# A CLINICAL CASE DEFINITION FOR POST COVID-19 CONDITION IN CHILDREN AND ADOLESCENTS BY EXPERT CONSENSUS

16 February 2023

World Health Organization

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WHO continues to monitor the situation closely for any changes that may affect this document. Should any factors change, WHO will issue a further update. Otherwise, this document will expire 2 years after the date of this publication.


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# Contents

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# Abbreviations

| | |
|---|---|
| CDC | Centers for Disease Control and Prevention |
| CRE | Compliance Risk management and Ethics (WHO) |
| DOI | declaration of interest |
| COVID-19 | coronavirus disease 2019 |
| ICD | International Classification of Disease |
| IHME | Institute for Health Metrics and Evaluation |
| LMIC | low- and middle-income countries |
| MeSH | Medical Subject Headings |
| PAHO | Pan American Health Organization |
| PCC | post COVID-19 condition |
| QNS | Quality Assurance Norms and Standards (WHO) |
| RT-PCR | real-time polymerase chain reaction |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| WHE | Health Emergencies Programme (WHO) |
| WHO | World Health Organization |

# Abstract

**Background:** The World Health Organization (WHO) published a clinical case definition of post COVID-19 condition, by a Delphi consensus, on 6 October 2021. That process concluded that a separate definition may be applicable for children. It is important to understand the frequency, characteristics and risk factors that lead to post COVID-19 condition, along with its impact on everyday functioning and development of children and adolescents. Long-term outcomes of the condition are currently unknown and need to be studied. For these reasons, a globally standardized clinical case definition is needed.

**Aim:** To develop a globally relevant standardized clinical case definition for children and adolescents by building on the WHO clinical case definition for post COVID-19 condition in adults.

**Methods:** An existing systematic review and meta-analysis completed by University College of London Great Ormond Street Institute of Child Health was updated to identify and map signs, symptoms and functional impairments of post COVID-19 condition in children and adolescents.

Data from this systematic review were mapped to the 12 domains defined by previous Delphi consensus and to develop the WHO case definition for adults and presented to an expert panel during a 1-day virtual meeting moderated by a methodologist. An iterative consensus process during and after the meeting was used to build consensus on the appropriate domains for the case definition in children and adolescents. Five groups of stakeholders were engaged: patient advocates, researchers, clinicians, WHO staff and others. Participants were chosen for balanced representation across age, gender, specialty, area of expertise and geography.

**Results:** 27 experts attended the meeting on 13 September 2022. A clinical case definition for post COVID-19 condition in children and adolescents was developed based on the available scientific data and expert consensus.

**Conclusion:** Informed by the best available evidence and through an expert consensus process, a clinical case definition for post COVID-19 condition in children and adolescents was developed. This definition may change over time as our understanding of the condition evolves, and more high-quality evidence becomes available.

# 1. Research in context

## 1.1 Objectives of the study

During the first wave of the global coronavirus disease 2019 (COVID-19) pandemic in 2020 reports emerged that some individuals had persistent symptoms weeks or months following SARS-CoV-2 infection *(1).*

The Institute for Health Metrics and Evaluation (IHME), estimated that by the end of 2021 globally 3.92 billion individuals had been infected with SARS-CoV-2 and that 3.7% (145 million) had developed post COVID-19 condition as defined by the WHO clinical case definition, with 15.1% (22 million) having persistent symptoms at 12 months after infection onset *(2,3).* While we continue to understand more about COVID-19, there remains limited information regarding medium- to long-term outcomes, particularly in children and adolescents *(4).* Persistent symptoms, complications and sequelae of COVID-19 have been increasingly reported, yet the underlying etiology, prevalence, risk factors and long-term sequelae are still not clearly understood.

This case definition will contribute to the global understanding of the medium- and long-term outcomes for children and adolescents with post COVID-19 condition. It will also:

1. Enable clinicians and researchers to further characterize the condition, assess and evaluate clinical management approaches, and understand how it affects child development and functional status at different ages.
2. Support families and carers seeking medical care via national or local coordinated care pathways to have tailored management based on their needs and have access to relevant specialists.
3. Assist in identifying emerging and effective models of care.

## 1.2 Added value of this case definition

On 6 October 2021, using the term post COVID-19 condition (also known as long COVID), the name proposed by the WHO International Classification of Diseases (ICD) – ICD-10 code (U09) and ICD-11 code (RA02), a clinical case definition was published. The method used to develop this case definition is described in the adult report *(3,5)*.

Development of the case definition underscored the need for a separate definition for children and adolescents. Recognizing the dearth of research in children and adolescents related to post COVID-19 condition, the importance of understanding this evolving condition is a priority for WHO.

The clinical case definition was developed based on pre-defined domains drawing from the adult case definition Delphi consensus and was informed by a commissioned systematic review and meta-analysis on post COVID-19 condition in children and adolescents. An expert panel comprised of patient advocates, clinicians, researchers and others representing all WHO regions was convened and wording was agreed upon via a consensus process with all members of the expert panel.

Post COVID-19 condition in children and adolescents occurs in individuals with a history of **confirmed or probable** SARS-CoV-2 infection, when experiencing symptoms lasting at least **2 months** which initially occurred within **3 months** of acute COVID-19.

Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are **fatigue, altered smell/anosmia** and **anxiety.** Other symptoms have also been reported.*

Symptoms generally have an impact on **everyday functioning** such as changes in eating habits, physical activity, behaviour, academic performance, social functions (interactions with friends, peers, family) and developmental milestones.

Symptoms may be **new onset** following initial recovery from an acute COVID-19 episode or **persist** from the initial illness. They may also **fluctuate** or **relapse** over time.

Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition.

**This can be applied to children of all ages, with age-specific symptoms and impact on everyday function taken into consideration.**

* Symptoms described thus far in children and adolescents are non-specific and can occur with other childhood infections and illnesses. Due to the lack of empirical evidence, a broad list of potential post COVID-19 condition symptoms affecting different organ systems should be considered until more data are available. See below

| | | |
|---|---|---|
| Chest pain | Cognitive difficulties | Cough |
| Diarrhoea | Dizziness | Dyspnoea |
| Earache/ringing in ears | Fever | Headache |
| Insomnia | Joint pain or swelling | Light sensitivity |
| Loss of appetite | Mood swings | Myalgia |
| Nausea | Palpitations | Postural symptoms |
| Rash | Stomach ache | Sore eyes or throat |

### 1.3 Implications of a unified clinical case definition

Having a unified clinical case definition simplifies our global common understanding and communication around post COVID-19 condition as it allows physicians, people with post COVID-19 condition, caregivers, epidemiologists, ministers of health, advocacy groups, policy-makers, governments, teachers, insurance providers and others to be aligned in their understanding and develop informed policy decisions. It also enables researchers to collect and aggregate data in a consistent and reliable manner and to conduct studies using common enrolment criteria, case record forms and a common core outcome set. Numerous uncertainties remain regarding risk factors, symptoms, natural history and sequelae of COVID-19 in children and adolescents, particularly in different childhood age groups. It is important that research and discussions related to the case definition continue to further characterize this condition and improve the management of persons affected.

## 2. Introduction

As of 1 January 2023, over 656 million confirmed cases and over 6.6 million deaths related to COVID-19 have been reported to WHO *(6).* As the number of individuals infected with COVID-19 continues to grow, so do those affected by post COVID-19 condition.

Persistent symptoms, complications and sequelae of COVID-19 have increasingly been reported globally, yet the underlying etiology, prevalence and risk factors are still not clearly understood. To better characterize the post-acute and long-term effects of COVID-19, WHO developed a case definition for post COVID-19 condition in April 2021. One purpose of this was to ensure that all stakeholders were aligned in their understanding; using one name and definition to enhance global common understanding of this condition. To develop the case definition a Delphi methodology was undertaken that included 12 domains (**Annex 1**) *(3).* This version was developed by persons living with post COVID-19 condition, researchers and others representing all WHO regions, with the understanding that a separate definition may be needed for children and adolescents. The case definition was published on 6 October 2021 *(3,5).*

Children and adolescents are more likely to be asymptomatic or develop mild illness following SARS-CoV-2 infection, compared with adults *(7).* As a result, the symptoms they experience in the post-acute period and their impact may differ from adults. For this reason, it is important to have a case definition specifically for children and adolescents. This will allow risk factors associated with post COVID-19 condition to be identified and to understand the prevalence and duration of long-term symptoms, and the clinical management required among children and adolescents infected with COVID-19.

# 3. Methods

## 3.1 Design

The clinical case definition for post COVID-19 condition in children and adolescents was developed by adapting the previously published WHO case definition of adults which had been developed using a two-phase Delphi process *(3,5).* The 12 "information domains" developed in this adult definition were used to organize the empirical information (**Annex 1**).

An update to an existing systematic review and meta-analysis of empirical studies on post COVID-19 condition in children and adolescents was commissioned by WHO and performed by the University College of London Great Ormond Street Institute of Child Health *(8)*. Results were available from studies published between 1 December 2019 and 3 June 2022 and included 60 studies (38 cohort studies, 16 cross-sectional studies and 6 case series) with 12 "controlled" studies included in the meta-analysis (**Annex 2**). The data from the systematic review were mapped to the 12 domains and variables from the previously published case definition Delphi process. This information was presented to and discussed by an expert panel during a meeting on 13 September 2022. A clinical case definition was developed based on an iterative consensus process. The phases of this project are described below.

## 3.2 Systematic review and meta-analysis

The University College of London Great Ormond Street Institute of Child Health conducted an initial systematic review and meta-analysis analysing persistent symptoms following SARS-CoV-2 infection in children and adolescents from 1 December to 31 July 2021 that was published in November 2021 in the *Journal of Infection (8).* In May 2022, WHO commissioned an update to this systematic review and meta-analysis to evaluate the evolving evidence for post COVID-19 condition in children and adolescents. The outcomes assessed in the review included the type, prevalence and duration of persistent symptoms in children and adolescents (defined as persons ≤ 19 years of age) with confirmed or probable SARS-CoV-2 infection.

Studies published in any language were included in the updated review and could have any design. Published studies, preprints or grey literature were searched using databases MEDLINE, EMBASE, CINHAL, Cochrane COVID-19 study registry, ProQuest coronavirus research database, COVID-19 Living Overview of the Evidence (L-OVE) subset of Episteminokos, WHO Global literature on coronavirus disease, MedRxiv, BioRxiv, ResearchSquare, Pre-prints.org and ZBMed's preview database on COVID-related pre-prints. Medical Subject Heading (MeSH) terms and free words included for the concepts were "COVID-19" "Children" "Adolescents" "Long COVID" "Post COVID" "Sequelae" and "Persistent symptom." The full search strategy and methodology is available in **Annex 2**.

Data reported from the studies included year, study design, study inclusion criteria, sample size, country, age of people with post COVID-19 condition, gender, ethnicity, method of SARS-CoV-2 diagnosis, baseline severity of COVID-19, duration of follow-up for post COVID-19 condition, pre-existing co-morbid medical conditions, symptoms investigated, symptom prevalence, method of symptom reporting and measurement tools used.

A total of 7773 records were screened with 7503 excluded based on title and abstract. Of the 270 remaining citations, 60 were included in the systematic review. Of the 60 studies (38 cohort studies, 16 cross-sectional studies and 6 case series), 22 included a control group and 12 were included in the meta-analysis (**Annex 2**). Children and adolescents following SARS-CoV-2 infection (cases) were compared with those without a history of COVID-19 or who had tested negative for SARS-CoV-2 (controls). Random effects meta-analyses were used to examine the pooled risk difference in prevalence of each symptom or symptom-combination in cases compared with controls. Given that different types and numbers of symptoms were reported by different studies, meta-analysis was only undertaken for those symptoms where at least three studies provided data. Forest plots were constructed to illustrate the risk difference in prevalence of symptoms reported by fewer than three controlled studies and were broadly grouped according to affected body area/function; no meta-analysis was performed.

### 3.3 Expert panel participants

Primary end-users of the clinical case definition for post COVID-19 condition in children and adolescents are people with post COVID-19 condition, physicians, caregivers, epidemiologists, ministers of health, policy-makers, advocacy groups, insurance providers, teachers, governments and others. To develop informed and effective policy, it is important for these groups to be aligned in their understanding. For this reason, we aimed to have diverse representation of participants on the expert panel including paediatricians with expertise in general paediatrics, child development, infectious disease, allergy and immunology, critical care, neurology, rehabilitation and rheumatology. We also included patient advocates, researchers, epidemiologists, policy-makers and others from countries representing all WHO regions and World Bank income levels.

Members for the expert panel were identified in a comprehensive manner which included:

- literature review;
- nominations from WHO regional office case management officers;
- members of the WHO COVID-19 clinical characterization and management research working group on post COVID-19 condition;
- members of Long Covid SOS and Long Covid Kids patient groups; and
- clinician and patient researchers who attended the WHO webinar on post COVID-19 condition "Expanding our understanding of post COVID-19 condition: children and adolescents" *(9)*.

127 individuals were identified as potential experts for the consensus meeting. After review by the WHO post COVID-19 condition Steering Committee, the list was narrowed to a group of 39 individuals which was balanced across gender, region, race, ethnicity and expertise. Eligible panel members were sent an online electronic mail invitation to participate in the consensus meeting, along with an explanation of objectives, instructions and outputs on 15 August 2022. Of the 39 invited experts, 27 accepted the invitation to attend the expert panel meeting which comprised 16 females and 11 males from all WHO regions. The characteristics of the 27 participants by stakeholder group, gender and WHO region are presented in **Annex 3**. There were 14 clinical researchers, five clinicians, three researchers, three patient advocates, one paediatric rehabilitation expert and one developmental paediatrician. The six WHO regions were equally represented with four from the African Region; five from the Region of the Americas; five from the South-East Asia Region; six from the European Region; four from the Eastern Mediterranean Region, and three from the Western Pacific Region.

Consent to participate in the meeting was implied by participants accepting the invitation from WHO and completing DOI and confidentiality forms. WHO technical staff collected and reviewed biographies and DOIs. Consultation with WHO's Quality Assurance Norms and Standards (QNS) methods support team and Compliance, Risk management and Ethics (CRE) unit were obtained, when necessary. Experts were able to withdraw from the panel at any time.

### 3.4 Consensus meeting procedures

Preparations for the expert panel meeting began in July 2022 with the methods chair for the meeting, the clinical lead for the WHO COVID-19 response and the WHO core Steering Committee for post COVID-19 condition. The group met virtually once or twice a week in advance of the consensus meeting in September 2022 to review results and clarify questions related to the systematic review, map data to the 12 pre-defined domains from the adult case definition, anticipate potential questions during the meeting, and discuss how to best present the data to the expert panel. During this time, regular communication with the systematic review team was maintained to clarify questions, discrepancies or queries as needed to ensure the most accurate and transparent data were presented to the expert panel.

Prior to the expert panel meeting all participants were sent the following documents to review:

- The WHO report published on 6 October 2021 "A clinical case definition of post COVID-19 condition by a Delphi consensus" *(3)*.
- Publication of the WHO adult clinical case definition in *Lancet Infectious Diseases* "A clinical case definition of post-COVID-19 condition by a Delphi consensus" *(5)*.
- A copy of the slide deck presented during the meeting, which was the basis for discussion to develop the clinical case definition.

On 13 September 2022, the expert panel consensus meeting for the clinical case definition for post COVID-19 condition in children and adolescents was held virtually from 13:00–17:00 Central European Time. At the start of the meeting the Delphi methodology for the adult case definition was presented and reviewed with the panellists. Representatives from the University College of London Great Ormond Street Institute of Child Health described the methods used to perform the systematic review and meta-analysis on post COVID-19 condition in children and adolescents. Members of the expert panel were asked to consider the following prior to the presentation of scientific data relating to each of the 12 domains:

1. Did they understand the domain, and if the data being presented for children and adolescents fit within it.
2. Consider if there were enough data to fulfil the domain to include it in the case definition.
3. Decide whether the domain should be included in the case definition.

After reviewing these considerations, the meeting chair presented data corresponding to the domain being discussed and encouraged participants to freely share their insights and views. This process was followed for all 12 domains to ensure a consistent process. In most cases there was a dearth of evidence, therefore the input and experiences of the expert panel were relied on to reach a consensus. For the purposes of developing this case definition, consensus was defined as having general agreement amongst members of the expert panel. Where members were unable to reach a universal agreement, this is documented in the text. For the case definition, consensus was achieved by non-dissent, That is sufficient time was allocated for robust discussion and debate, with members of the WHO Steering Committee monitoring the online discussion and taking notes. The chair encouraged all members to voice their opinions, and all were discussed to ensure members were in agreement with the decisions made. From an initial, comprehensive list of 12 domains, consensus was reached by the panel for seven domains as being relevant to the case definition for children and adolescents (**Annex 1**).

Based on the meeting discussion, the WHO Steering Committee developed a draft case definition for review and discussion, which was presented at the end of the meeting.

### 3.5 Post-meeting feedback process, impact survey

After the consensus meeting, members of the WHO Steering Committee further refined the text of the case definition to reflect feedback provided by the expert panel.

All participants were sent a copy of the case definition and invited to provide comments via an anonymous online survey. All comments were reviewed and considered by the WHO Steering Committee in two meetings.

Participants were also asked to take an anonymous impact analysis survey of the case definition. They were asked to assess whether the case definition met the objectives of the consensus meeting. To do so, they completed a five-point Likert scale evaluating the following aspects of the case definition:

- overarching reasons
- global use
- use and impact on jurisdiction of work.

Participants were invited to provide anonymous comments, suggestions or clarifications. All feedback provided by the expert panel on the impact analysis survey was recorded in an Excel spreadsheet. The WHO Steering Committee met to review and adjudicate each comment point-by-point before developing an updated case definition. A copy of the post-meeting survey is available in **Annex 4**.

## 4. Results

All scientific data presented to the expert panel are available in **Annex 2** and below is a description of the consensus meeting results presented by domain.

### 4.1 Symptoms and impairments

Data were presented to the panel which showed that the proportions of people with post COVID-19 condition with altered smell/anosmia, anxiety, fatigue, headache, loss of appetite, earache/ringing in the ears and sore eyes is more likely in a post COVID-19 condition cohort compared with controls who are children and adolescents who have not had COVID-19. Heterogeneity was low for loss of appetite, earache/ringing in the ears and sore eyes and heterogeneity was high for altered smell/anosmia, anxiety, fatigue and headache (**Table 1**).

