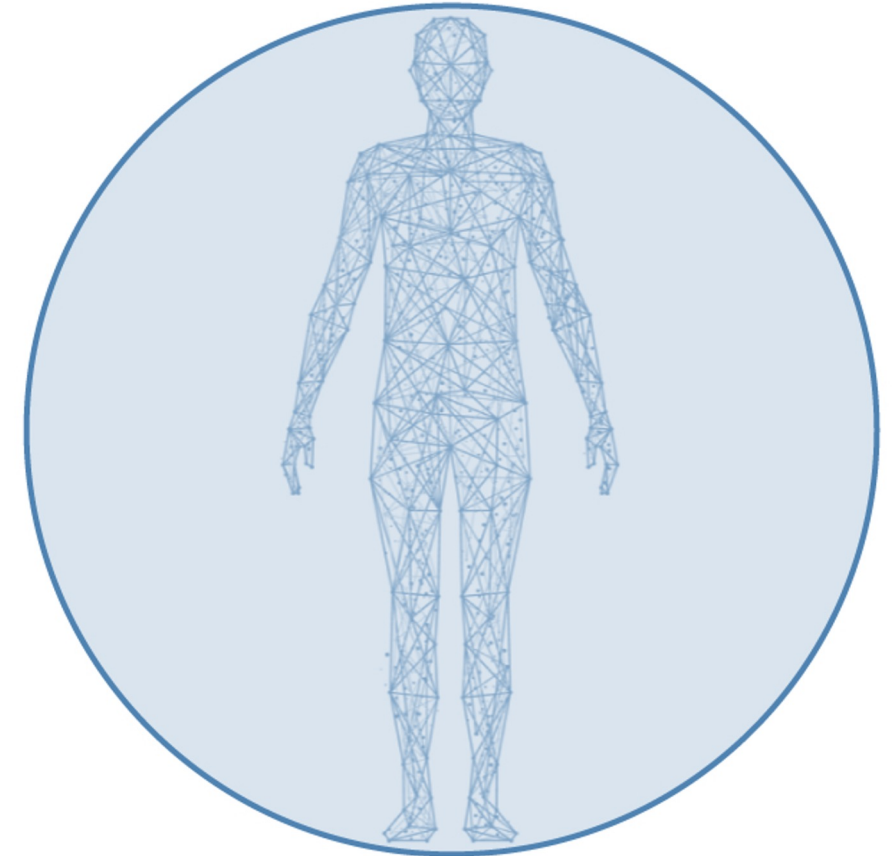


Post COVID-19 Condition in Children and Young Adults

An updated systematic review and meta-analysis
conducted by UCL Great Ormond Street Institute of
Child in collaboration with the World Health
Organisation

Behnood, S., Newlands, F., O'Mahoney, L., Takeda, A., Haghighat Ghahfarokhi, M.,
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Research Definition

- Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time¹.
- This is the first research definition of Long COVID (post-COVID-19 condition) in CYP and complements the clinical case definition in adults proposed by the WHO.

