here, we report on 5 months follow-up[10]; one study reported outcome data for multiple follow-up lengths between 2 and 6 months, here, we report on 6 months follow-up[13].

** Data for subgroups only reported for children with SARS-CoV-2 infection.

Abbreviations: n.r. = not reported.

eBox1: Reported action recommendations for children based on causal interpretations of their findings

- "Considering the millions of young people infected during the ongoing pandemic, our findings are a strong impetus for comprehensive infection control and population-wide mass vaccination." [2]
- "To the extent that these results reflect a higher long-run morbidity related to SARS-CoV-2 infections, they may indicate an important public health challenge that should be considered in discussions about adequate preventive measures." [5]

eTable2: Details and justification on risk of bias assessment (ROBINS-I)

	Asadi-Pooya 2021	Bergia 2021	Blomberg 2021	Bottino 2021	Capone 2021	Chowdhury 2021	Denina 2020	Isoldi 2021	Kahn 2022	Matsubara 2022	Matteudi 2021	Mei 2021	Osmanov 2021	Patnaik 2021	Penner 2021	Radtke 2021	Roessler 2021	Rusetsky 2021	Say 2021	Stephenson 2021	Sterky 2021
Bias due to confounding	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C
Bias due to selection of participants	C	C	C	C	C	C	C	S	C	C	C	S	C	C	S	S	L	C	C	L	C
Bias in classification of infection status/exposure	L	S	M	L	L	L	L	L	L	S	L	L	L	L	L	M	S	L	NI	M	L
Bias due to missing data	S	S	S	L	S	S	S	S	S	S	S	M	S	S	L	S	L	L	L	S	L
Bias in measurement of outcomes	S	S	S	NI	NI	S	S	NI	M	M	S	NI	S	NI	M	S	S	S	M	S	S
Bias in selection of the reported result	C	C	C	M	C	C	C	C	C	C	C	C	M	C	C	C	M	M	C	C	M

C: Critical risk of bias; S: Serious risk of bias; M: Moderate risk of bias; L: Low risk of bias; NI: No information to assess respective risk of bias.

BIAS DUE TO CONFOUNDING

All uncontrolled studies by design cannot adjust for confounders and are thus at a critical risk of confounding bias.

Roessler 2021 and **Stephenson 2021** used a matched case-control design. However, none of them adjusted the analysis for potential confounders such as housing and family setting and socioeconomic status that we assume to be likely associated with the risk of being exposed to SARS-CoV-2 and of reporting long COVID symptoms.

Radtke 2021 used a control group but did not make any formal comparison between the cases and controls nor mentioned the issue of confounders.

Blomberg 2021 used a control group but did not make any formal comparison between the pediatric cases and control nor mentioned the issue of confounders.

Although **Bergia 2021** and **Matsubara 2022** used a control group and alluded to confounding in the discussion and **Bergia 2021** mentioned that findings may be affected by residual confounding, and **Matsubara 2022** acknowledged specific non-adjusted confounders, both studies did not make any formal comparison between the pediatric cases and control.

BIAS DUE TO SELECTION OF PARTICIPANTS

Studies were deemed as having critical risk of bias if they included only hospitalized participants and/or participants who were aware of their COVID-19 status and/or children with multisystem inflammatory syndrome and were more likely to participate to the study if they had persistent symptoms due to self-selection.

Blomberg 2021 included outpatient and hospitalized patients; however the selection of the infection-negative was made from the same households as the cases and some cases were defined on serology with no clear indication if the timing of the infection. It was thus assessed at critical risk of bias.

Isoldi 2021, **Mei 2021,** and **Penner 2021** were deemed as having serious risk of bias as they included hospitalized participants but followed all participants until the end and there was no risk of self-selection.

Roessler 2021 and **Stephenson 2021** were deemed as having low risk of bias as cases and controls were selected from public health databases with hospitalized, non-hospitalized, symptomatic, and asymptomatic patients. In addition, in **Roessler 2021** outcome data were collected from electronic health records and in **Stephenson 2021** outcome data were collected through an online questionnaire with similar response rates in both groups; thus both studies were deemed at low risk of self-selection.