**Table 1.** **Symptoms amongst children and adolescents with post COVID-19 condition cohort compared with controls**

| Symptom | Number of studies | Post COVID-19 Condition (N) | Control (N) | Frequency Difference [Confidence Interval] | $I^2$ |
|---|---|---|---|---|---|
| Altered smell/anosmia | 4 | 16,472 | 19,294 | 9% [0.05, 0.13] | 96% |
| Anxiety | 4 | 10,625 | 53,779 | 7% [0.02,0.12] | 88 % |
| Fatigue | 12 | 75,899 | 170,480 | 6% [0.04,0.08] | 97% |
| Headache | 11 | 25,182 | 80,046 | 2% [0.02, 0.10] | 97% |
| Loss of appetite | 6 | 1,299 | 14,981 | 2% [0.01, 0.03] | 0.01% |
| Earache/ringing in the ears | 3 | 3,569 | 4,103 | 2% [0.01, 0.03] | 23% |
| Sore eyes | 3 | 3,390 | 3,998 | 2% [0.01, 0.03] | 0.00% |

- The proportions of patients with altered smell/anosmia, anxiety, fatigue, headache, loss of appetite, earache/ringing in the ears, and sore eyes is **more likely** in a post COVID-19 condition cohort compared to controls
- Heterogeneity is **low** for loss of appetite, earache/ringing in the ears and sore eyes
- Heterogeneity is **high** for altered smell/anosmia, anxiety, fatigue, and headache

Panel members agreed that children and adolescents present with a wide range of symptoms such as anosmia, fatigue, loss of appetite, headache, anxiety (including school refusal and social anxiety), shortness of breath, chronic gastrointestinal symptoms, rash, food intolerances and allergies, cognitive dysfunction, sensory abnormalities dizziness, nausea, changes in eating habits, behavioural changes (e.g. irritability, withdrawing, depression) and regression of developmental milestones.

It was agreed that symptoms should be well defined and have an impact on the daily functioning of the child or adolescent. Participants noted a challenge in assessing the symptoms and their impact when reported by carers and not the people with post COVID-19 condition themselves (**Table 2**). Thus, it is unclear how comprehensive and accurate symptom reporting was, particularly for younger children and infants.

**Table 2.** **Source of reported symptoms**

| Source of Information | Studies in Systematic Review (n=60) | Studies in Meta-analysis (n=12) |
|---|---|---|
| **Self-reported** | **17 (28%)** | **8 (66%)** |
| Caregiver and/or child or young person | 6 | 1 |
| Caregiver | 5 | 4 |
| Child or young person | 4 | 3 |
| Unspecified | 2 | 0 |
| **Interviews conducted by** | **29 (48%)** | **2 (16%)** |
| Conducted by medical professional | 14 | 1 |
| Unspecified who conducted interview | 15 | 1 |
| **Interviews conducted with** | | |
| Caregiver | 3 | 1 |
| Caregiver and/or child or young person | 3 | 1 |
| Child or young person | 0 | 0 |
| Unspecified | 23 | 0 |
| **Databases or medical records** | **11(18%)** | **2 (16%)** |
| **Survey of Pediatricians** | **1(2%)** | **0** |
| **Unclear** | **2(3%)** | **0** |

The inclusion of major and minor symptoms as criteria to define post COVID-19 condition was also considered and discussed. No consensus was reached on what these would be since many potential symptoms described thus far in children and adolescents are non-specific and can occur with other childhood infections and illnesses, as well. It was the decision of the panel that due to the lack of empirical evidence a broad list of symptoms should be considered until more data are available.

After a lengthy discussion consensus was reached to include altered smell/anosmia, fatigue and anxiety in the case definition. It was felt that these symptoms were important and impactful as they had the highest differences in frequency in those with post COVID-19 condition compared with controls based on the available empirical evidence. It was noted that "anxiety" is a problematic symptom in children, as young children often present their somatic unwellness with "somatopsychic" symptoms and adolescents may be anxious for many reasons that might not directly be virus-related. Currently, the pathophysiologic understanding and the meaning of the observed increased frequency of "anxiety" in children after an initial COVID-19 infection is subject to scientific debate and should be studied closer in prospective research studies. The panel recommended that the choice for these symptoms should be closely monitored and be re-evaluated as new information becomes available. The spectrum of symptoms should be updated as needed based on emerging empirical data.

### 4.2 Minimum number of symptoms

The panel reviewed data presented with a weak signal suggesting that three or more symptoms occur more frequently in children and adolescents with post COVID-19 condition compared with controls. This evidence included analysis from only three studies and was deemed to be low certainty.

Although some panel members reported having seen people with post COVID-19 condition in their clinical practice with multiple symptoms, there was a consensus that a single symptom, if impactful enough, should be enough to make a diagnosis of post COVID-19 condition.

### 4.3 Clustering of symptoms

No studies included in the meta-analysis demonstrated clustering of symptoms is more common in people with post COVID-19 condition. A few panel members reported noticing clustering of symptoms, such as such as fatigue and shortness of breath, in their clinical practice. Given limited data, experts felt there wasn't enough evidence to include clustering of symptoms in the case definition.

### 4.4 Impact on everyday functioning

There were four studies included in the meta-analysis that assessed impact of post COVID-19 condition on functional status. Each study used different tools to assess functional status and results were variable. Given the current limited data on the impact of symptoms on daily functioning among children and adolescents, the discussion relied on the expert opinion of the panel members.

The participants agreed functional status is important when considering a diagnosis of post COVID-19 condition and should be included in the case definition. Experts reported witnessing changes in eating habits, physical activity, participation in sports/athletics, behaviours, educational performance (school, cognitive), social functions (friends, relationships, family and play) and reaching and maintaining developmental milestones.

There is likely an age-specific nature to these impacts but currently there is lack of scientific evidence to delineate what they are. Other factors raised when assessing children's functional status is the importance of understanding the impact of the pandemic and related measures (e.g. lockdown, school closures) compared with those related to the individual's infection from SARS-CoV-2. It was agreed that disentangling these factors is challenging, and that in some cases impact on functional status could be multifactorial.

### 4.5 History of SARS-CoV-2 infection and laboratory confirmation

One component of the case definition that elicited vigorous discussion was whether the case definition should only apply to children and adolescents with laboratory-confirmed SARS-CoV-2 infection or whether those with "probable", clinical COVID-19 should also be included. The panel discussed if the available evidence regarding symptoms should still apply if a child with no prior positive diagnostic test developed symptoms of post COVID-19 condition. Studies included in the meta-analysis used reverse transcriptase polymerase chain reaction (RT-PCR), serology and lateral flow test (LFT) to test children for SARS-CoV-2 and compared those with a positive test (cases) to those with a negative test (controls) and generated (historical) symptom prevalence differences.

The rationale for including only those with laboratory-confirmed SARS-CoV-2 is that children develop an array of viral respiratory infections, thus including those with probable (e.g. not tested) COVID-19 may lead to overdiagnosis of post COVID-19 condition. Many felt that those with probable COVID-19 should be included in the case definition since there was lack of testing early in the pandemic which might exclude certain individuals. Additionally, people with post COVID-19 condition in resource-limited countries may not have access to testing and children may be asymptomatic and have unrecognized infection but still may develop post COVID-19 condition.

While members of the panel decided to include children and adolescents with both laboratory-confirmed and probable SARS-CoV-2 infection in the case definition, it was noted that in future research studies, to increase the accuracy and specificity of the results, only laboratory-confirmed cases should be used.

### 4.6 Minimum time period from onset of symptoms

There was no evidence to help understand what the minimum time period from onset of symptoms was in children and adolescents who developed post COVID-19 condition compared with controls. Members of the expert panel generally agreed that the acute phase of COVID-19 lasted approximately 4 weeks but that symptoms can continue as people are developing post COVID-19 condition.

In the adult case definition, the minimum time period from onset of symptoms is 3 months. There was concern that using the same duration in children could have a greater negative impact and reduce access to services (e.g. school support) until a child or adolescent reached this threshold. It was agreed that these timeframes should not exclude people with post COVID-19 condition from accessing care pathways sooner, particularly if they have symptoms that are impacting functional status and are concerning for post COVID-19 condition.

Members of the panel agreed the minimum time period from onset of symptoms should be > 1 month or persistence from the initial illness itself. It was also agreed that diagnostic workup and treatments should be accessed before 3 months based on the clinical symptoms and needs of the child or adolescent.

### 4.7 Minimum duration of symptoms

Most studies included in the meta-analysis reported symptoms following SARS-CoV-2 infection at a set time period rather than detailing the time from infection to symptom resolution. In the absence of data, a minimum duration of symptoms of 2–3 months was initially proposed for the case definition. Upon review of the draft case definition many panel members commented that 2–3 months was unclear and based on feedback, discussion, and acknowledgement of previously stated concerns regarding delayed access to essential services, the minimum duration of symptoms was changed to 2 months.

### 4.8 Time course nature of symptoms

Most scientific studies included in the meta-analysis reported symptoms at a single follow-up time point rather than describing them over time. This made it difficult to assess whether symptoms were static or dynamic. Participants described seeing people with post COVID-19 condition with fluctuating and relapsing symptoms in their clinical practice. It was suggested the absence of evidence was not a reason to exclude the time course nature of symptoms from the case definition but rather that this highlighted another area where more research is needed.

### 4.9 Sequelae of well described complications of COVID-19

No evidence was presented for this domain. It was agreed that sequelae of well described complications due to the acute COVID-19 infection should not be included in the case definition.

### 4.10 Symptoms not explained by an alternative diagnosis

No evidence was available for this domain. Members of the expert panel had a lengthy discussion about whether to include in the case definition that “post COVID-19 condition cannot be explained by an alternative diagnosis.” Participants raised concerns that making post COVID-19 condition a diagnosis of exclusion in the case definition could have a negative impact on people with post COVID-19 condition, families, health professionals and health systems. This could lead to unmanageable health care costs for people with post COVID-19 condition and families due to unnecessary tests, delays in initiating treatment, and use of valuable and limited health care resources. This was raised as a particular concern for people with post COVID-19 condition, families and health workers in resource-limited countries where there is already a shortage of human and system-wide resources and may also subject people with post COVID-19 condition to unnecessary testing. Participants felt strongly that the case definition needed to be clear that alternative diseases should be investigated and treated but this should not prevent access to care pathways for post COVID-19 condition.

### 4.11 Application of definition to different populations

Despite the lack of evidence, particularly in younger age groups, it was agreed that this case definition should apply to children and adolescents of all ages. Participants felt that specific information, for example on assessment for each age category, should be included as footnotes.

### 4.12 Results of impact analysis survey

The impact analysis survey was sent to all 27 experts who participated in the consensus meeting and was completed by 21 (78%) with the results shown in **Table 3**. When asked to evaluate the overarching reasons for the case definition > 95% strongly agreed or agreed the case definition for post COVID-19 condition in children and adolescents was:

- Clear and easily applicable for physicians, people with post COVID-19 condition, caregivers, epidemiologists, ministers of health, policy-makers and governments.
- Aimed at improving understanding and communication of this condition.
- Will allow all stakeholders to be aligned in their understanding and informed to make policy decisions for better alignment in understanding of this condition.
- Enables researchers to aggregate data in a consistent and reliable manner.

When asked about the global use of the case definition > 95% of participants strongly agreed or agreed it would help health care professionals with clinical management and care. They also agreed it would help families, children, adolescents and researchers who study post COVID-19 condition.

While developing this case definition we wanted to establish that its use would not have a negative impact. More than 85% of participants strongly disagreed or disagreed that the application of the case definition in their jurisdiction of work would have a negative impact on children, adolescents, families, health professionals, or the health system.

**Table 3.** **Impact analysis survey results**

| | Strongly disagree | Disagree | Neutral | Agree | Strongly agree |
|---|---|---|---|---|---|
| **Overarching reasons for this case definition** | | | | | |
| The case definition for post COVID-19 condition for children and adolescents is **clear and easily applicable** for physicians, patients, caregivers, epidemiologists, ministers of health, policy-makers, governments. | | | 1 (5%) | 13 (62%) | 7 (33%) |
| Applying and implementing this case definition will **improve our understanding and communication** of post COVID-19 condition in children and adolescents. | | | | 9 (43%) | 12 (57%) |
| Applying and implementing this case definition will allow physicians, patients, caregivers, epidemiologists, ministers of health, policy-makers, governments to be **aligned in their understanding** of post COVID-19 condition in children and adolescents and informed to make policy decisions. | | | | 12 (57%) | 9 (43%) |
| Applying and implementing this case definition will enable researchers to aggregate data in a **consistent and reliable manner** and to conduct interventional studies using common enrolment criteria, case record form and core outcome sets. | | | | 12 (57%) | 9 (43%) |
| **Global use of this case definition** | | | | | |
| This case definition will help health care professionals with the **clinical management and care** of children and adolescents with post COVID-19 condition. | | 1 (5%) | | 12 (57%) | 8 (38%) |
| Applying this case definition will help **families**, **children and adolescents** with post COVID-19 condition. | | | 1 (5%) | 11 (52%) | 9 (43%) |
| Applying this case definition will help **researchers** to study post COVID-19 condition in children and adolescents. | | 1 (5%) | | 10 (47.5%) | 10 (47.5%) |
| **In your jurisdiction of work** | | | | | |
| Application of this case definition will *put pressure on/harm/negatively impact (e.g. clinically, financially, resources)* **children and adolescents** with post COVID-19 condition and their **families.** | 8 (38%) | 10 (47.5%) | 2 (9.5%) | | 1 (5%) |
| Application of this case definition will *pressure on/harm/negatively impact (e.g. clinically, financially, resources)* **health professionals** providing care to children and adolescents with post COVID-19 condition. | 9 (42.5%) | 10 (47.5%) | | 1 (5%) | 1 (5%) |
| Application of this case definition will *put pressure on/harm/negatively impact (e.g. clinically, financially, resources)* the **health system.** | 9 (42.5%) | 8 (38%) | 2 (9.5%) | 1 (5%) | 1 (5%) |

Results from the impact analysis survey and all 24 received written comments to the clinical case definition were reviewed and adjudicated point-by-point during a WHO Steering Committee meeting in November 2022. An updated case definition was developed.

The updated case definition, along with a meeting report, was sent to all members of the WHO Steering Committee, the expert panel, and three external reviewers for feedback. After the time for review all comments were compiled in an Excel spreadsheet and the core members of the WHO Steering Committee met in December 2022 to review, address, and respond to all comments. At this time a final case definition was developed.

# 5. Discussion

We present a clinical case definition of post COVID-19 condition in children and adolescents that can be applied by stakeholders to improve the overall care of persons living with post COVID-19 condition by increasing recognition, research and rehabilitation needs.

Since there continues to be a dearth of scientific data related to post COVID-19 condition in children and adolescents, as information related to the clinical presentation, symptoms and the sequelae emerges, our case definition will evolve. It is important for all stakeholders to remember that post COVID-19 condition has only been known for a few years. It remains a new and evolving condition where much learning and research is being done to understand which patients are at risk, how to best treat the condition, and the long-term effects. However, there are numerous research gaps that need to be addressed to help further understand this condition in all populations, particularly in resource-limited countries where there are minimal data published to date.

## 5.1 Strengths and limitations

This study has several strengths: it is built on the Delphi consensus methodology that was used to develop the adult case definition; we commissioned a systematic review and meta-analysis to understand the data available on post COVID-19 condition specific to children and adolescents; and a multi-disciplinary group of experts from around the world who work with this patient population was convened to build consensus on the case definition. In addition, an impact analysis survey was performed to assess the potential applicability and usefulness of the case definition and received mostly positive responses. The aim of this survey was to ensure we did not develop a case definition that could cause harm and specifically surveyed our expert panel participants about this.

There are various limitations regarding the methodology used to develop this case definition. Most importantly, we did not undertake a new Delphi consensus process when developing this case definition. Rather, we adapted the original case definition by using information obtained from a systematic review and expert consensus. Had we undertaken a new Delphi consensus process different domains may have been deemed important for children and adolescents that were not considered for adults. A Delphi process may have helped us identify a different list of symptoms considered important beyond those from the systematic review. Although we did have 27 individuals on our expert panel who represented a broad range of expertise, regions, gender and expertise, having a larger more inclusive panel, particularly with individuals from resource-limited countries where there continues to remain a paucity of information, may have impacted the case definition.

There was a dearth of data specific to children and adolescents with most of the information generated in widely heterogeneously populations of not previously healthy children and adolescents mostly > 5 years of age. Few studies have been performed with control groups, which is something that will become increasingly challenging as a greater proportion of the population has been infected with COVID-19. Additionally, study designs and procedures are highly variable as there are non-uniform definitions of symptoms, control groups do not age-match or risk-match the post COVID-19 condition groups, and the source of reporting of symptoms is variable (e.g. in some studies symptoms are reported by carers and in others by people with post COVID-19 condition). Other limitations of the data include a lack of symptom collection or data analysis by age groups, limited data on impact on daily functioning, no data on duration and resolution of symptoms, and, importantly, limited data from resource-limited countries.

Based on these limitations, the definition presented here should be considered a description based on the information presented and the expert opinion of the panel on 13 September 2022. The symptoms, along with the impact on daily functioning, should be considered and each potential person should be assessed on a case-by-case basis. We remind all stakeholders this is an evolving field that requires more understanding, information and research, so it is important to integrate emerging evidence to help advance this field.

### 5.2 Future implications and research priorities

The field of post COVID-19 condition in children and adolescents is evolving and changing. Thus, it is important for all stakeholders to remember and understand that there are uncertainties, and still much to learn. The limited data point to key research priorities pertaining to children and adolescents; these were also identified by our expert panel:

- Understanding the presentation, natural history and prevalence of post COVID-19 condition in resource-limited countries.
- How symptoms impact daily functioning at different ages.
- If certain symptoms cluster together.
- Whether a minimum number of symptoms are needed to make a diagnosis of post COVID-19 condition.
- Understanding the duration of symptoms and how they may change over time.
- Understanding the impact of variants of concern and re-infection.

### 5.3 Next steps

WHO plans to distribute and follow the uptake and use of the case definition in the following ways:

- Disseminate the case definition through WHO regional focal points, post COVID-19 condition experts, advocates, and other partners/stakeholders.
- Update the evidence review on post COVID-19 condition in children and adolescents as evidence emerges on symptoms and duration, impact by age group, and on functional status, and becomes clearer.
- Work with people with post COVID-19 condition, families, health workers, researchers, and others to understand the use of this case definition.
- Encourage stakeholders to contribute anonymized patient data to the WHO Global Clinical Platform on post COVID-19 condition to understand the applicability of the case definition globally.
- Update the case definition as needed based on new evidence pertaining to post COVID-19 condition in children and adolescents.

## 6. Conclusion

Post COVID-19 condition in children and adolescents is one of the lasting legacies of the pandemic. There are numerous impending and unanswered questions surrounding COVID-19 and its medium- and long-term sequelae. An important step in trying to understand what these might be is to have a uniform case definition to help understand the true prevalence of the condition so that, as new data emerge, the consequences of COVID-19 in individuals can be appreciated, and new policies aimed to help those affected can be evaluated. And, most importantly, clinicians can use this clinical case definition to recognize individuals who may have this condition and link them to the appropriate care pathway.

