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

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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.

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
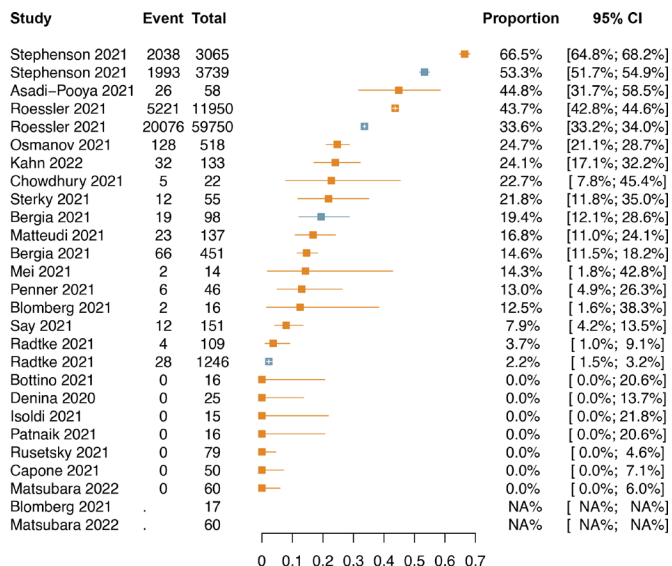
Study	Event	Total	Proportion	95% CI
Stephenson 2021	2038	3065	66.5%	[64.8%; 68.2%]
Stephenson 2021	1993	3739	53.3%	[51.7%; 54.9%]
Asadi–Pooya 2021	26	58	44.8%	[31.7%; 58.5%]
Roessler 2021	5221	11950	43.7%	[42.8%; 44.6%]
Roessler 2021	20076	59750	33.6%	[33.2%; 34.0%]
Osmanov 2021	128	518	24.7%	[21.1%; 28.7%]
Kahn 2022	32	133	24.1%	[17.1%; 32.2%]
Chowdhury 2021	5	22	22.7%	[7.8%; 45.4%]
Sterky 2021	12	55	21.8%	[11.8%; 35.0%]
Bergia 2021	19	98	19.4%	[12.1%; 28.6%]
Matteudi 2021	23	137	16.8%	[11.0%; 24.1%]
Bergia 2021	66	451	14.6%	[11.5%; 18.2%]
Mei 2021	2	14	14.3%	[1.8%; 42.8%]
Penner 2021	6	46	13.0%	[4.9%; 26.3%]
Blomberg 2021	2	16	12.5%	[1.6%; 38.3%]
Say 2021	12	151	7.9%	[4.2%; 13.5%]
Radtke 2021	4	109	3.7%	[1.0%; 9.1%]
Radtke 2021	28	1246	2.2%	[1.5%; 3.2%]
Bottino 2021	0	16	0.0%	[0.0%; 20.6%]
Denina 2020	0	25	0.0%	[0.0%; 13.7%]
Isoldi 2021	0	15	0.0%	[0.0%; 21.8%]
Patnaik 2021	0	16	0.0%	[0.0%; 20.6%]
Rusetsky 2021	0	79	0.0%	[0.0%; 4.6%]
Capone 2021	0	50	0.0%	[0.0%; 7.1%]
Matsubara 2022	0	60	0.0%	[0.0%; 6.0%]
Blomberg 2021	.	17	NA%	[NA%; NA%]
Matsubara 2022	.	60	NA%	[NA%; NA%]

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

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
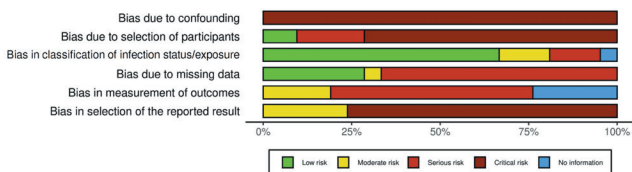
Figure 2 Summary of risk of bias assessment.

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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