BIAS IN CLASSIFICATION OF INFECTION STATUS/EXPOSURE

Uncontrolled studies were assessed as having low risk of bias, if the infection status classification was based on RT-PCR, antigen or serology testing during the acute phase of COVID-19.

Say 2021 did not provide information on the type of test/diagnosis and could not be assessed.

Radtke 2021 used serology for infection status classification with no clear indication of the timing of the infection for the positive SARS-CoV-2 infection status.

Blomberg 2021 defined positive SARS-CoV-2 infection status using RT-PCR test and in some cases serology testing while all negative SARS-CoV-2 infection status was defined using serology.

Stephenson 2021 SARS-CoV-2 infection status was defined using RT-PCR; however, it cannot be excluded that participants identified as SARS-CoV-2 negative had been infected in the past.

Roessler 2021 did not provide information on the type of testing, but positive SARS-CoV-2 infection status was defined as documented COVID-19 diagnosis with confirmed laboratory virus detection in the health insurance database while negative SARS-CoV-2 infection status was defined as lack of a documented COVID-19 diagnosis regardless of there was a record of laboratory virus detection.

Matsubara 2022 and **Bergia 2021** defined positive SARS-CoV-2 infection status using PCR test or serology, but controls were defined as pre-pandemic (**Matsubara 2022**) or as having no COVID-19 symptoms (**Matsubara 2022 and Bergia 2021),** testing was not required for controls.

BIAS DUE TO MISSING DATA

Bottino 2021, Penner 2021, Rusetsky 2021, Say 2021, and **Sterky 2021** were assessed as having low risk of bias as authors reported no or minimal loss to follow-up (≤ 20%). **Roessler 2021** was also assessed as having low risk of bias as data were collected using systematically routinely collected data.

Mei 2021 was assessed as having a moderate risk of bias as, although report following all eligible participants, data were collected from multiple data sources without further details (i.e., case reports, medical records, and self-reports).

Matsubara 2022 was assessed as having a serious risk of bias with >20% loss to follow-up in children with positive SARS-CoV-2 infection status and unclear loss to follow-up in controls.

All other studies were assessed as having a serious risk of bias and had >20% loss to follow-up except for **Asadi-Pooya 2021** and **Denina 2020** who report unclear information regarding missing data.

BIAS IN MEASUREMENT OF OUTCOMES

Studies deemed as having serious risk of bias if the outcomes were reported by the participants who had knowledge of their COVID-19 status; thus, cases were more likely to report subjective symptoms.

Roessler 2021 deemed as having serious risk of bias since they used routinely collected data but did not provide sufficient information on how the symptoms were assessed.

Say 2021 deemed as having moderate risk of bias since the outcomes were assessed during a clinical visit using structure clinical assessments but the outcome assessor was likely to be more attentive as aware of the COVID-19 status of participants.

Matsubara 2022, Penner 2021, and **Kahn 2022** deemed as having moderate risk of bias since they used routinely collected data based on structured clinical assessment.

For **Isoldi 2021, Bottino 2021, Patnaik 2021, Mei 2021,** and **Capone 2021**, no detailed information is provided for the outcome measurement and the risk of bias could not be assessed.

BIAS IN SELECTION OF THE REPORTED RESULT

Studies deemed as having critical risk of bias if they did not provide a protocol, did not clearly define their outcomes in the method section, did not provide the questionnaire as supplement and/or clearly did not report all outcomes.

Studies deemed as having moderate risk of bias if they did not provide a protocol (or the protocol was not freely available **Osmanov 2021**) but either defined their outcome in the methods section (**Bottino 2021** and **Rusetsky 2021**) or provided the questionnaire used as supplement (**Sterky 2021, Roessler 2021,** and **Osmanov 2021**) and reported on all outcomes.