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# Annex 1: Clinical case definition domains

**Domains from the adult clinical case definition for post COVID-19 condition**

| Domain no. | Domain name |
|---|---|
| 1 | History of SARS-CoV-2 infection |
| 2 | SARS-CoV-2 laboratory confirmation |
| 3 | Minimum time period from onset of symptoms (or from date of positive test for asymptomatic) 3 months |
| 4 | Minimum duration of symptoms at least 2 months |
| 5 | Symptoms and/or impairments |
| 6 | Minimum number of symptoms |
| 7 | Clustering of symptoms |
| 8 | Time-course nature of symptoms (fluctuating, increasing, new onset, persistent, relapsing) |
| 9 | Sequelae of well described complications of COVID-19 (stroke, heart attack, etc.) |
| 10 | Symptoms cannot be explained by an alternative diagnosis |
| 11 | Application of definition to different populations |
| 12 | Impact on everyday functioning |

**Domains for the clinical case definition for post COVID-19 condition in children and adolescents, reached by consensus**

| Domain no. | Domain name |
|---|---|
| 1 | History of SARS-CoV-2 infection |
| 2 | SARS-CoV-2 laboratory confirmation |
| 3 | Minimum time period from onset of symptoms (or from date of positive test for asymptomatic) 3 months |
| 4 | Minimum duration of symptoms at least 2 months |
| 5 | Symptoms and/or impairments |
| 6 | Time-course nature of symptoms (fluctuating, increasing, new onset, persistent, relapsing) |
| 7 | Impact on everyday functioning |

# A systematic review and meta-analysis conducted by UCL Great Ormond Street Institute of Child in collaboration with the World Health Organization

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## Abstract

**Background:** There is emerging evidence of Post COVID-19 Condition in children and adolescents. We sought to update our original systematic review and meta-analysis to assess the current and evolving evidence on the long-term effects of COVID-19 by estimating the prevalence, risk factors, type and duration of symptoms in children and adolescents following SARS-CoV-2 infection.

**Methods:** A systematic literature search was conducted using databases MEDLINE, EMBASE, CINHAL, Cochrane COVID-19 study registry, ProQuest coronavirus research database, COVID-19 Living Overview of the Evidence (L-OVE) subset of Episteminokos, World Health Organization (WHO) Global literature on coronavirus disease, and ZBMed's preview database of COVID-related pre-prints to identify studies published from July 31, 2021 to June 3, 2022 to update the systematic review for studies identified from December 1, 2019 to July 31, 2021. Eligible studies were those reporting on children and adolescents (those aged ≤19 years) with confirmed or probable diagnosis of SARS-CoV-2 presenting with any symptoms persisting beyond the acute phase of their illness.

**Findings:** 60 studies were included in this systematic review. 38 were cohort studies, 16 cross-sectional and six case-series. Twenty-two studies included a control group. The number of children and adolescents in these studies ranged from 3 to 117,776 with a total of 328,875 participants, [median 130.5, IQR (44.5-759.5)]. Pooled estimates of proportions of children and adolescents with 3 or more persistent symptoms were significantly higher in those cases following SARS-CoV-2 infection (pooled risk difference 17% [95% confidence interval 4-31%]) than in controls, with high heterogeneity. There were significantly higher pooled estimates of proportions of symptoms in cases following 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%). No significant difference in proportions between cases and controls were found for other symptoms including fevers, chest pain, cognitive difficulties, cough, diarrhoea, dizziness, dyspnoea, insomnia, joint pain or swelling, light sensitivity, mood swings, myalgia, nausea, palpitations, postural symptoms, rashes, stomach ache or sore throat.

**Interpretation:** This systematic review and meta-analysis underlines the need for control groups in studying symptoms in children and adolescents following SARS-CoV-2 infection and the need for a clinical case definition for use in these studies.

# 1. Research in context

## 1.1 Evidence before this study

Prior to this study, there five systematic reviews had been published which focused exclusively on Post COVID-19 Condition in people under the age of 18:

| Authors | Number of included studies | Number of participants |
|---|---|---|
| Ludvigsson (2021) | 19 | Not specified |
| Lopez-Leon et al. (2022) | 21 | 80,071 |
| Behnood et al. (2021) | 22 | 23,141 |
| Zimmermann et al. (2021) | 14 | 19,426 |
| Zimmermann et al. (2022) | 27 | 73,652 |

## 1.2 Overview and added value of this study

This study is an update to (1) and identifies an additional eight controlled studies, whose data have been added to the meta-analyses previously performed of symptoms which were reported by more than three studies. These are included as forest plots with pooled risk differences for the prevalence of symptoms.

The updated searches also identified an additional 30 uncontrolled studies that met the inclusion criteria. The main findings from these studies are included in the Summary of Study Findings (Table 1), which describes the most frequent symptoms reported and the prevalence of persistent symptoms (where reported) for each study. The controlled studies used for the meta-analyses are also included in this table. The Characteristics of Included Studies table (Table 2) describes all the studies that met the inclusion criteria for the review.

We assessed the quality of each study meeting the inclusion criteria, using either the Newcastle-Ottawa Quality Assessment Scale for cohort studies or the JBI Critical Appraisal Checklist for analytical cross-sectional studies and case-series, as appropriate.

This systematic review and meta-analysis is the largest to date with 60 studies included in total. The study protocol was registered on PROSPERO (Reference: CRD42021233153). The searches were conducted in June 2022 making it the most up-to-date synthesis of information available including data from two large influential Danish studies of 10,997 Children (aged 0-14) and 6,630 Young People with Post Covid-19 Condition. (2, 3)

## 1.3 Implications of all the available evidence

Together the available evidence indicates three priority areas.

a) The need for a core outcome set to allow international comparisons between studies. This work is underway (4).

b) The need for a clinical case definition of post COVID-19 condition in children and adolescents. This is the focus of the current work being conducted by WHO.

c) The need to develop, deliver and evaluate accessible, multi-component interventions for Post COVID-19 Condition that are acceptable to children and adolescents and their parents.

# 2. Introduction

Persistent symptoms following COVID-19 are emerging as a prevalent health issue with a broad spectrum of manifestations in adults and children. The condition has been described as a complex multisystem disease appearing during the typical convalescence phase of illness, with persistent, heterogenous and recurring symptoms which may wax and wane, lasting beyond four weeks from the date of SARS-CoV-2 infection. (5, 6) A research definition of Post COVID-19 Condition in children has been developed as a result of a Delphi consensus (7) and is aligned to the WHO's adult clinical case definition. (8) It is acknowledged that this research definition may evolve and will almost certainly need to be adapted to different contexts (e.g., where testing has not been widely available). The research definition proposed is:

***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 SARS-CoV-2 infection, and may fluctuate or relapse over time.***

Post COVID-19 Condition in children and adolescents is distinct from "Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)" or "Multisystem Inflammatory Syndrome in Children (MIS-C)", a novel paediatric hyperinflammatory disease phenotype with features of Kawasaki disease and Toxic Shock Syndrome that typically occurs 2-4 weeks after SARS-CoV-2 infection in children. (9-14)

Our previous systematic review, conducted in July 2021, was conducted using databases MEDLINE, EMBASE, CINHAL, Cochrane COVID-19 study registry, ProQuest coronavirus research database, COVID-19 Living Overview of the Evidence (L-OVE) subset of Episteminokos, World Health Organization (WHO) Global literature on coronavirus disease, and ZBMed's preview database of COVID-related pre-prints. Eligible studies were those reporting on children and adolescents, aged ≤19 years with confirmed or probable diagnosis of SARS-CoV-2 presenting with any symptoms persisting beyond the acute phase of their illness. A supplementary systematic literature search was conducted between May 25, 2021, and July 31, 2021. From 3,357 unique titles, 22 observational studies (n=23,141) were included; 15 were cohort studies, six cross-sectional and one was a case-series. The mean duration of follow-up after COVID-19 was 125.3 days (SD: 72). We identified 101 symptoms reported to be persistent after SARS-CoV-2 infection in children and adolescents, across cardiovascular, respiratory, gastrointestinal, musculoskeletal, skin and nervous systems as well as more general symptoms. Our analyses focused on

persistence of individual symptoms and combination of symptoms where these were reported by multiple studies. 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.

Since that time, additional viral variants have emerged and more studies have been conducted. For the purpose of deriving a clinical case definition of Post COVID-19 Condition in children and adolescents, 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.

# 3. Methods

We updated a systematic review, originally registered with PROSPERO on 01 March 2021 (Reference: CRD42021233153).

## 3.1 Eligibility

Population

- We included studies of people 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) with persistent symptoms as defined by the study authors.
- If studies had mixed populations and only a subset of participants ≤ 19 years, we included the data for the relevant age-group if these were available in the publication. It was not possible to contact study authors for the data if they were not readily available, due to the timescales required.
- We aimed to include as broad a range of participants as possible, but 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.
- Post-COVID-19 symptoms reported at the longest follow-up period after COVID-19 diagnosis were extracted.

Study design

- We included any study design except case reports of individual children.
- Studies could have been controlled or uncontrolled in design, and either published, or preprints. We used systematic reviews as a source for checking the references of the included studies.
- We did not place any restrictions on language of publications, and used Google translate where required if studies were published in a language other than English.

Outcomes

- The type, prevalence and duration of persistent symptoms and their impact on everyday functioning, measured at least four weeks after initial SARS-CoV-2 infection.

## 3.2 Search methods

The lead reviewer (SAB) conducted a search on June 3, 2022 from July 31, 2021 to June 3, 2022 in seven electronic databases, MEDLINE (via OVID), EMBASE (via OVID) CINAHL (via EBSCO), Cochrane COVID-19 study registry, ProQuest coronavirus research database, COVID-19 Living Overview of the Evidence (L-OVE) subset of Episteminokos, World Health Organization (WHO) Global literature on coronavirus disease, and 5 pre-print databases (ZBMed's preview database of COVID-related pre-print from MedRxiv, bioRxiv, ChemRxiv, ResearchSquare and pre-prints.org). Each database was searched by using medical subject heading (MeSH) terms and free words including synonyms (in the title and abstract) for the concepts "COVID-19", "children", "adolescents", "long-COVID", "post COVID", "sequelae" and "persistent symptom" (combined with the Boolean logic operation "OR"/ "AND"). Additional literature was also found through contact with researchers in the area. A detailed search strategy and search terms used for MEDLINE(R) is provided in Appendix 1.

Five reviewers (SAB, FN, AT, MHG, LO'M) independently screened the titles and abstracts identified by the searches, with two reviewers assessing each record and with disagreements resolved by a third reviewer. The reviewers extracted data independently. Where necessary, a third reviewer assessed any records with disagreements that could not be resolved by the two reviewers.

The reviewers extracted descriptive variables about diagnostic methods, recruitment source, study design, participant characteristics and symptom prevalence. A second reviewer spot-checked characteristics, double-checked the data on symptom prevalence, and resolved any disagreements with the person who extracted the data.

### 3.3 Risk of bias

The methodological quality of included studies was assessed independently using the Newcastle-Ottawa Scale (NOS) for observational studies. (15, 16) The Joanna Briggs Institute (JBI) critical appraisal checklists were used for the cross-sectional and case-series studies. (17, 18) All methodological assessments were carried out by one of three reviewers (SAB, FN, AT) and checked by a second reviewer.

### 3.4 Analyses

As in our original study, the main analysis was restricted to controlled studies: children and adolescents following SARS-CoV-2 infection (cases) were compared with those who tested negative for SARS-CoV-2 (controls). We used random effects meta-analyses to examine the pooled risk difference in prevalence of each symptom or symptom combination in cases following SARS-CoV-2 infection compared with controls. Analyses were undertaken in Stata v17 using the *meta* commands. Statistical heterogeneity between the results of each study were represented as small if $I^2 < 50\%$, and large if statistical heterogeneity between the results of the studies was $I^2 \geq 50\%$. Given that different types and numbers of symptoms were reported by different studies, meta-analysis was only undertaken for symptoms where ≥ 3 studies provided data.

Forest plots were also constructed to illustrate the prevalence of symptoms reported by <3 controlled studies, broadly grouped according to affected body area/function (but no meta-analysis performed).

This report did not undertake an analysis of pooled prevalence of persistent symptoms in post-COVID-19 combining children and adolescents from uncontrolled studies and positive cases from controlled studies nor meta-regression to examine study-level factors. Instead, results from the uncontrolled studies are presented in the Summary of Study Findings (Table 1) and Characteristics of Included Studies (Table 2).

# 4. Results

## 4.1 Systematic review

### Studies identified since initial systematic review

The updated systematic review identified 4,416 articles after the removal of duplicates. The full text of 198 studies was reviewed and an additional 38 studies were added to the 22 reported in our original review (1). All 38 additional studies were published during 2021-22 and included participants mostly from high-income countries: Australia, Czechia, Denmark, France, Germany, Italy, Israel, Latvia, Norway, Poland, Saudi Arabia, Spain, Sweden, Switzerland, United Kingdom and United States of America. The number of children and adolescents in each study ranged from 3 to 117,776 with a total of 310,331 participants [median 142, Interquartile Range (IQR) 61-660] with age ranging from 0-19 years. Sixteen of the 38 additional studies (42%) included less than 100 participants (19-34). Fourteen (37%) of the 38 additional studies included a control group (2, 3, 21, 35-45), of which, 7 (18%) had comparative data and were included in the meta-analysis (2, 3, 35, 36, 40, 42, 43). The median duration of follow-up of symptoms was 91.25 days (IQR 57.9-167.3).

### Systematic review

Combined with the previous 22 studies from the earlier systematic review, a total of 60 studies were included in this systematic review as outlined in Table 2 (Characteristics of Included Studies) and Figure 1 (PRISMA diagram). Thirty-eight of the reports described cohort studies (21-24, 30, 32-38, 40-65), 16 cross-sectional studies (2, 3, 19, 20, 26, 29, 39, 66-74) and 6 case-series (25, 27, 28, 31, 75, 76). The number of children and adolescents in each study ranged from three to 117,776 with a total of 328,875 participants, [median 130.5, IQR 44.5-759.5]. Twenty-seven studies (45%) included less than 100 participants (19-34, 49, 54, 57, 59, 61, 62, 64, 68, 73, 74, 76). Twenty-two (37%) of the 60 studies included a control group (2, 3, 21, 35-46, 48, 51, 60, 63, 65, 72, 74), of which, 12 (20%) had sufficient comparative data and were included in the meta-analysis (2, 3, 35, 36, 40, 42, 43, 46, 51, 60, 63, 65).

All 60 studies assessed outcomes at >1 month after SARS-CoV-2 infection (range 1- 24 months). Of these, 15 (25%) studies assessed outcomes at >1 month, 9 (15%) assessed outcomes at >2 months, 22 (37%) assessed outcomes at >3 months and 12 (20%) assessed outcomes at >6 months. Two studies (3%) did not report the follow-up time for symptom assessment. The median duration of follow-up of symptoms was 91.25 days (IQR 54-140) with the longest follow-up time being 730 days from SARS-CoV-2 infection.

Duration of symptoms from time of symptom onset until documented symptom resolution amongst children and adolescents was generally not reported in the included studies.

Laboratory-confirmed SARS-CoV-2 infections were reported in 56 (93.3%) of the 60 studies with probable cases of COVID-19 reported in two (3.3%) studies. Two other studies (3.3%) did not report the method for detection of COVID-19 cases.

Of the 56 studies reporting laboratory-confirmed COVID-19 cases, 35 studies diagnosed cases of COVID-19 by RT-PCR, 3 studies using serology testing, 10 studies using RT-PCR and/or serology testing and 8 studies using a combination of two or more methods with RT-PCR, serology, lateral flow test (LFT), clinical diagnosis (CD), antigen and probable diagnosis.

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.

Risk of bias was classified as high, moderate, or low. Twenty-nine studies (48%) had low risk of bias, nine (15%) had moderate and 22 studies (37%) had high risk of bias.

### 4.2 Meta-analysis of Controlled Studies

Twenty-seven analyses were undertaken for symptoms where three or more studies reported data: two analyses were for number of persistent symptoms and 25 for the individual symptoms. Pooled estimates of proportions of children and adolescents with three or more persistent symptoms were significantly higher in cases following SARS-CoV-2 infection (pooled risk difference 11% [95% confidence interval 6-17%]) than in controls, with high heterogeneity (Figure 2). There was no significant difference for 1-2 reported symptoms.

There were significantly higher pooled estimates of proportions of symptoms in cases following 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%). No significant difference in proportions between cases and controls were found for other symptoms including fevers, chest pain, cognitive difficulties, cough, diarrhoea, dizziness, dyspnoea, insomnia, joint pain or swelling, light sensitivity, mood swings, myalgia, nausea, palpitations, postural symptoms, rashes, stomach ache or sore throat (See Figure 2). Heterogeneity was low for loss of appetite, earache/ringing in the ears and sore eyes but high for altered smell/anosmia, anxiety, fatigue and headache.

Forty-five persistent symptoms were reported by fewer than three controlled studies and therefore not included in the meta-analyses. Forest plots to display the prevalence of persistent clinical features reported by <3 studies, were broadly grouped according to affected body area/function and are displayed in Figure 3 (without meta-analysis). The clinical features included blisters/skin peeling, cold hands/feet, dark circles under eyes, discoloured fingers/toes, dermatological symptoms, extreme paleness, hair loss, hyperhidrosis, red/cracked lips, red welts, tingling feeling, twitches, chronic fatigue syndrome, impaired attention, listlessness, muscle weakness, orthostatic intolerance, tiredness/weakness, dizziness when standing, altered taste, anosmia/ageusia or parosmia/eusomia, body weight changes, constipation, problem swallowing, skipping meals, vomiting, depression, memory impairment, psychiatric symptoms, sadness, unexplained irritability, change in menstruation, chills, enlarged lymph nodes, neurological symptoms, problem seeing/blurred vision, problem speaking/communicating, seizures/fits, stiffness, hoarse voice, chest tightness, hearth rhythm disturbances, pulmonary embolism, respiratory symptoms, shortness of breath with activity, tachypnoea, nasal congestion and wheezing.

### 4.3 Other Findings

Whilst the majority of included studies only reported individual symptoms, two studies provided data on symptom clusters or combinations. One study (38) reported that 16.7% (30/179) of children and adolescents questioned at 1-3 months following SARS-CoV-2 infection had symptoms from at least two different symptom categories, falling to 5.1% (7/138) at 6–9 months follow-up. However, co-existence of symptoms across multiple categories was lower in children and adolescents than in adults in the same study at both time points. Numbers were small but frequent symptom combinations in children and adolescents included headache together with either gastrointestinal or sensory symptoms, and dermatological symptoms with either musculoskeletal or respiratory symptoms.

A separate study analysed symptom combinations in children and adolescents who had been hospitalised with SARS-CoV-2 infection after a median 256 (223–271) days since discharge (58). The study reported symptoms from more than one category in 8.5% and in three or more categories in 2.7%. Frequently reported symptom combinations were fatigue with sleep problems (1.9%) and fatigue with sensory problems (1.5%) although absolute numbers were small and the population highly selected.

### Symptom time-course

Most included studies reported symptoms at a single follow up time-point, precluding assessment of whether symptoms were static or dynamic in nature. However, one study described 25% of children and adolescents reporting constant symptoms after SARS-CoV-2 infection, whilst 49% had periods of apparent recovery with symptoms returning and 19% having prolonged symptom-free periods followed by symptom return (69).