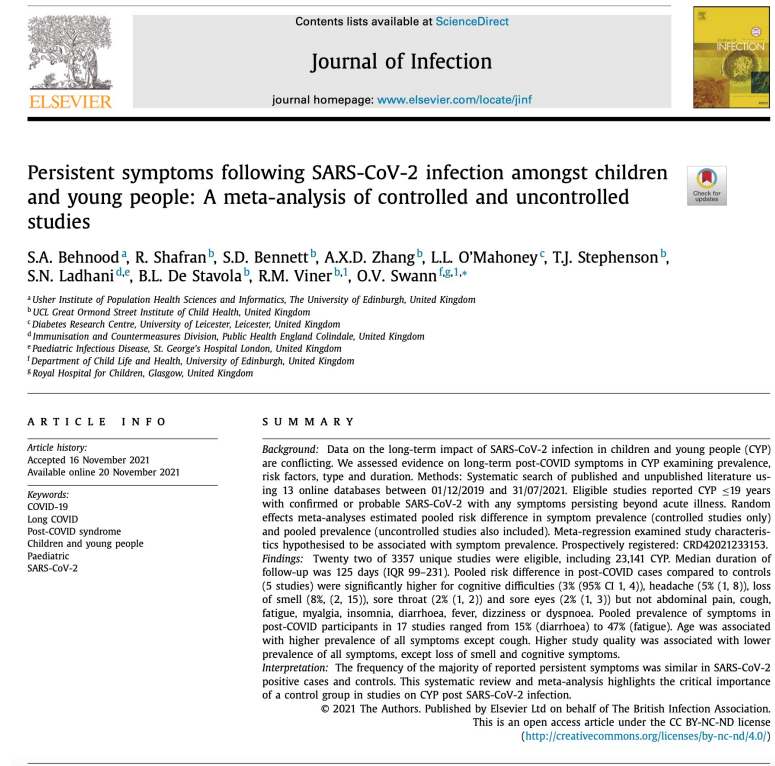


¹Stephenson T, Allin B, Nugawela MD, Rojas N, Dalrymple E, Pinto Pereira S, Soni M, Knight M, Cheung EY, Heyman I; CLoCk Consortium, Shafran R. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. Arch Dis Child. 2022 Jul;107(7):674-680. doi: 10.1136/archdischild-2021-323624.

Previous Review

- In February 2022 the research team published a review on persistent symptoms following SARS-CoV-2 infection in children and young people (CYP)².
- We performed a systematic search of published and unpublished literature using 13 online databases between 01/12/2019 and 31/07/2021.
- We identified 101 symptoms reported to be persistent after SARS-CoV-2 infection in CYP, across cardiovascular, respiratory, gastrointestinal, musculoskeletal, skin and nervous systems as well as general somatic symptoms.

²Behnood SA, Shafran R, Bennett SD, Zhang AXD, O'Mahoney LL, Stephenson TJ, Ladhani SN, De Stavola BL, Viner RM, Swann OV. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. J Infect. 2022 Feb;84(2):158-170. doi: 10.1016/j.jinf.2021.11.011.



Previous Review

- Data were sufficient for us to examine 14 of the most common symptoms in controlled studies and 10 symptoms in uncontrolled analyses. Five studies included SARS-CoV-2 positive cases from controlled studies.
- The frequency of the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and controls.
- This systematic review and meta-analysis highlights the critical importance of a control group in studies on CYP post SARS-CoV-2 infection.

Since the previous review

- Since that time, additional variants have emerged, and more studies have been conducted. For the purpose of deriving a clinical case definition of Post Covid-19 condition in CYP, it is essential to ensure that the most up-to-date literature is systematically searched, and a meta-analysis of controlled studies conducted to inform decision-making.
- Subsequently we updated the existing review by rerunning searches from from 31 July 2021 to 03 June 2022 in 7 electronic databases and 5 pre-print databases.



Inclusion and Exclusion criteria

Studies meeting the following criteria were included:

- **Population**

CYP aged ≤ 19 years with confirmed evidence of SARS-CoV-2 infection (Reverse transcription polymerase chain reaction (RT-PCR), lateral flow antigen test (LFT) or serology) or probable COVID-19 (clinician defined or suspected COVID-19) who have persistent symptoms as defined by the study authors. To increase generalisability we excluded studies where all participants were admitted to intensive care. For studies which included specialised populations, for example immunocompromised children, we extracted the data but did not include them in any quantitative synthesis.

- **Study type**

Any study design excluding systematic reviews or other reviews. We included published and preprint literature.

- **Outcomes**

The type, prevalence and duration of persistent symptoms in the study population or risk factors for development of persistent symptoms in CYP. We included all symptoms described in each eligible study and included all studies of persistent symptoms regardless of time after infection.