eReferences

1. Bergia M, Sanchez-Marcos E, Gonzalez-Haba B, et al. Study of Prevalence and Characteristics of Long Covid in Spanish Children: Preprint. *ResearchSquare*. 2021. doi:10.21203/rs.3.rs-1068678/v1.
2. Blomberg B, Mohn KG, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med*. 2021;9:1607-1613. doi:10.1038/s41591-021-01433-3.
3. Matsubara D, Chang J, Kauffman HL, et al. Longitudinal Assessment of Cardiac Outcomes of Multisystem Inflammatory Syndrome in Children Associated With COVID-19 Infections. *J Am Heart Assoc*. 2022;10:e023251. doi:10.1161/JAHA.121.023251.
4. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA*. 2021;326(9):869-871. doi:10.1001/jama.2021.11880.
5. Roessler M, Tesch F, Batram M, et al. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19: Preprint. *medRxiv*. 2021. doi:10.1101/2021.10.21.21265133.
6. Stephenson T, Pereira SP, Shafran R, et al. Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study: Preprint. *ResearchSquare*. 2021. doi:10.21203/rs.3.rs-798316/v1.
7. Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents. *World J Pediatr*. 2021;17(5):495-499. doi:10.1007/s12519-021-00457-6.
8. Bottino I, Patria MF, Milani GP, et al. Can Asymptomatic or Non-Severe SARS-CoV-2 Infection Cause Medium-Term Pulmonary Sequelae in Children? *Front Pediatr*. 2021;9:621019. doi:10.3389/fped.2021.621019.
9. Capone CA, Misra N, Ganigara M, et al. Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children. *Pediatrics*. 2021;148(4):e2021050973. doi:10.1542/peds.2021-050973.
10. Chowdhury ATMM, Karim R, Ali A, Islam J, Li Y, He S. Clinical Characteristics and the Long-Term Post-recovery Manifestations of the COVID-19 Patients-A Prospective Multicenter Cross-Sectional Study. *Front Med*. 2021;8:663670. doi:10.3389/fmed.2021.663670.
11. Denina M, Pruccoli G, Scolfaro C, et al. Sequelae of COVID-19 in Hospitalized Children: A 4-Months Follow-Up. *Pediatr Infect Dis J*. 2020;39(12):e458-e459. doi:10.1097/INF.0000000000002937.
12. Isoldi S, Mallardo S, Marcellino A, et al. The comprehensive clinic, laboratory, and instrumental evaluation of children with COVID-19: A 6-months prospective study. *J Med Virol*. 2021;93(5):3122-3132. doi:10.1002/jmv.26871.
13. Kahn R, Berg S, Berntson L, et al. Population-based study of multisystem inflammatory syndrome associated with COVID-19 found that 36% of children had persistent symptoms. *Acta Paediatr*. 2022;111(2):354-362. doi:10.1111/apa.16191.
14. Matteudi T, Luciani L, Fabre A, et al. Clinical characteristics of paediatric COVID-19 patients followed for up to 13 months. *Acta Paediatr*. 2021;110(12):3331-3333. doi:10.1111/apa.16071.

15. Mei Q, Wang F, Yang Y, et al. Health Issues and Immunological Assessment Related to Wuhan's COVID-19 Survivors: A Multicenter Follow-Up Study. *Front Med*. 2021;7/8:617689. doi:10.3389/fmed.2021.617689.
16. Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study. *Eur Respir J*. 2021;Article in Press. doi:10.1183/13993003.01341-2021.
17. Patnaik S, Jain MK, Ahmed S, et al. Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Rheumatol Int*. 2021;41(11):1957-1962. doi:10.1007/s00296-021-04932-1.
18. Penner J, Abdel-Mannan O, Grant K, et al. 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health*. 2021;5(7):473-482. doi:10.1016/S2352-4642(21)00138-3.
19. Rusetsky Y, Meytel I, Mokoyan Z, Fisenko A, Babayan A, Malyavina U. Smell Status in Children Infected with SARS-CoV-2. *Laryngoscope*. 2021;131(8):E2475-E2480. doi:10.1002/lary.29403.
20. Say D, Crawford N, McNab S, Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health*. 2021;5(6):e22-e23. doi:10.1016/S2352-4642(21)00124-3.
21. Sterky E, Olsson-Åkefeldt S, Hertting O, et al. Persistent symptoms in Swedish children after hospitalisation due to COVID-19. *Acta Paediatr*. 2021;110(9):2578-2580. doi:10.1111/apa.15999.