### Impact on daily function

Several studies reported the impact of long-term symptoms on the daily functioning of children and adolescents. Two large Danish studies ((2, 3) included assessments of paediatric quality of life scores. In comparing those aged 0-14 years with SARS-CoV-2 infection against matched controls, (3) a tendency was seen towards better quality-of-life scores for emotional and social functioning in cases than in controls, most pronounced in the 12-14 year old group. In the associated study examining those aged 15-18 years (2) better quality of life scores were again reported for cases rather than in the controls for physical, emotional, social and school functioning, However, cases did report more sick days and more school absences in comparison to the control group.

A large, controlled study from England (63) found no differences in mental health, wellbeing and fatigue scores between children and adolescents at three months after testing positive or negative for SARS-CoV-2. A small English study of 71 children and adolescents followed up after hospitalization with SARS-CoV-2 reported that although 15% (11/71) had symptoms beyond 4 weeks of discharge, none had symptoms that limited their daily activities (22). In an unmatched Danish cohort study (36) examining wellbeing in those aged 9-17 years, the authors reported a higher sense of wellbeing for those who had tested positive for SARS-CoV-2 in comparison to those who had never tested positive. However, SARS-CoV-2 positive children and adolescents who experienced symptoms for > 4 weeks reported a lower sense of wellbeing than those without symptoms. In a report comparing 70 immunocompromised and 77 immunocompetent children and adolescents after hospitalization with SARS-CoV-2 (53), parents felt that daily activity was limited more frequently (42%) in immunocompetent than immunocompromised (25%) groups, although the timescale for assessment was unclear.

In a small study of children and adolescents identified as having long COVID by pediatricians (68), 36% (32/89) reported severe limitations on daily functioning (for example reduced or no attendance at school). In another study (38) parents reported reduced physical activity in 55% (95/174) of children and adolescents at 1-3 months after SARS-CoV-2 infection (falling to 40% (55/136) at 6-9 months) as well as changes in emotions in 36% (49/136) at 1-3 months (rising to 48% 20/42 at 6-9 months). However, parents did attribute some of these changes to the pandemic situation rather than the infection.

In a small case-series of seven patients at a specialist COVID-rehabilitation clinic (28) most reported their symptoms had substantial impact on their quality of life. A further small study from Israel reporting the characteristics of 90 patients referred to a designated long COVID clinic (20) found that 59% of these children and adolescents reported impairment in daily activities due to symptoms when assessed at a median of 112 days (range: 33–410). A small study of 52 people from Brazil aged 8-18 years were followed up a median of 4.4 (0.8-10.7) months after SARS-CoV-2 infection with a comparator group of age-matched controls attending hospital outpatient clinics (41). Fifty seven percent (30/53) were asymptomatic on review. PedsQL scores were significantly lower in the cases than controls in the physical and school domains.

### Sequalae of COVID-19 complications

The sequelae of complications of COVID-19 were outwith the scope of this review. In order to maximise generalizability of this review, studies limited to children and adolescents who had been admitted to intensive care units with SARS-CoV-2 (i.e. those who had experienced severe COVID-19 complications) were specifically excluded. Those who were diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C, a complication of SARS-CoV-2 seen in children and adolescents) were reported within some study populations, but data was not available to analyse this subset of patients. Symptoms following MIS-C have been explored elsewhere (77).

### Duration of COVID-19 symptoms

The majority of included studies reported symptoms following SARS-CoV-2 infection at a set time period, rather than detail the time from infection to symptom resolution. However, one study from Denmark examined symptom duration and reported symptoms resolution in 54-75% of children and adolescents within 1-5 months of infection (36). A second study from England, reported that 4.4% continued to present with symptoms four weeks after SARS-CoV-2 infection, which decreased to 1.8% at 8 or more weeks (51). Another study from Switzerland, following symptoms lasting greater than four and 12 weeks, reported that 4% of seropositive children had at least one symptom lasting beyond 12 weeks (60).

# 1. Discussion

This updated systematic review and meta-analysis summarises a significant body of work undertaken by the scientific community on Post COVID-19 Condition in children and adolescents. The clinical manifestations which have been reported after SARS-CoV-2 infection in children and adolescents are very broad and encompass cardiovascular, respiratory, gastrointestinal, musculoskeletal, skin and nervous systems as well as general somatic symptoms. However, meta-analysis found that pooled estimates of proportions with three or more persistent symptoms were significantly higher in following SARS-CoV-2 infection (pooled risk difference 17% [95% confidence interval 4-31%]) than in controls. There was no significant difference for 1-2 reported symptoms indicating that a clinical case definition to differentiate between cases and controls may wish to focus on three or more symptoms. The persistence of certain symptoms following acute SARS-CoV-2 infection may also be useful in identifying children and adolescents with Post COVID-19 Condition and these include anxiety, fatigue, headache, loss of appetite, altered smell/anosmia, earache and sore eyes.

There is still room for improvement in study design in this research area and the majority of studies in our review were uncontrolled and of poor or moderate quality. Furthermore, almost all studies were from high income countries, limiting generalisability for low- and middle-income countries. The impact of symptoms on daily function was also infrequently reported, making it hard to assess the effect of symptoms on the lives of children and adolescents. In addition, with 75% of children and adolescents in the US now estimated to have had been infected with SARS-CoV-2 (78), the value of considering thosewho have never had COVID-19 as the control group for future research in this area is a challenge, particularly as this becomes an increasingly small and select population.

# 2. Conclusion

Post COVID-19 condition in children and adolescents is an active area for research. The findings indicate significant heterogeneity in presentations that need to be considered in any clinical case definition and service provision. The persistence of three or more symptoms following acute SARS-CoV-2 infection may be useful in identifying these children and adolescents, as may certain individual symptoms such as anxiety, fatigue, headache, loss of appetite, altered smell/anosmia, earache and sore eyes.

# Figures and Tables

## Figure 1. PRISMA diagram to show studies identified between 01 December 2019 and 03 June 2022

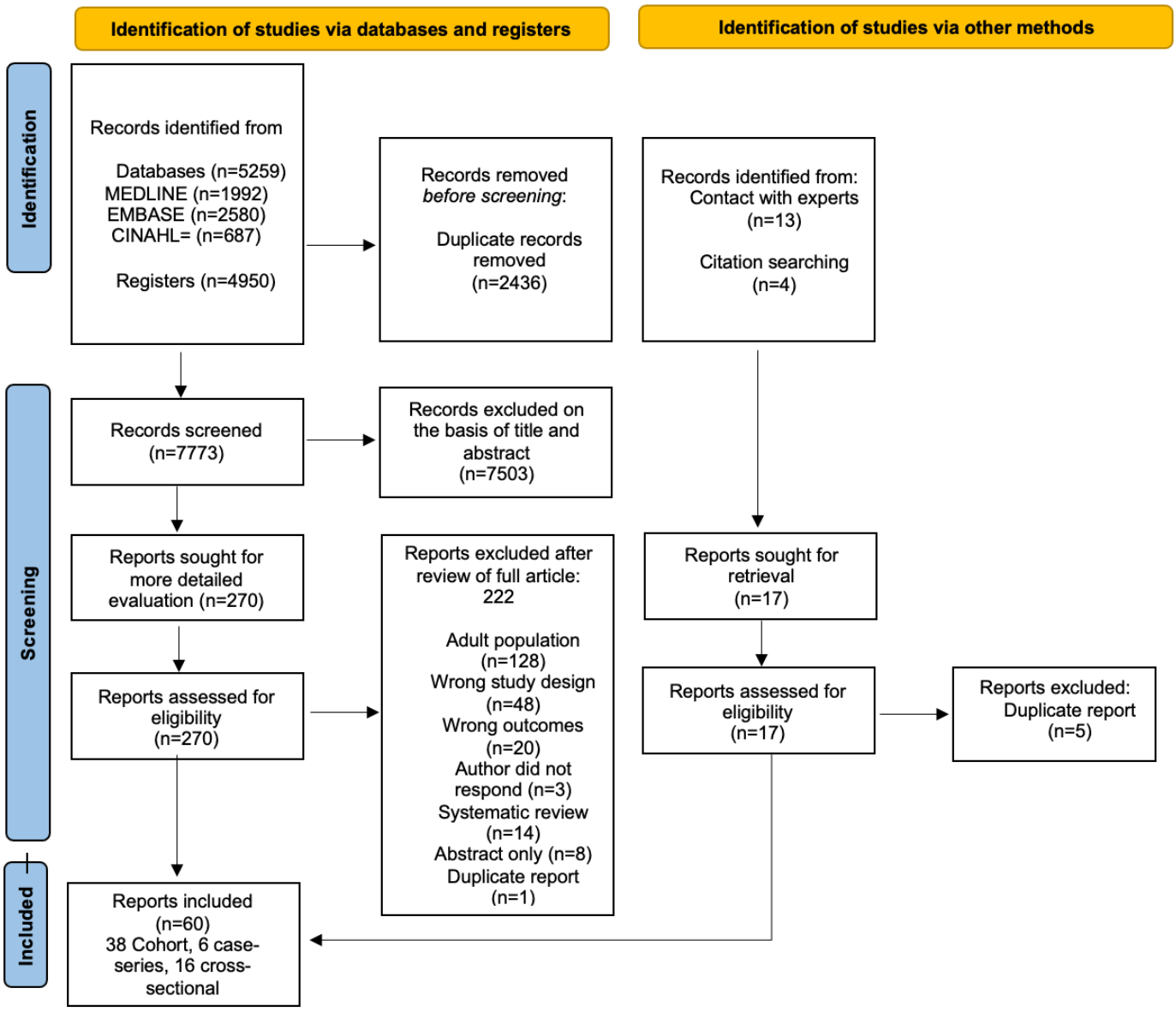

Table 1. Summary of study findings

| Study ID (author and year) | Measurement Tool | Method of Reporting | Prevalence of symptoms | Persistent symptoms | Other findings |
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| Alghamdi 2022 | Questionnaire | Self-report of symptoms on questionnaire distributed via social media platforms | **Symptoms for > 6 months**<br>Cognitive dysfunction: 9%<br>Mood alteration: 10%<br>Depression: 8%<br>Tinnitus: 5%<br>Sleeping disorders: 5%<br>Loss of taste/smell: 6% | NR | NR |
| Asadi-Pooya 2021 | Questionnaire | Phone interview | 45% of children and adolescents reported symptoms/complaints of long-COVID. **Frequent symptoms included** fatigue (21%), shortness of breath (12%), exercise intolerance (12%), and weakness (10%).<br><br>**Other symptoms reported were** walking intolerance (9%), cough (7%), sleep difficulty (5%), muscle pain (5%), joint pain (5%), headache (5%), excess sputum (5%), other symptoms (e.g., chest pain, palpitations, loss of smell, sore throat, dizziness, excess sweating, anorexia) in fewer than three individuals | NR | Older age, muscle pain during acute COVID and those admitted to ICU were significantly associated with experiencing long-COVID in children and adolescents. |
| Ashkenazi-Hoffnung 2021 | Medical evaluation | Structured interview conducted by senior pediatrician | **Most frequent symptoms:** Fatigue (71%), dyspnea (50%) and myalgia (46%) were the most frequently reported symptoms, and were significantly associated with older age > 11 years<br><br>**Other symptoms report**ed sleep disturbances (33%), chest pain (31%), paresthesia (29%), headache (29%), hair loss (27%), anosmia-ageusia or parosmia/euosmia (26%) gastrointestinal symptoms (20%) dizziness (19%), weight | 59% of children reported impairment in daily activities due to symptoms | Uncommon clinical features in young children included recurrent febrile episodes (2%), developmental regression (2%) and obstructive sleep apnea (2%)<br><br>Changes on chest radiograph (13%), abnormal spirometry (6%), abnormal exercise challenge test (6%), air trapping by plethysmography (17%), abnormal |

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| | | | loss of >5% of body weight (19%), memory impairment (18%), vasomotor complaints (14%), arthralgia (14%), tremor (13%), cough (10%), palpitations (9%), difficulty in concentration (9%), tic exacerbation (2%) and tinnitus (1%). | | electrocardiograph (2%), abnormal cardiac MRI (1%)<br>For 51 patients who underwent an exercise stress test, the maximal pulse was lower than the age-specific mean; for 67%, the value was below the minimal threshold value (−2 SDs), suggesting some degree of chronotropic incompetence |
| Bergia 2022 | Questionnaire | Telephone questionnaire | **Most frequent symptoms**<br>Fever (79%), rhinorrhea (47%) and coughs (48%) were the most frequent symptoms, and these generally had a short duration, with a median of <5 days. | 18% had 1+ symptoms at 4–12 weeks<br><br>15% had symptoms at more than 12 weeks+ | Odds risks were higher for: (1) children aged 5 years or more (OR 3.0); (2) hospitalised (OR 3.9), admitted to the PICU (OR 4.3); (3) with relatives who were symptomatic for 12 weeks or more (OR 2.8).<br><br>Controls had similar frequency of persisting symptoms despite not having COVID-19 (particularly if over 5 years old) |
| Blankenburg 2021 | Long-COVID survey | Student self-report | **Most frequent symptoms:** 35% reported the presence of at least one neurocognitive, pain or mood symptom with tenseness, listlessness and difficulties concentrating being reported most. However, there was no statistical difference comparing the reported symptoms between seropositive students - with mild to asymptomatic courses of SARS-CoV-2 infections - and seronegative students | NR | Females reported a consistently higher prevalence of neurocognitive and pain symptoms compared to men, except for myalgia and arthralgia where there was no significant association with sex. |
| Bloise 2022 | Telephone survey | Paediatrician conducted telephone survey then used web-form link to collect data from children and parents. | **Most frequent symptoms:**<br>asthenia (40%), difficulty in concentration and memory (21%), trouble sleeping-depression and other neuropsychiatric disorders (18%), headache (17%), persistence of ageusia and anosmia (17%, n=43), arthralgias and myalgias (14%, n=37) | 20% had persistent symptoms | 62% of those with persistent symptoms were female.<br>Risk factors for long-term symptoms: older age, higher BMI, longer duration of infection |

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| Blomberg 2021 | Telephone interview for and in-person interview with clinical staff | Telephone interview for demographic/clinical data, then follow-up interview at clinic at 2 months (6–8 weeks) and 6 months (±1 month) about long-term symptoms | **Most frequent symptoms:**<br>13% had disturbed taste/smell and 6% had stomach upset.<br>at 6 months | 13% had persistent symptoms | No cases of fever, cough, dyspnea, palpitations, sleep problems, headache, dizziness, tingling in fingers reported in this age group (0-15-year-olds) at 6 months. |
| Borch 2022 | Electronic Questionnaire | Parent and/or adolescent Self-report | **Most frequent symptoms** in the SARS-CoV-2 +<br>group were fatigue (11%), loss of smell (10%) and loss of taste (8%), headache (7%) and concentration difficulties (6%).<br><br>In the control group, the most reported symptoms were concentration difficulties (9%), cough (7%), headache (6%) and fatigue (4%). | From the SARS-CoV-2 positive children who reported symptoms lasting >4 weeks, 35% reported one symptom, 29% reported two symptoms and 37% reported three or more symptoms.<br><br>From the children in the control group who reported symptoms lasting >4 weeks, 54% reported one symptom, 23% reported two symptoms and 23% reported three or more symptoms.<br><br>Most children (54-75%) recovered within a maximum of 1–5 months. | Within the age group 0–5 years, more children in the control group reported symptoms lasting>4 weeks compared to SARS-CoV-2 positive children (15% vs 18%; p=0.001)<br><br>Within the age group 6–17 years, 1% more SARS-CoV-2 positive children reported symptoms lasting >4 weeks than children in the control group (28% vs 27%; p=0.020)<br><br>SARS-CoV-2 positive children presenting with symptoms lasting>4 weeks reported a higher sense of well-being compared to children with symptoms >4 weeks who have never been tested positive for SARS-CoV-2<br><br>Age distribution of symptoms differed with older school children being more frequently affected compared to younger school and pre-school children |

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| Bossley 2022 | Telephone questionnaire | Paediatric Respiratory consults used a standard clinical pro-forma in a telephone follow-up | **Most frequent symptoms**: dry cough (7%); shortness of breath (6%); fatigue (4%), headache (3%), anosmia (1%) | 15% had symptoms > 4 weeks, resolving within 1-3 months in 45%. | None had symptoms that limited daily activities (eating, drinking, getting dressed). |
| Brackel 2021 | Long-COVID on-line survey | Reporting by Pediatricians | **Most frequent symptoms:** fatigue (87%), dyspnea (55%), concentration difficulties (45%), headaches (38%), thoracic pain complaints (35%), stomach-ache (33%), myalgia (28%), diarrhea (24%), memory loss (13%), cardiac palpitations (18%), skin irritation (7%), dizziness (3%), brain fog (2%), weight loss (2%), persistent fever (2%), coughing (1%), myocarditis (1%), anosmia (1%) | NR | **Limitations in daily function:**<br>36% had severe limitation in daily function<br>48% had mild limitations in daily function<br>8% had no limitations |
| Buonsenso 2021a | Long-COVID kids Rapid Survey to establish quantity and type of symptoms | Parent self-report | **Most frequent symptoms:**<br>Tiredness and weakness (87%), fatigue (80%), headache (79%), abdominal pain or cramps (76%), muscle aches and pains (68%), muscle and joint pain (61%), post-exertional malaise (54%), rash (52%), unexplained irritability (51%), and dizziness (48%) | Children had persistent symptoms for a mean duration of 8.2 months SD (3.9) | **Changes in Children:**<br>Energy levels (83%), mood (58.8%), sleep (56%), and appetite (50%).<br><br>All children had at least 1 change and 64% children have had at least 4 changes.<br><br>25% children have suffered constant COVID-19 infection symptoms, 49% have had periods of apparent recovery and then symptoms returning, and 19% had a prolonged period of wellness followed by symptoms. |

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| Buonsenso 2021b | Questionnaire developed by Long COVID ISARIC study group | Interview with caregivers by phone or in person at outpatient department | **Most frequent symptoms**:<br>Insomnia (19%), respiratory symptoms (including pain and chest tightness; 15%), nasal congestion (12%), fatigue (11%), muscle (10%) and joint pain (7%), and concentration difficulties (10%)<br><br>**Other symptoms report**ed Weight loss (8%), skin rash (7%), joint pain and swelling (7%), constipation (6%), persistent cough (5%) | 67% of those assessed between 60 and 120 days after initial COVID-19 had at least one persisting symptom (13 had one or two symptoms, seven had three or more)<br>27% had at least one symptom 120 days or more after diagnosis (21 had one or two symptoms, 14 had three or more).<br>43% children assessed ≥120 days from diagnosis were still distressed by these symptoms. | 42% completely recovered, 36% had one or two symptoms and 22.5% had three or more. |
| Buonsenso c 2021 | Survey developed by Long COVID ISARIC study group | Phone call or face to face interview | **Most frequent symptoms at 6-9 month follow up** included insomnia (19%), asthenia (14%), cough (12%), rash (12%), fever (12%), constipation (12%), weight loss (12%), muscle weakness (8%), chest pain (7%), abdominal pain (4%) and poor appetite (4%)<br><br>28% of children were assessed at both 1-3 month and 6–9-month follow-up. 38% of children experiencing symptoms at 1-3 months had recovered at 6-9 months | At the 1–3 months follow-up the positive cases reported persistent cardiovascular, dermatological, neurological symptoms including headache, more frequently compared to controls, but not at the 6–9 months follow-up. | 17% of children and adolescents experienced concomitant symptoms from at least two different symptom categories at 1–3 months, 3% experienced symptoms from three or more categories. At 6–9 months follow-up, 5% experienced persisting symptoms from at least two and 1% from three or more categories<br>Parents reported changes in emotional behaviours, social relationships, and activity levels in a significant number of children and adolescents, mostly perceived by the parents as due to the pandemic |