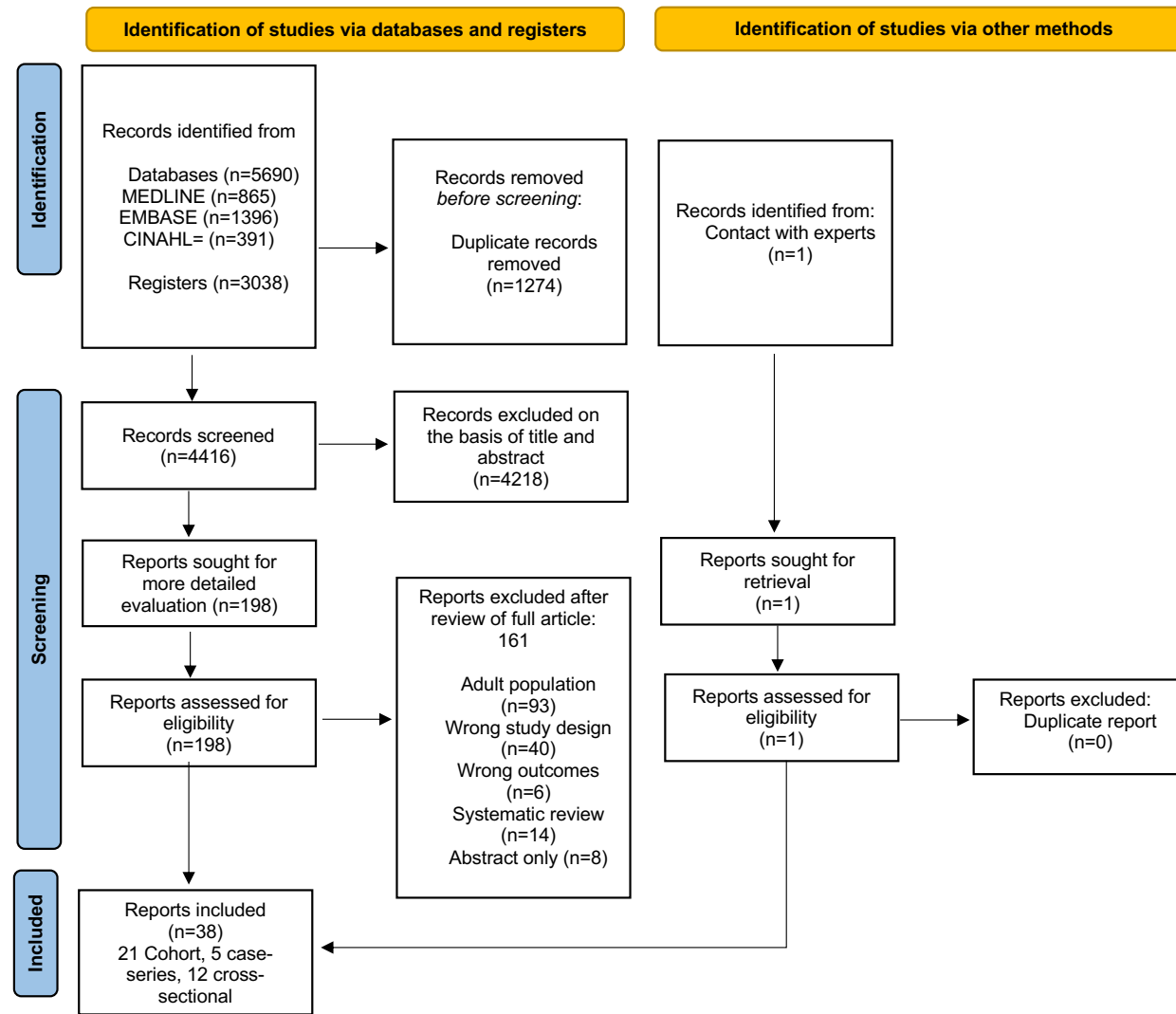


Figure 1. PRISMA diagram to show studies identified between 31 July 2021 and 03 June 2022

Results

- All 38 studies were published during 2021-22 and included participants mostly from high-income countries; Australia, Czech Republic, Denmark, France, Germany, Italy, Israel, Latvia, Norway, Poland, Russia, Saudi Arabia, Spain, Sweden, Switzerland, United Kingdom and United States.
- The number of CYP in each study ranged from 3 to 117,776 CYP with a total of 310,331 participants [Median 142, Interquartile Range (IQR) 61-660] with age ranging from 0-19 years. 16 studies (42%) included less than 100 participants.
- Only eight (21%) of the 38 studies included a control group.



Results

- All studies assessed outcomes at >1 month after COVID-19 infection (range 1- 24 months), with 6 (16%) assessing outcomes at >2 months, 13 (34%) at >3 months and 8 (21%) at >6 months. The median duration of follow-up of symptoms was 91.25 days (IQR 55.5-167.3).
- Combined with the previous 22 studies from the earlier systematic review, a total of 60 studies are included in the updated systematic review; 39 were cohort studies, 15 cross-sectional and 6 case-series. The number of CYP in each study ranged from 3 to 117,776 CYP with a total of 333,472 participants, [median 123.5, IQR (44.5-856.5)].

Results

Across all 60 studies, over 140 symptoms were identified. Many persistent symptoms were reported by < 3 studies and therefore not included in the meta-analysis

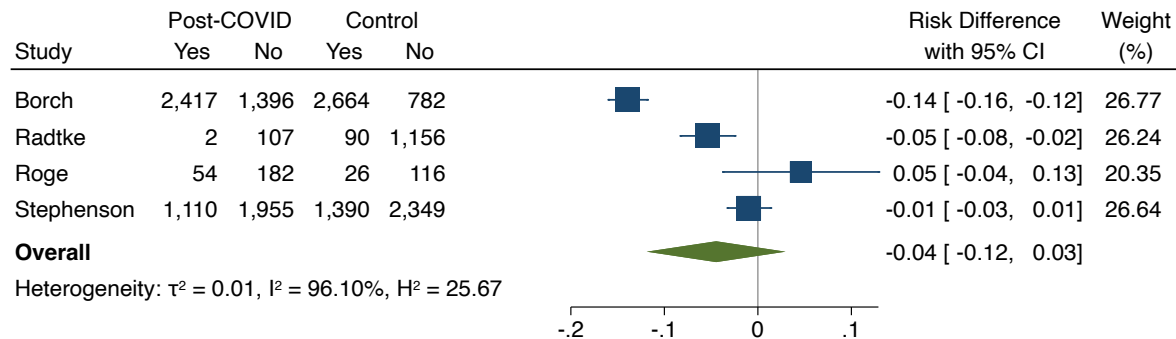
- 1-2 persistent symptoms
- 3 or more persistent symptoms
- Altered smell / taste
- Anxiety
- Appetite loss
- Bleeding
- Blood pressure problems
- Body weight changes
- Cardiovascular problems
- Chest pain/tightness
- Cognitive symptoms
- Constipation
- Cough
- Depression
- Diarrhea
- Difficulties with movement
- Dizziness / fainting / postural symptoms
- Eye symptoms
- Fatigue
- Fever
- Gastrointestinal symptoms
- General symptoms
- Hair loss
- Headache
- Infections
- Inflammatory condition
- Intra-abdominal problems
- Joint pain / swelling
- Lymph node symptoms
- Menstrual symptoms
- Mood changes
- Mucous membrane symptoms
- Muscle symptoms
- Neurological symptoms
- No persistent symptoms
- Obstructive sleep apnoea
- Peripheral symptoms
- Photophobia
- Problems swallowing
- Psychiatric symptoms
- Pulmonary embolism
- Respiratory symptoms
- Sensory symptoms
- Skin symptoms
- Sleep symptoms
- Speech symptoms
- Temperature regulation problems
- Tic symptoms
- Tremor / shakiness
- Upper airway / ENT symptoms
- Urinary problems
- Vomiting / nausea
- Weight loss

Results

26 analyses with 3 or more included studies were undertaken: 2 for persistent symptoms and 24 for individual symptoms.