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| Buonsenso d 2022 | NR | Assessed by single paediatrician at a post-COVID clinic | **Most frequent symptoms** headache (17%), dyspnoea on exertion (15%), muscle pain (12%), chest pain (9%), joint pain (8%), cough (8%), gastrointestinal symptoms (7%), palpitations (6%), altered smell (5%), altered taste (4%), nasal congestion/rhinorrhea (4%), rash (4%), fever (3%), dyspnoea at rest (2%), and asthma (2%). | 46% had no persistent symptoms | NR |
| Castro 2021 | Database | Analysis of electronic health records for particular ICD-10 codes and natural language processing terms | **New-onset symptoms:** 7% had ≥ 1 new-onset neuropsychiatric symptom between 90-150 days.<br>**Most common incident symptoms**<br>headache (2%), mood and anxiety symptoms (2%), cognitive symptoms (2%) and fatigue (1%) | Authors concluded that neuropsychiatric symptom prevalence at 3-5 months follow-up was similar to that observed prior to SARS-CoV-2 infection. | Older age, female sex, Hispanic ethnicity and overall medical comorbidity burden linked to likelihood of subsequent symptoms. |
| Chevinsky, 2021 | Database | Data included from an all-payer administrative database | NR | NR | Children with COVID-19 were not more likely to experience new diagnoses than children without COVID-19. |
| Clavenna 2021 | Questionnaire | Paediatricians reported follow-up using questionnaires | **New-onset symptoms**<br>Wheezing (0% in +ve group, 6% in –ve group); dermatological (3% +ve, 6% -ve); psychological distress (15% +ve, 17% -ve). | During 6-month follow-up, 72% of children had contacted or visited the pediatrician for a health issue (range: 1-8 visits), 26% had no health problems, and 2% were lost to follow-up. | No differences between positive and negative children were observed during the follow-up. |
| Denina 2020 | NR | Phone evaluation followed up evaluation at clinic | NR | No duration of symptoms reported | All children had a clinical and complete laboratory recovery about a month after discharge with no manifestations of any COVID-19 related sequelae 4 months later. |

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| Dobkin 2021 | | Retrospective chart review | Persistent dyspnea and/or exertional dyspnea were present in 96.6% of the patients. Other reported chronic symptoms included cough 52%, exercise intolerance 48% and Fatigue in 14% of subjects. | Duration of persistent symptoms: Mean 3.2 months (SD: 1.5) Range: 1.3 to 6.7 months post-acute infection | 3% required supplemental oxygen. 7% had abnormal auscultatory findings including decreased breath sounds and intermittent wheezing |
| Dolezalová 2022 | Physical examination and verbal medical history | Self-reported/reported by parents' symptoms, physical examination and laboratory tests. | Dominant symptoms at > 12 weeks<br>Exertional dyspnoea (77%), chronic cough (49%), dyspnoea at rest (31%), chest pain (18%).<br>> 50% had > 1 symptom. | 87% had complete remission of tracked symptoms within 1.5 to 8 months (median 4 months).<br><br>13% lost to follow-up or followed up < 6 months. | Although follow-up was 6 months, symptoms reported are at study entry (> 12 weeks after diagnosis)/ 6-month follow-up was to measure symptom resolution. |
| Donnachie 2022 | Claims data | Retrospective data submitted by licenced general practitioners, office-based specialists and psychotherapists | **Most frequent symptoms** in the COVID-19 group were psychological disorder (9%), fatigue (7%), dyspnoea (4%), loss of taste/smell (2%), myalgia (2%) and cognitive difficulties (0%)<br><br>**Most frequent symptoms** in the control group were psychological disorder (7%), fatigue (4%), dyspnoea (2%), myalgia (1%), loss of smell/taste (0%) and cognitive difficulties (0%) | The treatment incidence of Post-COVID Syndrome among children aged below 12 years was 3%. | Among 12–17-year-olds, persistent disturbances of taste and smell occurred in 3% of COVID-19 patients<br><br>Chronic fatigue syndrome was diagnosed in only 0% of children with COVID-19 |
| Dumont 2021 | Questionnaire | Serosurvey of households self-report of symptoms | Specific symptoms only reported at 2 weeks | Prevalence of symptoms at > 4 weeks<br>2-5 yrs: 4% in -ve, 0% in +ve<br>6-11 years; 4% in -ve, 0% in +ve<br>12-17 yrs: 1% in –ve, 6% in +ve | Compared with seronegative adolescents, age- and sex-adjusted prevalence of symptoms lasting > 4 weeks was 4% (95% CI –3.8 to 13.6) |

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| Elvan-Tuz 2022 | Smell awareness questionnaire | Interview by phone | 8% of children and adolescents had anosmia persist after 1 month and 7% of children and adolescents had ageusia persist after 1 month<br><br>Anosmia and ageusia were detected at a low rate as the only symptom in COVID-19 cases | NR | Anosmia did not improve in 8% of cases in the mild clinical severity group, and it did not improve in 13% in the moderate/ severe/critical clinical severity group with a statistically significant difference between the groups (P = 0.04). |
| Erol 2021 | NR | Evaluation by 2 paediatric cardiologists | **Most frequent symptoms reported included** chest and backache (51%) dizziness ± syncope (16%), palpitation (11%), shortness of breath (9%), headache (7%), loss of balance (2%), coughing (2%) and fatigue (2%).<br><br>There was no correlation between the severity of COVID-19 and persisting symptoms | 37% of children and adolescents had persistent symptoms for at least 1 month after COVID-19 recovery | Statistically significant differences were found in systolic blood pressure, left ventricular ejection fraction, relative wall thickness, and tricuspid annular plane systolic excursion between the cases and control groups. |
| Esmaeilzadeh 2022 | Electronic repository of health records | Phone and clinic visits | Rates of symptoms were significantly elevated in the group of patients with both COVID-19 and asthma-like compared to COVID-19 patients without asthma. | 42% of COVID-19 patients had persistent cough and asthma-like symptoms after discharge | NR |
| Fink 2021 | Database | Data from Research Electronic Data Capture database | **Most frequent symptoms**<br>headache (19%), severe recurrent headache (9%), tiredness (9%), dyspnea (8%), and concentration difficulty (4%) | 43% children and adolescents reported at least one persistent symptom at follow-up<br><br>23% reported at least one symptom lasting beyond 12 weeks and were classified as having long COVID | School and physical domains of the Pediatric Quality of Live Inventory 4.0 were significantly lower in children and adolescents with COVID-19 at follow up than controls. Median physical score (69 [0-100] versus 81 [34-100], p=0.012), and school score (60 [15-100] versus 70 [15-95], p=0.028). |

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| Haddad 2022 | Questionnaire | Parent/self-report using online RAND 36-item health survey & questionnaire | **Most frequent symptoms:** moderate or severe reduction in physical resilience in adolescent girls (14-18 years).<br>Physical functioning and fatigue: no significant difference for adolescents and children. | Persistent symptoms significantly higher in infected than exposed adolescent girls (32% vs 9%). years.<br>Moderate/severe symptoms were not more common in infected than exposed adolescent boys or children < 14 | Adolescent girls with acute symptoms during infection had more symptoms that persisted to follow-up than those who were asymptomatic (IRR=9.58; p = 0.033); but this was not found for adolescent boys or children <14 years. |
| Kikkenborg Berg 2022a | Online Survey | Questionnaire | **Most frequent symptoms** in the long-COVID group were headache, fatigue, loss of appetite, trouble breathing and trouble remembering or concentrating.<br><br>The long-COVID group reported a decreasing number of symptoms over time | Participants in the case group had greater odds of having at least one long-COVID symptom lasting at least 2 months compared with the control group 62% vs 57%<br><br>In both groups, more female participants had symptoms lasting more than 2 months in comparison to males.<br>72% vs 48% in the case group and 67% vs 44% in the control group | Participants in the case group reported significantly lower symptom scores on the CSSI-24 than in the control group: mean 10·7 vs 11·9 and better quality of life scores on the PedsQL: physical functioning mean score 88·7 vs 86·5,<br>emotional functioning 77·1 vs 71·7, social functioning 93·1 vs 88·4 and school functioning<br>66·9 vs 62·9.<br>More participants in the case group than in the control group reported 16 or more sick days 18% vs 12%, and 16 or more days of school absence 11% vs 8% |

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| Kikkenborg Berg 2022b | Online Survey | Questionnaire | **Most frequent symptoms** reported among children aged 0–3 years were mood swings, rashes, stomach aches, cough, and loss of appetite.<br><br>Among those aged 4–11 years, mood swings, trouble remembering or concentrating, and rashes were most common; and among those aged 12–14 years, fatigue, mood swings, and trouble remembering or concentrating were most common | In cases aged 12–14 years, more girls than boys had at least one symptom lasting more than 2 months (53% *vs* 40%). Similarly in control group (46% *vs* 37%).<br><br>Cases had higher odds of reporting at least one symptom lasting more than 2 months than did controls in the 0–3 years age group (40% vs 27%); 4–11 years age group (38% vs 34%) and 12–14 years age group (46% vs 41%)<br><br>Cases had higher odds of reporting at least one symptom lasting more than 3 months in children aged 0–3 years (36% *vs* 23%), 4–11 years (34% *vs* 29%), and 12–14 years (42% *vs* 37%) | Differences in CSSI-24 symptom scores between cases and controls were statistically significant but not clinically relevant.<br><br>Small clinically relevant differences in PedsQL quality-of-life scores related to emotional functioning were found in favour of cases in the children aged 4–11 years median score 80 in cases *vs* 75 in controls; and 12–14 years 90 vs 85.<br>PedsQL social functioning scores were also higher in cases 100 than controls 95 in the 12–14 years age group. |

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| Knoke 2021 | NR | Interview by medical personnel | 27% of children in COVID-19 group reported persistent or newly emerged symptoms after SARS-CoV-2 infection. 11% reported at least one respiratory symptom, 9% of whom suffered ongoing breathing problems and 3% persistent cough | NR | NR |
| Kostev 2022 | Database | Database from general and specialized practices in Germany | The prevalence of post COVID-19 condition in the sample was 2% | NR | Older age, anxiety disorders, somatoform disorders, and allergic rhinitis were positively and significantly associated with post-COVID-19 condition compared with younger age and the absence of these chronic conditions |
| Kuczborska 2022 | Questionnaire | Parent self-report | During the first 12 weeks post-infection, the immunocompetent cohort suffered more often from fatigue, reduced exercise tolerance, difficulty in concentrating, sleep disorders, and chronic coughing, however, children and adolescents in the immunocompromised cohort experienced gastrointestinal symptoms more often.<br><br>Beyond the 12-week post-infection period, the prevalence of almost all symptoms had significantly decreased. However, children in the immunocompetent cohort continued to display post-COVID-19 symptoms, including difficulty in concentrating, reduced exercise tolerance, fatigue, headache and frequent infections. children and adolescents in immunocompromised cohort continued to suffer from fatigue, irritation and gastrointestinal symptoms | The prevalence of ongoing symptomatic COVID-19 in the first 12 weeks post-infection, defined as the presence of at least one symptom, was 60% and 36% in control vs cases, respectively ($p = 0.02$).<br><br>In the period beyond 12 weeks post-infection, the percentages dropped to 35% and 11%, respectively ($p = 0.01$). | Immunocompetent children were more significantly affected by prolonged COVID-19 symptoms when compared to the immunocompromised cohort.<br><br>During the first 12 weeks post-infection, the presence of long-COVID symptoms was found to be correlated with age in the immunocompromised children and adolescents. This was not the case beyond the 12-week post-infection period.<br><br>Long-COVID symptoms limited daily activities of immunocompetent children more frequently 42% than it did for the immunocompromised children 25 % |

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| Ludvigsson 2020 | N/A | Symptoms reported by parents | **Most frequent symptoms:** Fatigue, dyspnoea and heart palpitations or chest pain. These were seen in all five of the children.<br><br>4 children complained of headaches, difficulties concentrating, muscle weakness, dizziness and a sore throat.<br>The parents reported that three of the children experienced abdominal pain, memory loss, depression and skin rashes and muscle pain | All 5 children had symptoms for 6–8 months after their clinical diagnoses of COVID-19 | Less common symptoms, experienced by 2 children, were remitting fever, sleep disorders, joint pain, diarrhoea and vomiting and hyper anaesthesia. Several symptoms were each reported by one child after 2 months, and they were persistent deranged smell and taste, poor appetite, a chronic cough and numbness. |
| Marino 2022 | NR | Examination by paediatric rheumatologists | Symptoms included intense joint pain (50%), diffuse and persistent joint pain along with antalgic gait (17%), persistent low-grade fever (17%), weight loss (17%), polyarthralgia of the hands (17%), intraarticular swelling of the right hip with arthralgia (17%), COVID toes (17%) | No children developed chronic inflammatory conditions | All patients recovered during the follow-up. However, these patients showed several degrees of limitations in daily life for some months |
| Matteudi 2021 | Questionnaire | Phone call via paediatric team | The most common long COVID-19 symptoms were asthenia (10%), learning difficulties (8%) and headache (6%). | 17% had symptoms of long COVID-19, of which 44% had persistent symptoms and 57% had new late-onset symptoms, which appeared long after the acute infection, at a mean of 180 days (range 36–345) | Those who were symptomatic during the acute phase were statistically significantly more susceptible to develop long-term symptoms |
| Miller 2021 | Online long COVID survey | Participant or parent self-report | Among children who reported persistent symptoms the most common reported symptom types were general, ENT and respiratory symptoms.<br><br>Among the 22 children who had reported at least one “general symptoms”, fatigue was the most common reported by 22%. | The median duration of symptoms was 46 days (IQR 32-188) for the 18 children who reported start and end dates of symptoms. | Risk factors were not reported for those with persistent symptoms |

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| Mohiuddin Chowdhury 2021 | NR | Phone evaluations | 3 Children in the 1–10-year-old group had no complaints or report of persistent symptoms | NR | NR |
| Molteni 2021 | Mobile application | Data recorded by adult proxy | **Most frequent symptoms:** Headache (62% [55% younger, 66% older children]) and fatigue (55% [44% younger, 61% older children]).<br><br>Symptoms in younger children: fever (44%), sore throat (36%), abdominal pain (28%), and persistent cough (25%)<br><br>Symptoms in older children: sore throat (51%), anosmia (48%), fever (35%), and persistent cough (26%). | Overall, 4% had illness duration ≥28 days more commonly experienced by older vs. younger children (5% vs. 3%).<br><br>2% of 1,379 children experienced symptoms for ≥56 days.<br><br>Median illness duration 6 days (vs. 3 days in children testing negative) and associated with age with median duration of 7 days in older vs. 5 days in younger children.<br>Few children 1% in the negative group experienced prolonged symptom duration | Age is a risk factor for longer symptom duration. |
| Morand 2022 | Database | Electronic patient record system | **Most common symptoms** Fatigue (71%); Cognitive impairment (71%); Dyspnoea (57%); Headache (57%); Hypersomnia (57.14%); Fever/Hyperthermia (43%); Anorexia (43%); Musculoskeletal pain (43%); Hyposmia/anosmia (43%); Dysgeusia/ageusia (43%); Stressed felling (43%); Depression (43%); Decrease of scholar implication (43%); Limitation of extrascholar activities (43%); Significative weight loss (29%); Cough (29%); Chilliness (14%); Bulimia (14%); Diarrhoea (14%); Skin rash (14%); Dysautonomic symptoms (palpitations and Vagal malaise; 14%); Visual impairment (14%); Insomnia (14%) | NR | “paediatric patients demonstrated on average 5 months later a similar brain hypometabolic pattern as that found in adult long COVID patients, involving bilateral medial temporal lobes, brainstem and cerebellum (p-voxel < 0.001, p-cluster < 0.05 few-corrected), and also the right olfactory gyrus after small volume correction (p-voxel = 0.010 FWE-corrected), with partial PET recovery in two children at follow-up.” |

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| Morrow 2021 | Medical assessment | Retrospective medical record | The most common presenting symptoms were fatigue (89%), headaches (67%), difficulty with school-work (75%), “brain fog” (44%), and dizziness/light-headedness (44%) | NR | Most patients had decreased scores on self-reported quality-of-life measures compared with healthy controls. In the patients who participated in neuropsychological testing, a subset demonstrated difficulties with sustained auditory attention and divided attention; however, most of these patients had pre-existing attention and/or mood concerns. There were also some who self-reported elevated depression and anxiety symptoms |
| Namazova-Baranova 2020 | Survey and clinical examination | Survey conducted by a pediatrician | Recovery time for smell disorder after COVID-19 infection is 3-4 weeks | NR | NR |
| Nogueira López 2021 | Structured Questionnaire | Interview by phone | **Most frequent symptoms**: were persistent low-grade fever, intense asthenia and severe headaches.<br>Parents referred to those symptoms as disabling in most of the children. | Children with persistent symptoms were characterised by significantly longer clinical manifestations, with a median duration of low-grade fever of 53.5 days (IQR=12.3-64.5) and overall symptom duration of 60 days (IQR=37-70) | NR |

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| Osmanov 2021 | Standardised ISARIC Covid-19 Health and Wellbeing paediatric follow up survey. | Telephone interview with parent and child | **Most frequent symptoms:** 24% participants reported persistent symptoms among which fatigue (11%), sleep disturbance (7%), sensory problems (6%), gastrointestinal (4%) and dermatological (4%) problems.<br>Smaller number of patients experienced neurological (3%), respiratory (3%), cardiovascular (2%) and musculoskeletal (2%) problems long-term. | Multiple symptoms were experienced by 8% of participants. Most commonly co-occurring categories were fatigue and sleep problems in 2% of children, and fatigue and sensory problems were present in 2% of participants. 3% of children had persistent symptoms from three or more different categories | **Risk factors** for persistent symptoms were age “6-11 years” (OR 2.74 (95% CI 1.37 to 5.75) and “12-18 years” (2.68, 1.41 to 5.4), and a history of allergic diseases (1.67, 1.04 to 2.67). |
| Öztürk 2022 | Retrospective review | Retrospective review of patients followed up in clinic | Respiratory symptoms were present in 28% patients; common symptoms were dyspnea (36%), exertional dyspnea (36%), dry cough (21%), and chest pain and tightness (21%) | Persistent respiratory symptoms were present in 50% of patients who had severe disease and 13% with non-severe disease. | NR |
| Peterson 2020 | Standardized questionnaire | Telephone interview with Parent | NR | NR | **At last follow-up**: 30% of children experienced persistent symptoms. The mean number of symptoms reported was 3.5 symptoms.<br>33% of children reported mild symptoms, 20% reported moderate symptoms and 15% reported severe symptoms. |
| Radtke 2021 | Online Questionnaire | Parent self-report | **Most frequent symptoms** among seropositive vs seronegative children, Tiredness 6% versus 4% reported beyond 4 weeks, 3% versus 1% reported beyond 12 weeks, Headache 5% vs 3% beyond 4 weeks, 0% vs 1% beyond 12 weeks, Congested or runny nose, 3% vs. 3% beyond 4 weeks, 1% vs. 0% beyond 12 weeks | Among seropositive and seronegative children, 9% versus 10% reported at least one symptom beyond 4 weeks, and 4% versus 2% at least one symptom beyond 12 weeks | NR |