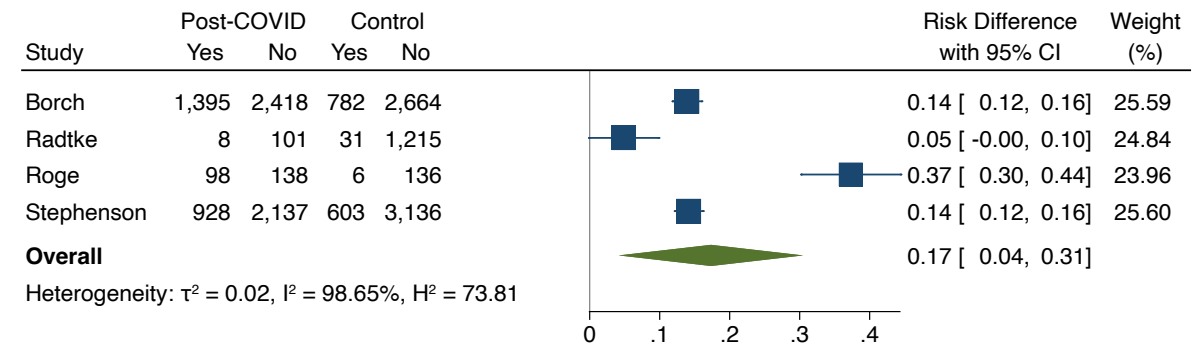
In summary, pooled estimates of proportions with 3 or more persistent symptoms were significantly higher in cases with confirmed SARS-CoV-2 infection (pooled risk difference 17% (95% confidence interval 4-31%) than in controls, with high heterogeneity. There was no significant difference for 1-2 reported symptoms.