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| Roessler 2021 | Health insurance data | Estimates of IRR | IRRs were significantly higher in 10 out 13 diagnosis/symptom complexes in the COVID-19 cohort than in the control cohort with malaise/fatigue/exhaustion IRR=2.3, cough IRR=1.74, and throat/chest pain IRR=1.72 complexes as the highest IRR. Others included adjustment disorder IRR=1.71, somatization disorder IRR=1.61, headache IRR=1.58, fever IRR=1.56, anxiety disorder IRR=1.54, abdominal pain IRR=1.45 and depression IRR=1.45<br><br>There were significantly higher IRRs in the COVID-19 cohort than in the control cohort across outcome domains of physical health IRR=1.31, mental health, IRR=1.39 and the physical/mental overlap domain, IRR=1.32 | NR | IRR estimates were similar for the age groups 0-11 and 12-17. |

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| Roge 2021 | Questionnaire (in person) | Patients or their parents/caregivers/legal guardians | **Most common symptoms**<br>Persistent fatigue (25%), cognitive sequelae including irritability (24%), mood changes (23%), impaired attention (17%), headaches (17%), rhinorrhea (16%), coughing (14%), and disturbed taste and/or smell (12%). | 70% of children and adolescents in the study group had at least one persisting symptom at follow up (median 73.5 days (43–110 days)) after infection 54% multiple long-lasting symptoms. 53% reported two or more concurrent symptoms. | Differences amongst age groups:<br><br>For infants and toddlers, parents reported persistent upper respiratory symptoms including (11% and 29%) and rhinorrhea (33% and 32%).<br><br>Diarrhea (11%) and nocturnal sweating (22%) reported more in infants than in any other age group.<br><br>Higher rates of fatigue and cognitive complaints with increasing age teenagers (15% of 1-4 year-olds and 37% of 15–18-year-olds).<br><br>Irritability (28%) and mood changes (27%) most frequent amongst pre-schoolers and school age children and adolescents<br><br>“Fever, fatigue, rhinorrhea, loss of taste and/or smell, headaches, cognitive sequelae, and nocturnal sweating were significantly associated with the COVID-19 experience when compared with the controls.” |
| Rusetsky 2021 | Standardized questionnaire<br><br>Odor identification test battery<br><br>Telephone survey at follow-up visit | Standardized questionnaire to patients.<br><br>Parent self-report of SNOT-22 survey | NR | NR | Recovery of the olfactory function occurred within 10 days in 71%, 11 to 29 days - in 23%, and later than 30 days in 6%. 94% had no subjective olfactory complaints by the end of the first month. All patients had no complaints of olfactory disorders after 2 months |

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| Sante 2021 | Standardised ISARIC Covid-19 paediatric survey. | NR | Persistent symptoms included:<br>Fatigue (41.6%), chronic headache (33.3%), gastrointestinal symptoms (33.3%), post-exertional malaise (25%), muscle or joint pain (25%), chest pain (25%), low grade fever (16.6%), chronic cough (16.6%), tachycardia (8.3%), sleep disorder (8.3%) | NR | NR |
| Savino 2022 | Clinical case review | Detailed medical history was obtained from their parent | "Abnormal movements, anxiety, and emotional dysregulation were the most recurrent symptoms observed from a few weeks to months after the resolution of the acute infection"<br>Patient 1: Acute psychotic state<br>Patient 2: Complex motor and vocal tics<br>Patient 3: Acute-onset ocular tics, food restriction, separation anxiety, sleep disturbances, enuresis<br>Patient 4: Aggressive behavior, separation anxiety, ocular tics<br>Patient 5: Involuntary ocular movements, grimaces, upper limbs myoclonus | NR | Later onset in younger patients |

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| Say 2021 | Standard clinic proforma used to collect data | Data extracted from hospital electronic medical records | 8% of children had post-acute COVID-19 symptoms, all of whom were symptomatic with acute COVID-19.<br>**Most frequent symptoms of post-acute COVID-19** were mild post-viral cough (4%), fatigue (2%) or both post viral cough and fatigue (1%) | The duration of post-viral cough ranged from 3- 8 weeks and of post-viral fatigue ranged from 6- 8 weeks from the time of symptom onset.<br>At the end of the follow-up period (6 months) all 151 children had returned to their baseline health status and post-acute COVID-19 symptoms had resolved. | NR |
| Smane 2020a | Questionnaire | Medical staff | **Most common symptoms** were low-grade fever (7%), Joint pain (3%), Headache (3%), Anosmia (3%), Ageusia (3%) and Microhaematuria (3%) | Patients were assessed at a mean of 101 days (SD, 17) after the onset of the first SARS-CoV-2 symptom. 30% had at least one symptom at the follow-up visit. | NR |
| Smane 2021b | Questionnaire | Structured questionnaire completed by medical staff | **Most common symptoms**<br>Tiredness (38%); loss of taste and/or smell (16%); headaches (15%); sensory disturbances (photophobia, sound sensitivity; 11%); cognitive disturbances (memory, attention, and information processing problems; 10%) | "49% were completely free of any COVID-19-related symptoms; 19% had 1 symptom; 0% had 2; and 22% had 3 or more" | NR |

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| Stephenson 2021 | Standardised ISARIC Covid-19 Paediatric COVID-19 follow-up questionnaire<br><br>Mental Health of Children and Young People in England Surveys | children and adolescents self-report | **Most common symptoms** among test-positives were tiredness (39%), headache (23%) and shortness of breath (23%).<br>**Most common symptoms** among test-negatives were tiredness (24%), headache (14.2%) and "other" (15.8%)<br><br>67% of test-positives and 53% of test negatives had any symptoms 3 months after testing while 30% of test-positives and 16% of test-negatives had 3+ symptoms | Completed questionnaires were returned a mean time of 14.9 weeks after testing [13.1, 18.9] | For both test-positives and test-negatives, those assigned to the latent class with "multiple symptoms" at 3 months were more likely to be female, older and have poorer physical and mental health before COVID-19,<br>No differences found in mental health, wellbeing and fatigue scores between the groups. However, a large proportion (~ 40%) in both groups reported feeling worried, sad or unhappy. |
| Sterky 2021 | Questionnaire | Telephone interview with parent and child | **Most frequent symptom**s were fatigue (67%), Myalgia/headache (33%), Depression/dysphoria (25%), Respiratory symptoms (25%), Gastrointestinal (25%), Cognitive difficulties (25%), and reduced smell/taste (17%) | 22% of children had persistent symptoms at the end of the follow-up period. | NR |
| Uysal 2022 | Questionnaire | Assessment at outpatient clinics | 28% of children and adolescents had elevated blood pressure of which 16% had elevated blood pressure, 11% had stage-1 hypertension and 1% had stage-2 hypertension.<br><br>children and adolescents with COVID-19 had significantly higher systolic blood pressures than the control group | NR | Systolic blood pressure values were higher in children and adolescents with fatigue, while diastolic blood pressure values were higher in those with lung involvement. |
| Weldetsadik 2022 | WHO acute respiratory infection clinical characterization data tool case report form | Post-discharge follow-up data collected by phone calls | NR | Almost 5% of children and adolescents complained of persistent symptoms including fatigue, fever, cough, joint pain, headache and other non-specific symptoms up to the end of the 3 months follow-up. | NR |

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| Zavala 2021 | On-line and paper questionnaire | Parent or guardian self-report | Of the 64 symptoms potentially associated with long-COVID, 9 were more prevalent among symptomatic cases compared to symptomatic controls. They were confusion (6% vs. 0%), loss of taste (5% vs. 1%), loss of smell (7% vs. 1%), eye pain (3% vs. 0%), sadness (7% vs. 1%), difficulty sleeping (9% vs. 3%), depression (4% vs. 1%), mood swings (8% vs. 2%) and anxiety (8% vs. 3%). | At one month after PCR test, 7% of symptomatic cases and 4% of symptomatic controls were still unwell although not statistically significant | Mental health symptoms at one month later, included sadness (aOR 5.3 [1.2-23.1]), difficulty sleeping (aOR 2.8 [1.1-7.6]), mood swings (aOR 3.94 [1.2-13.4]) and anxiety (aOR 3.0 [1.0-8.9]).<br><br>High prevalence of mental health symptoms among symptomatic cases as well as symptomatic controls, asymptomatic cases and controls highlighting the toll of the pandemic in children and adolescents. |
| Zulu 2022 | Questionnaire | Telephone call interview and home visits by hospital staff | 10% of children and adolescents had persistent symptoms and they mainly complained of cough, fever, chills, arthralgia, headache, and rhinorrhea | | 43% had resolved symptoms |
| **Abbreviations:** ISARIC: International Severe Acute Respiratory and emerging Infection Consortium, NR :Not Reported; OR: Odds Ratio; aOR: adjusted odds ratio; CI: Confidence Intervals; ENT: Ear, Nose, Throat, IRR: Incidence Rate Ratios | | | | | |

Table 2. Characteristics of Included Studies

| Study ID (author) | Country | Sample size (n) | Study Design | Age (years) mean±SD median (IQR) or [Range] | Sex (% Female) | Baseline severity of COVID-19 | Diagnostic Criteria | Duration of Follow-up: mean±SD, median (IQR) or [Range] | Pre-existing Comorbidities | Inclusion Criteria | Risk of Bias |
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| Alghamdi, (66) | Saudi Arabia | 153 | Cross-sectional | Range [12-17] | NR by age-group | NR by age-group | RT-PCR (100%) | > 6 months | NR | Positive PCR test, study included 12–17-year-old among other age groups. | Low |
| Asadi-Pooya (19) | Iran | 58 | Cross-Sectional | 12±3.3<br>Range [6-17] | 52% | 100% initially hospitalised<br><br>17% needed ICU admission | RT-PCR (100%) | >3 months | 28% had comorbidities<br>(9% malignancy, 7% diabetes mellitus, 7% asthma) | People aged 6-17 years discharged from hospital (alive), having an available phone number registered in the database and oral consent by the parent | Low |
| Ashkenazi-Hoffnung (20) | Israel | 90 | Cross Sectional | 12±5 | 41% | 12% admitted to hospital during acute illness | All microbiologically confirmed COVID-19 | 112 days Range [33-410] after COVID-19 diagnosis | 32% background medical conditions<br>25% overweight | People ≤18 years old referred to a designated multidisciplinary clinic for long-COVID | Low |
| Bergia, (35) | Spain | 451 Seropositive<br><br>98 Control group | Cohort | Seropositive 4.0 years (IQR 1.0–10.5)<br><br>Seronegative 7.8 years (IQR 4.1–10.3) | Seropositive 45%<br><br>Control 43% | 82% had mild COVID-19,<br>5% required PICU admission | PCR, and antigen test or serology | 351 days (IQR 330–471 days) | Seropositive group<br><br>13% respiratory chronic diseases or asthma and immunosuppression were the most frequent<br><br>Control group-14% | Seropositive group: people under 18 yrs. old with diagnosis of SARS-CoV-2 infection which had been confirmed by PCR, antigen or serology between 14 March and 31 December<br>Parents/guardians needed to agree.<br>Excluded children and adolescents with asymptomatic SARS-CoV-2 infections. | High |

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| Blankenburg (46) | Germany | 188 Seropositive<br><br>1365 Seronegative | Cohort | Seropositive: 15 (14-17)<br>Range [10-35]<br><br>Seronegative:<br>15 (14-16)<br>Range [10-38] | 55% Seropositive<br><br>56% Seronegative | NR | Serology (100%) | NR | NR | 14-17 year-old students in 14 secondary schools with seroprevalence assessment | Moderate |
| Bloise (67) | Italy | 1413 | Cross Sectional | 10 (IQR: 6 – 13) years | 49% | 28% asymptomatic/mild symptoms; 1% hospitalised (3 had pneumonia, 1 had pericarditis with pericardial effusion, 1 had MIS_C). | NR | 87.49 ± 56.44 days after COVID-19 diagnosis | 77% had no comorbidities (comorbidities: 3% respiratory, 1.6% cardiac, 1.6% gastroenterological, 2% neurological, 1% nephrological, 1% endocrinological, 1% genetic, 0% immunodeficiencies, 0% rheumatological | Families with children infected by SARS-CoV-2 March 2020-March 2021 living in Latina Local Health Authority. | Low |
| Blomberg, (21) | Norway | 33 (16 COVID +ve, 17 seronegative controls) | Cohort | 8 (IQR 6-12) in COVID +ve group | 56% in COVID +ve group | None in this age group were hospitalised. | RT–PCR and serological antibody positivity. | 6 months | NR by age-group | Home-isolated patients with COVID-19 from 28 February to 4 April 2020, diagnosed with PCR test at Emergency Clinic. Household contacts of infected patients served as secondary cases or seronegative controls. | High |

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| Borch, (36) | Denmark | 15,041 SARS-CoV-2 +<br><br>15080 Control | Cohort | SARS-CoV-2 +:<br><br>Mean age 0–5 years was 2.7 years<br><br>Mean age 6–17 years was 12.0 years<br><br>Control:<br>Mean age 0–5 years was 2.8 years<br><br>Mean age 6–17 years was 10.5 years | NR | 7% asymptomatic | RT-PCR (100%) | >4 weeks after diagnosis of COVID-19 | 5% of children in both groups suffered from a chronic disease, mainly a respiratory diagnosis | People aged 0–17 years with verified SARS-CoV-2 infection by RT-PCR and a control group of randomly selected children, who had not been tested positive for SARS-CoV-2. | Low |
| Bossley, (22) | UK | 71 | Cohort | Mean age 6.7<br>Range [11 days–17 years] | 41% | All hospitalised; of the original cohort (n=88): 27% asymptomatic or incidental findings, 48% mild, 13% moderate, 6% severe, 7) critical | SARS-CoV-2 RNA positivity | 3-12 months | 49% of original 88 and 5/11 with >4-week symptoms had comorbidities | People ≤ 18 years with SARS-CoV-2 RNA positivity, admitted between 1 March 2020 and 19 January 2021 to King's College Hospital3. None had PIMS-TS | High |
| Brackel, (68) | The Netherlands | 89 | Cross-sectional | 13 (9-15) | NR | 18% hospitalised | RT-PCR - 53%, Serology - 35%,<br>CD - 38%,<br>Suspected - 9% | ≥12 weeks after diagnosis of COVID-19 | NR | children and adolescents referred to pediatricians across hospitals in The Netherlands for long-COVID assessment | Moderate |

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| Buonsenso a, (69) | UK | 510 | Cross-Sectional | 10.3±3.8 | 56% | 12% asymptomatic, 74% managed at home, 4% hospitalised, 9% attended hospital (not admitted) | RT-PCR-28%, LFT-1%, CD-31%, Suspected 41% | >4 weeks after symptom onset | 56% had comorbidities | children and adolescents with symptoms persisting for more than 4 weeks included. Self-selected from online patient group | High |
| Buonsenso b, (70) | Italy | 129 | Cross-Sectional | 11±4.4 | 48% | 26% asymptomatic, 74% symptomatic<br>5% hospitalised, 2% PICU | RT-PCR (100%) | 163 ±114 days after microbiological diagnosis | 10% neurological, 5% skin problems, 4% asthma, 3% allergic rhinitis | All people ≤18 years diagnosed with microbiologically confirmed COVID-19 presenting to single hospital | Low |
| Buonsenso c, (38) | Italy | SARS-CoV-2 +ve 249<br>SARS-CoV-2 –ve 37 | Cohort | SARS-CoV-2 +ve 10.4 ± 4.5<br>SARS-CoV-2 - ve 10.5 ±3.2 | 51% | 2% hospitalised and of these 33% required PICU | RT-PCR (100%) | 77 days (47-169) after COVID-19 diagnosis | 52% were reported to have comorbidities and risk factors | People ≤18 years old diagnosed with RT-PCR confirmed SARS-CoV-2 infection between April 1st, 2020 and April 31st, 2021 | Moderate |
| Buonsenso d, (75) | Italy | 169 | Case-series | Range [0-18] | 54% | 13% asymptomatic 79% mild, 7% moderate, 1% severe<br>7% admitted to hospital and 2% to PICU | NR | NR | 10% had comorbidities | People 0-18 years old seen at a single post-COVID unit followed at the outpatient setting | Moderate |
| Castro (47) | USA | 5058 | Cohort (preprint) | 12.4 (8.9 - 5.6) | 50% | NR | RT-PCR (100%) | 90-150 days | NR | Children aged 5-18 across 2 New England health systems who had a positive SARS-CoV-2 PCR test between 3/12/2020 and 4/18/2021 and at least 90 days of follow-up visits documented in electronic health record. | High |

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| Chevinsky ,(48) | USA | 305 inpatients 2,368 outpatients | Matched cohort | Range [≤1-17] | 44% inpatient 51% outpatient | NR | CD (100%) | Range [31-120 days] after diagnosis of COVID-19 | NR | People aged <18 years identified from all payer databases including inpatient and outpatient data from April-June 2020 | Low |
| Clavenna, (37) | Italy | 148 children (41 +ve, 107 –ve) | Cohort | +ve: 7 (4-11.5) -ve: 6 (3-10) | +ve 54% -ve 49% | 10% hospitalized, 1 later to ICU: length of hospital stays: 5 days to 1 month; | RT-PCR or serology | 6 months | 7% cases and 8% controls | children with flu-like symptoms and children with family members who had a suspected or confirmed COVID-19 infection | Low |
| Denina, (49) | Italy | 25 | Cohort | 7.8 Range [0.4-15] | 52% | 28% mild, 56% moderate, 16% severe | Serology or RT-PCR | 130 days from discharge (IQR 106–148). | 1 cystic fibrosis 1 congenital heart disease | children and adolescents admitted to the paediatric COVID-department, with COVID-19 from March 1 to June 1, 2020 | High |
| Dobkin,(54) | USA | 29 | Cohort | 13.1±3.9 Range [4-19] | 59% | 93% symptomatic, 14% hospitalised, 3% MIS-C | RT-PCR or confirmed close household contacts with positive SARS-CoV-2 testing | 3.2 ± 1.5 months Range [1.3-6.7 months] after SARS-CoV-2 PCR testing or confirmed close household contact | 62% overweight /Obese, 38% asthma | children and adolescents referred to pulmonary clinic at single hospital with history of SARS-CoV-2 RNA positivity or confirmed close household contact | High |
| Dolezalova, (23) | Czech Republic | 39 (34 for 6-month follow-up) | Cohort | 13.5 (8-15) | 56% | Mild; 1 required hospitalisation but no ventilatory support or oxygen therapy; none had MIS-C. | PCR (64.1%), serology 10%, both 26% | 6 months follow-up for symptom resolution; specific symptoms for > 12 weeks (inclusion criteria). | NR | Paediatric referrals aged 2-18 with persistent respiratory symptoms > 12 weeks after COVID-19. | High |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Donnachie, (40) | Germany | Cases 43,903<br><br>73,873 Controls | Cohort | Range [0-17] | NR | NR | RT-PCR (100%) | 24 months after diagnosis of COVID-19 | NR | Claims data of all patients with a physician consultation related to COVID-19, together with a control group of 1 million patients without treatment related to COVID-19 | Low |
| Dumont, (71) | Switzerland | 660 | Cross-sectional | 9.3 (SD 4.5) | 49% | NR | Tested for anti-SARS-CoV-2 antibodies | 4 weeks | NR | Household survey, selected at random | Low |
| Elvan-Tuz, (50) | Turkey | 1053 | Cohort | 15.8 (14-17) | 61% | 0% asymptomatic 87% mild, 12% moderate, 0% severe, 0% critical | RT-PCR (100%) | 1 month after diagnosis of COVID-19 | NR | 10–18 years old with SARS-CoV-2 detected in respiratory samples by reverse transcriptase-polymerase chain reaction method | High |
| Erol, (39) | Turkey | Cases 121<br><br>Control 95 | Cross Sectional | Cases 9.16 (10.9-17.9)<br>Control 8.42 (8.7-17.4) | Cases 46%<br>Control 47% | 9% asymptomatic | “Children who had COVID-19" | 1 month to 12 months after diagnosis of COVID-19 | NR | Cases: People between the ages of 0-18 who tested positive for COVID-19 or those with a history of COVID-19 seen at the hospital.<br>Control: People between 0-18 who did not have Covid-19 and any diseases that might cause cardiac pathologies | Low |

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| Esmaeilzadeh, (24) | Iran | Asthma-like symptoms group<br>27<br><br>Without Asthma group<br>42 | Cohort | Range [≤6-18] | 39% | NR | RT-PCR (100%) | >1 month after diagnosis of COVID-19 | Asthma-like group cases had a very high familial history of asthma 63%, past medical history of asthma 33%, and Allergic rhinitis 85%. | People <18 years old, being evaluated from February 2020 to January 2021 and having received the diagnosis of COVID-19 | Low |
| Fink, (41) | Brazil | 53 cases<br><br>52 case controls | Cohort | 14.65 (8-18) | 42% | 77% mild; 11% moderate; 6% severe; 6% critical | RT-PCR) or antibody testing | 4.4 months (0.8-10.7) | 89% had pediatric pre-existing chronic conditions, including:<br>83% Immunosuppressive conditions<br>45% Others pre-existing chronic conditions<br>26% Autoimmune conditions | Cases: (1) People 8 -18 years old symptomatic inpatients and outpatients, laboratory-confirmed SARS-CoV-2 infection | Low |
| Haddad (45) | Germany | 544 (140 adolescents, 404 children < 14 years old) | Prospective cohort study | 16 (1) for adolescents,<br>8 (4) for children | 50% | NR | Positive RT-<br>PCR or seropositive on at least 2/3 commercial antibody tests | 11-12 months | NR | Families recruited via local health authorities and an in-hospital database of households with at least one laboratory-confirmed SARS-CoV-2 infection. | Low |
| Kikkenborg Berg, 2022a (2) | Denmark | 6630<br>Case<br><br>21640<br>Control | Cross Sectional | 17.6 (16.4-18.5) | 58% | 34% asymptomatic<br>57% mild, 9% severe | RT-PCR (100%) | >8 weeks after diagnosis of COVID-19 | Case: 48% had comorbidities<br><br>Control: 60% had comorbidities | Adolescents aged 15–18 years who tested positive for SARS-CoV-2 and matched controls who had not tested positive for SARS-CoV-2 in the period Jan 1, 2020, to July 12, 2021 | Low |

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| Kikkenborg Berg, 2022b, (3) | Denmark | 10997 Case<br><br>33016 Control | Cross Sectional | Cases: 10.2 (6.6-12.8)<br>Control: 10.6 (6.9-12.9) | 48%<br><br>48% | 54% asymptomatic, 44% mild, 2% severe | RT-PCR (100%) | >8 weeks after diagnosis of COVID-19 | Cases:<br>0-3 years: 26% comorbidities<br>4-11 years:<br>31% had comorbidities<br>12-14 years: 41% comorbidities<br><br>Control:<br>0-3 years: 27% comorbidities<br>4-11 years: 40% comorbidities<br>12-14 years: 50% comorbidities | People aged 0–14 years with a positive SARS-CoV-2 test with a matched control group who never had a positive PCR test for SARS- CoV-2 in the period between Jan 1, 2020, and July 12, 2021 | Low |
| Knoke, (72) | Germany | 73 SARS-CoV-2 +<br><br>45 SARS-CoV-2 - | Cross-sectional (Preprint) | SARS-CoV-2 +: 10.8±-3.3<br>SARS-CoV-2 - 10±3.5 | 52%<br>62% | 36% symptomatic,<br>64% asymptomatic | Serology or RT-PCR | 2.6 months Range [0.4–6.0] "following COVID-19" | SARS-CoV-2 +: 23% pulmonary disease<br><br>SARS-CoV-2 - 10% pulmonary disease | SARS-CoV-2 positive People 5-18 years, both inpatients and outpatients or seropositive from community study. Seronegative children served as controls | Low |
| Kostev, (52) | Germany | 6568 | Cohort | 10.1 (4.9) | 49% | NR | CD or RT-PCR | 106 ± 87 days after diagnosis of COVID-19 | Most frequent chronic conditions were dermatitis and eczema 24%, disorders of psychological development 16%, and chronic bronchitis 8% | People aged <18 years who were diagnosed with COVID-19 between October 2020 and August 2021 | Low |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Kuczborska, (53) | Poland | Immunocompromised 70<br><br>Immunocompetent 77 | Cohort | Cases: 7.0 (4.0-13.0) Range [8 months-17 years]<br><br>Control: 9.0 (4.0-13.0) Range [4 months-17 years] | 47%<br><br>47% | Cases: 46% asymptomatic39% mild,<br><br>Control: 48% mild, 31% moderate<br>1% MIS-C | RT-PCR (100%) | ≥ 3 months | Allergic disease in control group 29% | Immunocompetent and immunodeficient children and adolescents, who were admitted to the COVID- 19 Subunit of a tertiary referral hospital in Warsaw, Poland. | High |
| Ludvigsson, (76) | Sweden | 5 | Case series | 12 Range [9-15] | 80% | 100% mild disease | CD (100%) | 6-8 months after clinical diagnosis of COVID-19 | 1 comorbidity (asthma, allergies and mild autism spectrum disorder) | Inclusion of children and adolescents whose parents contacted the study author after experiencing symptoms more than 2 months after clinical diagnosis of COVID-19 | Low |
| Marino,(25) | Italy | 6 | Case series | 10.1 ± 3 | 33% | 0% hospitalised | RT-PCR or serology | 5 ± 1.3 months after diagnosis of COVID-19 | NR | Children referred to a tertiary referral hospital in paediatric rheumatology for musculoskeletal manifestation | Moderate |
| Matteudi, (55) | France | 137 | Cohort | Range [0-15] | NR | 28% asymptomatic, 72% symptomatic, 14% hospitalised | RT-PCR (100%) | 10-13 months after diagnosis | NR | People aged <16 years old that were tested positive for SARS-CoV-2 in Marseille public hospitals | High |
| Miller, (56) | England and Wales | 4678 (175 with evidence of past or present SARS-Cov-2 infection) | Cohort (Preprint) | Age <2: 7%<br>Age 2-11 years: 54%<br>Age 12-17 years: 39% | 41% | NR | 63% RT-PCR, 27% serology, 10% RT-PCR and serology | ≥28 days after symptom onset | 8% had at least 1 comorbidity | People ≤17 years who "a) had answered the question about persistent symptoms in the 3rd monthly survey or b) whose household had participated in at least 3 weekly surveys in a 5-week period before 20th of January 2021" | High |

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| Mohiuddin Chowdhury, (26) | Bangladesh | 3 | Cross-sectional | Range [0-10] | NR | NR | RT-PCR (100%) | ≥20 weeks after diagnosis of COVID- 19 | NR | SARS-CoV-2 confirmed cases by RT-PCR identified and collected from the local health facilities of the Chattogram division in Bangladesh | Low |
| Molteni, (51) | UK | 1734 RT-PCR +<br><br>1734 RT-PCR - | Cohort | 13 (10-15) PCR+<br><br>13 (10-15) PCR-<br>Range [5-17] | 50% PCR +, 50% PCR - | 2% of PCR + visited hospital<br><br>2% of PCR - visited hospital | RT-PCR or lateral flow test | ≥28 days after diagnosis of COVID-19 | 13% had asthma PCR+<br><br>13% had asthma PCR- | Data from a mobile smartphone application<br>PCR +: People5-17 years with positive SARS-CoV-2 test<br>PCR -: People 5-17 years with negative SARS-CoV-2 test | Low |
| Morand, (27) | France | 7 | Case series | Mean and median age was 12 years old (10–13 years), | 86% | Mild-moderate | RT-PCR, serology or symptoms highly suggestive of COVID-19 | > 4 weeks | NR | People under 18 with history compatible with SARS-CoV-2 infection who had a medical evaluation 4 weeks+ after infection | Moderate |
| Morrow, (28) | USA | 9 | Case series | Range [4-18] | 67% | NR | Nucleic acid test [NAT], serum antibody test or an acute clinical presentation consistent with COVID-19 | Range between 2-12 months | Patient 1: Type 1 diabetes, anxiety, depression<br>Patient 3: Speech delay<br>Patient 4: Anxiety, asthma, seasonal allergies<br>Patient 5: Dyslexia, seasonal allergies<br>Patient 7: Eosinophilic esophagitis, speech delay (resolved) | The first 9 patients who presented to Pediatric Post COVID-19 Rehabilitation Clinic; < 21 years-old, self-referred with either a history of a positive COVID-19 test or an acute clinical presentation consistent with COVID- 19. | Moderate |

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| | | | | | | | | | Patient 8: Sensory processing disorder, vitiligo, fructose malabsorption, scoliosis<br>Patient 9: Migraine, multiple concussions, sensory integration disorder | | |
| Namazova-Baranova (29) | Russia | 61 | Cross-sectional | 11.4 ± 3.5 | 39% | NR | RT-PCR | 37.9 ± 10.0 days | NR | Inclusion criteria:<br>age from 6 to 18 years; positive PCR; 1 wk-2months from negative test result; parent consent if under 15 yrs old | Low |
| Nogueira López, (57) | Spain | 8 | Cohort | 11.8 (9.8-13.9) | 50% | None hospitalised | 25% RT-PCR,<br>Otherwise, CD or confirmed COVID-19 contact | 52.5 (25–60.5) days after diagnosis with COVID-19 | 13% had comorbidities | People ≤18 years old with confirmed or probable diagnosis of COVID-19 | High |
| Osmanov, (58) | Russia | 518 | Cohort | 10.4 (3–15.2) | 52% | All hospitalised,<br>3% severe | RT-PCR (100%) | 256 days (223-271) after hospital admission | 27% had 1 comorbidity, 17% had ≥2 comorbidities | People≤18 years old with RT-PCR confirmed SARS-CoV-2 infection admitted to single hospital between April and August 2020 | High |

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| Öztürk, (30) | Turkey | 50 | Cohort | 15.3 years (8.1- 18) | 44% | All were hospitalised for acute infection. 40 had non-severe disease and 10 had severe disease (WHO classification). None had ARDS, sepsis, septic shock or any requirement for mechanical ventilation or vasopressor therapy. | Confirmed SARS-CoV-2 infection | 3 months | NR | Patients aged 5–18 years who were hospitalized with a confirmed SARS-CoV-2 infection between May 15 and August 1, 2020, and followed up at the clinic | High |
| Petersen, (59) | Faroe Islands | 21 | Cohort | Range [0-17] | NR | None hospitalised | RT-PCR (100%) | 125± 17 days<br>Range [45-153] after symptom onset | NR | All consecutive RT-PCR positive patients in the Faroe Islands from March to April 2020 | High |
| Radtke, (60) | Switzerland | Seropositive 109<br><br>Seronegative 1246 | Cohort | Range [6-16] | 53% seropositive<br>54% seronegative | None hospitalised | Serology (100%) | >4 weeks, >12 weeks and<br>6-month follow-up after serological testing | 16% had 1 comorbidity in seropositive group<br><br>20% had 1 comorbidity in seronegative group | Children with positive and negative serology results selected from 55 randomly selected primary and secondary schools in Zurich in October/November 2020 | Low |

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| Roessler, (42) | Germany | Cases 11950<br><br>Control 59750 | Cohort | Range [0-17] | 48% Cases | 99% outpatient, 1% hospitalised, 0% in ICU | 100% Laboratory confirmed diagnosis of COVID-19 | ≥3 months after COVID-19 diagnosis | 10% of cases had comorbidities | children and adolescents with documented COVID-19 diagnosis and confirmed laboratory virus detection and children and adolescents without COVID-19 diagnosis regardless of laboratory virus detection through June 30th, 2020 | Low |
| Roge (43), | Latvia | 236 COVID- 19 patients<br><br>142 comparison group patients | Cohort | Study group 10.0 years (IQR: 5–14 years)<br><br>Control group 2 years (IQR: 1–6 years) | 45% study group<br><br>42% control group | Study group 13% required hospitalisation | Positive PCR test or retrospective seroconversion | Study group 73.5 days (43–110 days)<br><br>Control group 69 days (58–84 days) | 22% of study group had known pre-existing comorbidities<br><br>17% control group had comorbidities | Study group<br>(1) People aged 1 month- 18 years<br>(2) history of confirmed SARS-CoV-2 infection or subsequent seroconversion,<br>(3) acute phase of COVID-19 1–6 months before enrollment in the study<br><br>Control group<br>(1) People aged 1 month-18 years,<br>(2) no history of COVID-19<br>(3) clinical and laboratory findings confirming other non-SARS-CoV-2 infections. | Low |

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| Rusetsky, (73) | Russia | 79 | Cross-sectional | 12.9±3.4 | 53% | All hospitalised | RT-PCR (100%) | 60 days after hospital discharge | NR | children and adolescents ≥5 years admitted with SARS-CoV-2 at single hospital | Low |
| Sante, (74) | Italy | 12 Long-COVID<br>17 Recovered | Cross-sectional | Long-COVID: 10.3±4.5<br>Recovered: 7.7±5.5 | 33% Long-COVID<br>36% Recovered | Long-COVID: 8% asymptomatic 92% mild, 0% hospitalised<br>Recovered: 12% asymptomatic, 59% mild, 18% moderate, 12% severe 29% hospitalised | RT-PCR (100%) | 98.5 ± 41.5 "days after acute SARS-CoV-2 infection" | Long-COVID: 25% had comorbidities<br>Recovered: 18% had comorbidities | children and adolescents "fully recovered or with PASC assessed in a dedicated post-COVID outpatient service" | Moderate |
| Savino, (31) | Italy | 5 | Case series | 2-15 years old | 44% | NR | RT-PCR | 3-15 months | NR | All patients < 18 years with a previous history of COVID-19 consecutively admitted to unit due to new-onset neuropsychiatric symptoms. | Moderate |
| Say, (61) | Australia | 12 | Cohort | 3.7±3.5 | 42% | 92% mild, 8% severe 50% admitted to hospital (17% for observation, 8% for fluid rehydration, 25% ICU) | "Children who tested positive for SARS-CoV-2" | Range [3-6 months] after diagnosis | 17% chronic respiratory condition 8% congenital cardiac disease | People aged ≤18 years referred to a dedicated COVID-follow up clinic | High |
| Smane, (62) | Latvia | 30 | Cohort | 9.2±5.2 Range [3 months-17 years] | 43% | 17% asymptomatic, 80% mild, 3% moderate, 17% hospitalised | RT-PCR (100%) | 101 ± 7 days after infection | 23% had comorbidities | SARS-CoV-2 positive People 0-17 years enrolled after recovery from COVID-19 at a post-acute outpatient centre | High |

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| Smane b, (32) | Latvia | 92 | Cohort | median 12 years (8–15 years) | 39% | NR | RT-PCR | 55 days (IQR 30–104 days) | NR | NR | High |
| Stephenson, (63) | England | 3065 RT-PCR +<br><br>3739 RT-PCR - | Cohort | Age: 11-15 PCR + (56%)<br>Age: 16-17 PCR + (44%)<br><br>Age: 11-15 PCR - (57%)<br>Age: 16-17 PCR - (43%) | 64% PCR +<br><br>63% PCR - | 65% of PCR + asymptomatic<br>35% of PCR + symptomatic<br><br>92% of PCR - asymptomatic<br>8% of PCR- symptomatic | RT-PCR (100%) | 14.9 weeks (13.1-18.9) after testing | NR | SARS-CoV-2 PCR-positive people aged 11-17 years selected from a national database of test results held by Public Health England from January-March 2021 | Low |
| Sterky, (64) | Sweden | 55 | Cohort | Range [<1-18] | 42% | 9 children had MIS-C, 2 of which required ICU<br>Other reasons for admission: 38% dehydration, 35% “infection observation”, 23% for “inhalations” | RT-PCR (100%) | 219 days (123-324) after hospital admission | 35% had comorbidities | People aged 0-18 years who were admitted to one of the two paediatric hospitals in the Stockholm Region and RT-PCR positive for SARS-CoV- 2 | High |
| Uysal, (44) | Turkey | 100 Cases<br><br>32 Control | Cohort | 15.8±2 years Range [10-18.4] | 61% Cases<br><br>46% Control | 3% mild lung involvement | RT-PCR (100%) | 208.09 ± 59.41 days after PCR positivity | NR | People aged 10-18 years of age with a normal weight, defined as a body mass index below the 85th percentile, not having been hospitalized after COVID-19 positivity and having passed at least 8 weeks after PCR positivity | Low |