Reported symptom: 1-2 persistent symptoms



Random-effects REML model

Reported symptom: 3 or more persistent symptoms

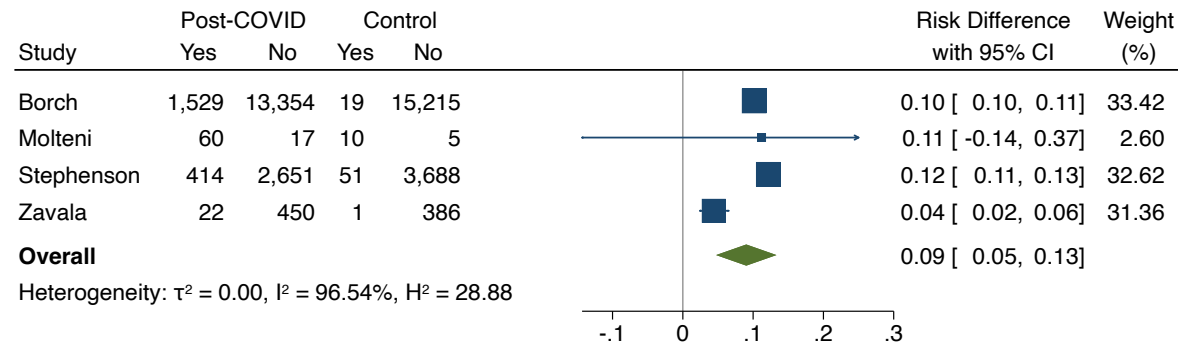


Random-effects REML model

Results

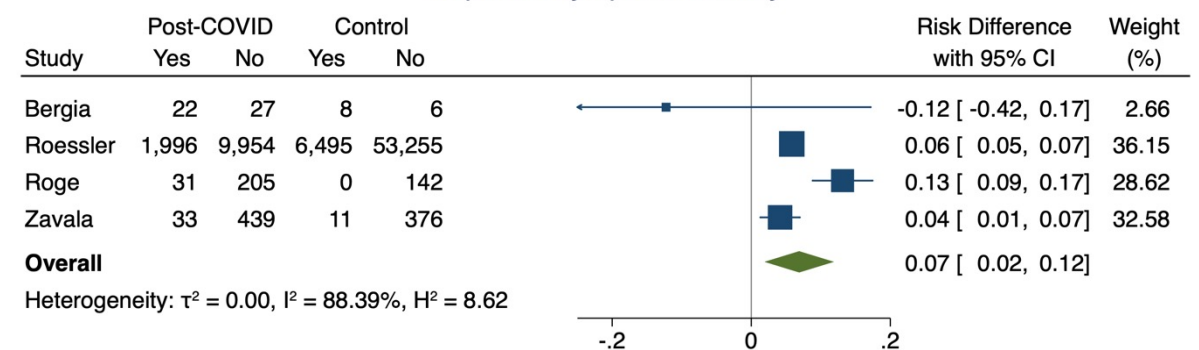
There were significantly higher pooled estimates of proportions of symptoms in cases with confirmed SARS-CoV-2 infection than controls for each of: altered smell/anosmia (risk difference 9%), anxiety (7%), fatigue (6%), headache (6%), loss of appetite (2%), earache/ringing in the ears (2%) and sore eyes (2%).

Reported symptom: altered smell



Random-effects REML model

Reported symptom: anxiety

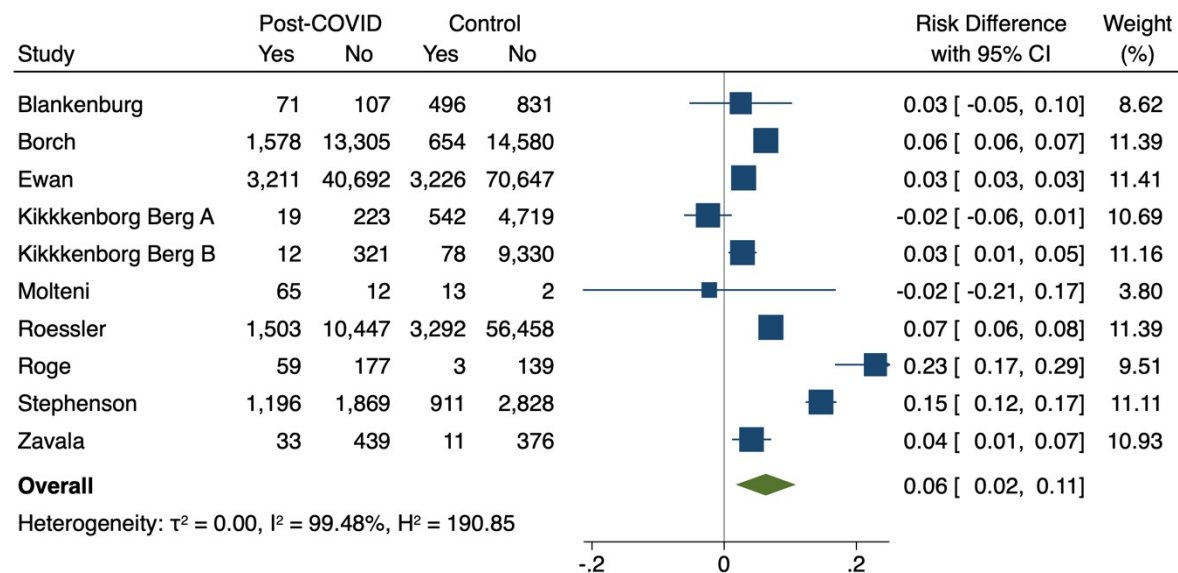


Random-effects REML model

Results

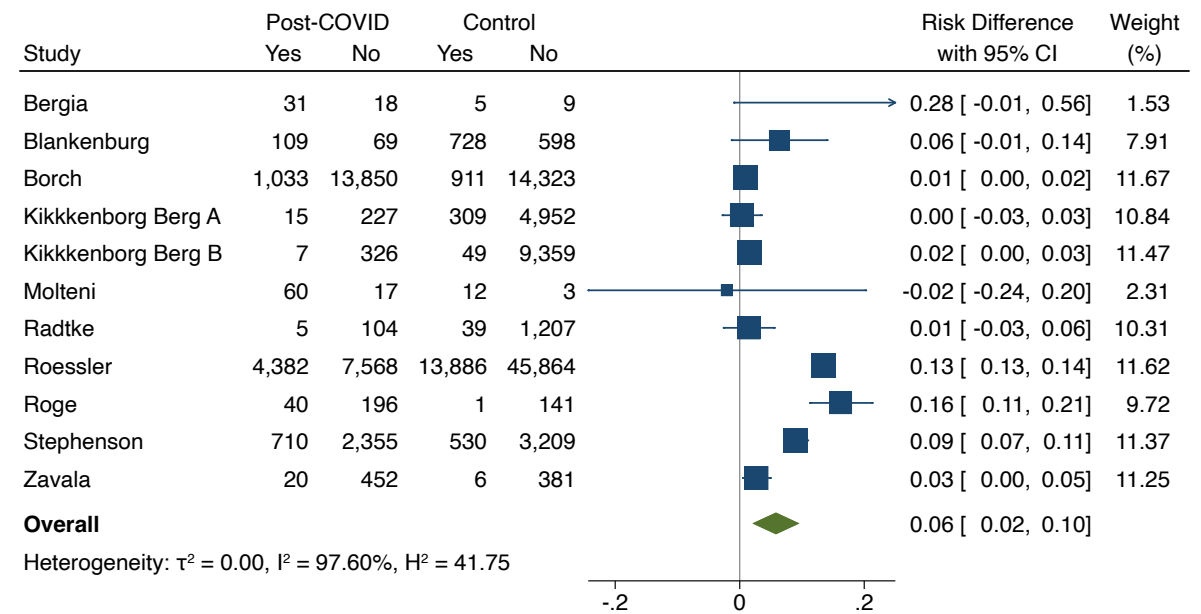
There were significantly higher pooled estimates of proportions of symptoms in cases with confirmed SARS-CoV-2 infection than controls for each of: altered smell/anosmia (risk difference 9%), anxiety (7%), fatigue (6%), headache (6%), loss of appetite (2%), earache/ringing in the ears (2%) and sore eyes (2%).

Reported symptom: fatigue



Random-effects REML model

Reported symptom: headache



Random-effects REML model

Conclusions

- The majority of studies are still uncontrolled and of poor or moderate quality with very few indicating whether symptoms were impairing.
- Given how widespread Covid-19 infection is among children and young people the question of the value of CYP who have never had Covid-19 as control groups for research is an ongoing discussion as well as the practicalities in recruitment for future research.
- Furthermore, almost all studies were from high income countries, limiting generalisability for low- and middle-income countries.

Implications of all the available evidence

Together the available evidence indicates three priority areas.

- I. The need for a core outcome set to allow international comparisons between studies; this work is underway by Munblit and colleagues³.
- II. The need for a clinical case definition of post Covid-19 condition in children and young people. This is the focus of the current work being conducted by WHO.
- III. The need to develop, deliver and evaluate accessible, multi-component interventions for post Covid-19 condition that are acceptable to children and young people, and their parents.

³Munblit D, Buonsenso D, Sigfrid L, Vijverberg SJH, Brackel CLH. Post-COVID-19 condition in children: a COS is urgently needed. Lancet Respir Med. 2022 Jul;10(7):628-629. doi: 10.1016/S2213-2600(22)00211-9.

Thank you!

If you have any questions, please feel free to email me

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