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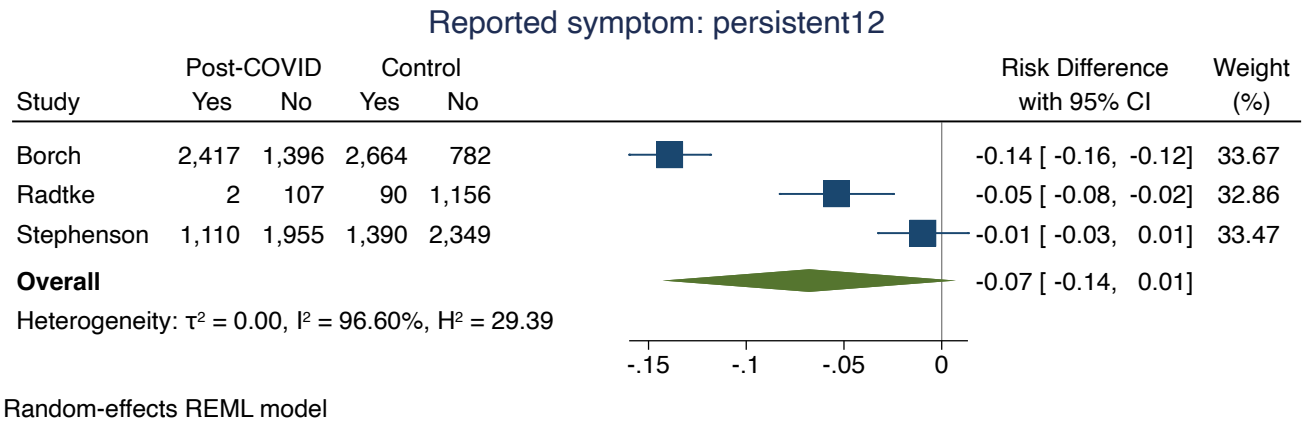
|---|---|---|---|---|---|---|---|---|---|---|---|
| Weldetsadik, (33) | Ethiopia | 79 | Cohort | 6.9 ±6.36<br>Range [0-19] | 51% | 17% asymptomatic, 56% mild, 19% moderate, 6% severe, and 2% critical | RT-PCR (100%) | "3 months follow-up after discharge" | 67% with comorbid disease | RT-PCR confirmed COVID-19 children and adolescents admitted the COVID-19 treatment center during August 2020 to January 2021 | High |
| Zavala, (65) | UK | Case: 472<br><br>Control: 387 | Cohort | 10 (6-13) | 50% cases, 47% controls | Cases:<br>68% symptomatic, 32% asymptomatic<br><br>Controls: 40% symptomatic 60% asymptomatic | RT-PCR (100%) | >1 month after testing | 7% had one or more co-morbidities | People aged 2-16 years tested for SARS-CoV-2 by RT-PCR identified from the national testing data in England during the first week of January 2021c | Low |
| Zulu, (34) | Zambia | 63 | Cohort | NR | 67% | 44% asymptomatic | RT-PCR (100%) | 54 days (IQR): 46-59 days) after positive test | NR | Participants who tested positive for SARS-CoV-2 by RT-PCR and were not hospitalised | High |

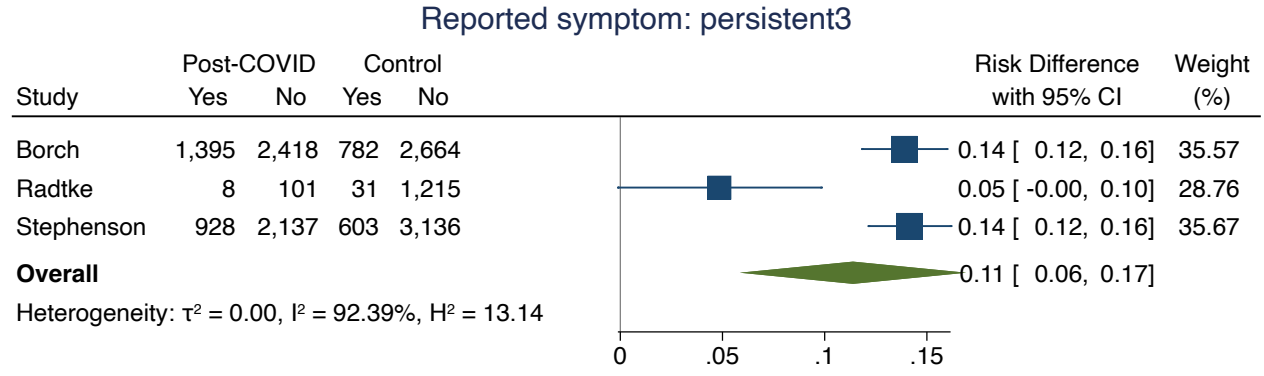
NOTE: Data are means ± standard deviations, medians with interquartile ranges (IQR) or [ranges]. Abbreviations: RT-PCR: Positive Reverse transcription Polymerase chain reaction; NR: not reported; CD: Clinical Diagnosis, LFT: Lateral Flow Test; MIS-C: Multisystem Inflammatory Syndrome in Children; ICU: Intensive Care Unit; PICU: Paediatric Intensive Care Unit; PASC: Post-Acute Sequelae of SARS-CoV-2

Figure 2. Meta-analysis

## Persistent Symptoms

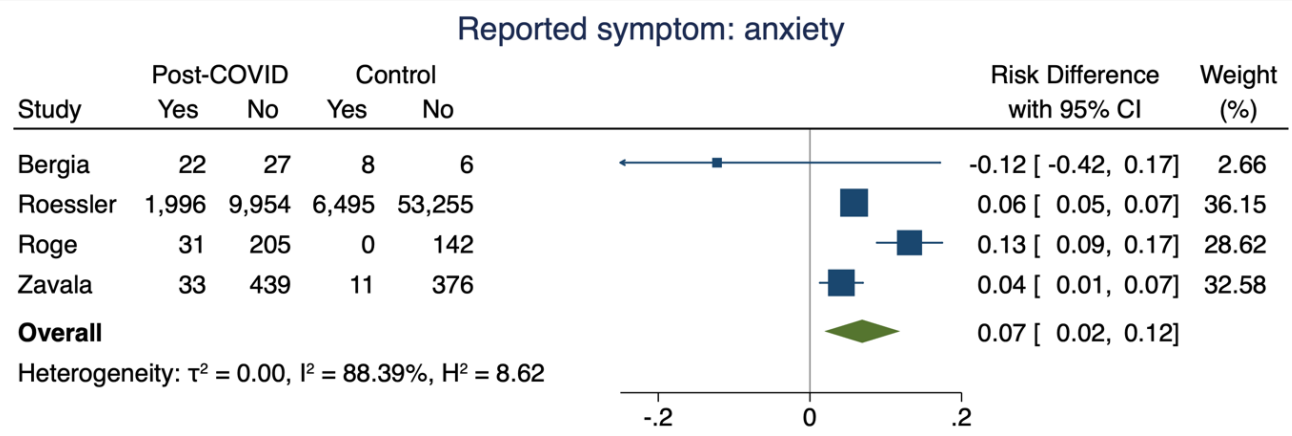



Random-effects REML model




Random-effects REML model

## Individual Symptoms (in alphabetical order)

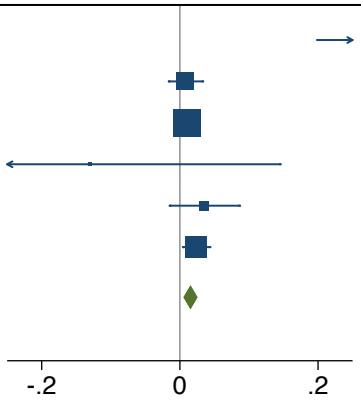



Random-effects REML model

## Reported symptom: loss of appetite

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 28 | 21 | 2 | 12 | 0.43 [ 0.20, 0.66] | 0.20 |
| Kikkkenborg Berg A | 9 | 233 | 153 | 5,108 | 0.01 [ -0.02, 0.03] | 17.56 |
| Kikkkenborg Berg B | 6 | 327 | 72 | 9,336 | 0.01 [ -0.00, 0.02] | 49.91 |
| Molteni | 31 | 46 | 8 | 7 | -0.13 [ -0.41, 0.14] | 0.14 |
| Roge | 20 | 216 | 7 | 135 | 0.04 [ -0.01, 0.09] | 4.09 |
| Zavala | 16 | 456 | 4 | 383 | 0.02 [ 0.00, 0.04] | 28.10 |
| **Overall** | | | | | 0.02 [ 0.01, 0.03] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.01\%$, $H^2 = 1.00$

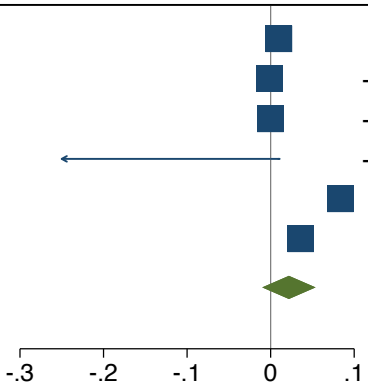



Random-effects REML model

## Reported symptom: chest pain

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 215 | 14,668 | 68 | 15,166 | 0.01 [ 0.01, 0.01] | 19.96 |
| Kikkkenborg Berg A | 2 | 240 | 48 | 5,213 | -0.00 [ -0.01, 0.01] | 19.46 |
| Kikkkenborg Berg B | 0 | 333 | 2 | 9,406 | -0.00 [ -0.00, 0.00] | 19.98 |
| Molteni | 16 | 61 | 7 | 8 | -0.26 [ -0.53, 0.01] | 1.33 |
| Roessler | 2,391 | 9,559 | 6,967 | 52,783 | 0.08 [ 0.08, 0.09] | 19.75 |
| Stephenson | 216 | 2,849 | 129 | 3,610 | 0.04 [ 0.03, 0.05] | 19.53 |
| **Overall** | | | | | 0.02 [ -0.01, 0.05] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 99.79\%$, $H^2 = 486.72$

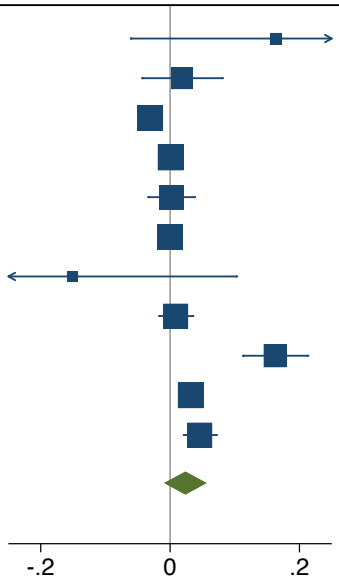



Random-effects REML model

## Reported symptom: cognitive difficulties

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 15 | 34 | 2 | 12 | 0.16 [ -0.06, 0.39] | 1.81 |
| Blankenburg | 144 | 34 | 1,049 | 278 | 0.02 [ -0.04, 0.08] | 8.32 |
| Borch | 910 | 13,973 | 1,408 | 13,826 | -0.03 [ -0.04, -0.03] | 11.75 |
| Ewan | 58 | 43,845 | 43 | 73,830 | 0.00 [ 0.00, 0.00] | 11.80 |
| Kikkkenborg Berg A | 20 | 222 | 426 | 4,835 | 0.00 [ -0.03, 0.04] | 10.37 |
| Kikkkenborg Berg B | 7 | 326 | 201 | 9,207 | -0.00 [ -0.02, 0.02] | 11.49 |
| Molteni | 14 | 63 | 5 | 10 | -0.15 [ -0.41, 0.10] | 1.46 |
| Radtke | 2 | 107 | 12 | 1,234 | 0.01 [ -0.02, 0.03] | 11.00 |
| Roge | 40 | 196 | 1 | 141 | 0.16 [ 0.11, 0.21] | 9.28 |
| Stephenson | 198 | 2,867 | 123 | 3,616 | 0.03 [ 0.02, 0.04] | 11.66 |
| Zavala | 29 | 443 | 6 | 381 | 0.05 [ 0.02, 0.07] | 11.05 |
| **Overall** | | | | | 0.02 [ -0.01, 0.06] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 98.81\%$, $H^2 = 83.91$

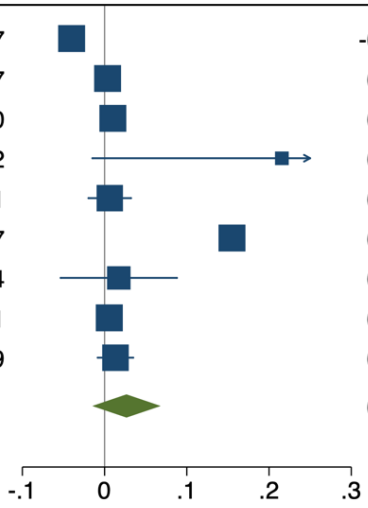



Random-effects REML model

## Reported symptom: cough

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 397 | 14,486 | 1,017 | 14,217 | -0.04 [ -0.04, -0.04] | 12.78 |
| Kikkkenborg Berg A | 2 | 240 | 24 | 5,237 | 0.00 [ -0.01, 0.02] | 12.67 |
| Kikkkenborg Berg B | 4 | 329 | 18 | 9,390 | 0.01 [ -0.00, 0.02] | 12.67 |
| Molteni | 32 | 45 | 3 | 12 | 0.22 [ -0.01, 0.45] | 2.58 |
| Radtke | 2 | 107 | 15 | 1,231 | 0.01 [ -0.02, 0.03] | 12.18 |
| Roessler | 4,368 | 7,582 | 12,583 | 47,167 | 0.15 [ 0.15, 0.16] | 12.72 |
| Roge | 34 | 202 | 18 | 124 | 0.02 [ -0.05, 0.09] | 9.31 |
| Stephenson | 98 | 2,967 | 98 | 3,641 | 0.01 [ -0.00, 0.01] | 12.73 |
| Zavala | 16 | 456 | 8 | 379 | 0.01 [ -0.01, 0.03] | 12.36 |
| **Overall** | | | | | 0.03 [ -0.01, 0.07] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 99.06\%$, $H^2 = 106.12$

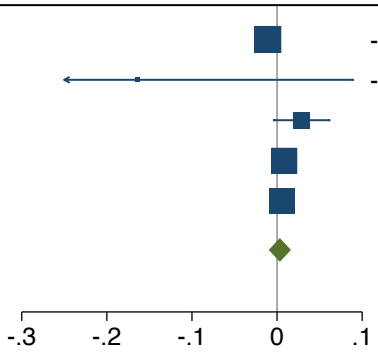



Random-effects REML model

## Reported symptom: diarrhoea

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 100 | 14,783 | 267 | 14,967 | -0.01 [ -0.01, -0.01] | 32.27 |
| Molteni | 13 | 64 | 5 | 10 | -0.16 [ -0.42, 0.09] | 0.25 |
| Roge | 10 | 226 | 2 | 140 | 0.03 [ -0.00, 0.06] | 10.67 |
| Stephenson | 92 | 2,973 | 80 | 3,659 | 0.01 [ 0.00, 0.02] | 29.28 |
| Zavala | 4 | 468 | 1 | 386 | 0.01 [ -0.00, 0.02] | 27.52 |
| **Overall** | | | | | 0.00 [ -0.01, 0.02] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 86.58\%$, $H^2 = 7.45$

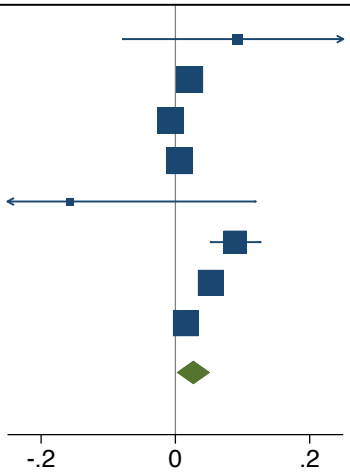



Random-effects REML model

## Reported symptom: dizziness

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 8 | 41 | 1 | 13 | 0.09 [ -0.08, 0.26] | 1.90 |
| Borch | 504 | 14,379 | 188 | 15,046 | 0.02 [ 0.02, 0.02] | 17.53 |
| Kikkkenborg Berg A | 2 | 240 | 79 | 5,182 | -0.01 [ -0.02, 0.01] | 16.91 |
| Kikkkenborg Berg B | 2 | 331 | 2 | 9,406 | 0.01 [ -0.00, 0.01] | 17.25 |
| Molteni | 29 | 48 | 8 | 7 | -0.16 [ -0.43, 0.12] | 0.78 |
| Roge | 21 | 215 | 0 | 142 | 0.09 [ 0.05, 0.13] | 12.77 |
| Stephenson | 419 | 2,646 | 314 | 3,425 | 0.05 [ 0.04, 0.07] | 16.51 |
| Zavala | 11 | 461 | 3 | 384 | 0.02 [ -0.00, 0.03] | 16.36 |
| **Overall** | | | | | 0.03 [ 0.00, 0.05] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 96.20\%$, $H^2 = 26.35$

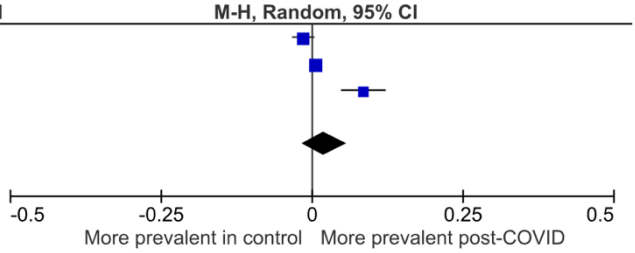



Random-effects REML model

## Reported symptom: postural symptoms

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Kikkenborg Berg 2022a | 5 | 242 | 187 | 5261 | 34.9% | -0.01 [-0.03, 0.00] |
| Kikkenborg Berg 2022b | 2 | 333 | 2 | 9408 | 37.6% | 0.01 [-0.00, 0.01] |
| Roge 2021 | 20 | 236 | 0 | 142 | 27.5% | 0.08 [0.05, 0.12] |
| **Total (95% CI)** | | **811** | | **14811** | **100.0%** | **0.02 [-0.02, 0.06]** |
| Total events | 27 | | 189 | | | |

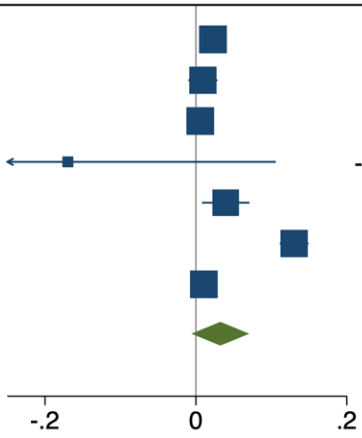
Heterogeneity: Tau² = 0.00; Chi² = 23.06, df = 2 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.09 (P = 0.28)




## Reported symptom: dyspnoea

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Ewan | 1,671 | 42,232 | 1,147 | 72,726 | 0.02 [ 0.02, 0.02] | 16.90 |
| Kikkkenborg Berg A | 5 | 237 | 60 | 5,201 | 0.01 [ -0.01, 0.03] | 16.28 |
| Kikkkenborg Berg B | 2 | 331 | 2 | 9,406 | 0.01 [ -0.00, 0.01] | 16.77 |
| Molteni | 28 | 49 | 8 | 7 | -0.17 [ -0.44, 0.10] | 1.73 |
| Roge | 11 | 225 | 1 | 141 | 0.04 [ 0.01, 0.07] | 15.28 |
| Stephenson | 717 | 2,348 | 388 | 3,351 | 0.13 [ 0.11, 0.15] | 16.30 |
| Zavala | 5 | 467 | 0 | 387 | 0.01 [ 0.00, 0.02] | 16.74 |
| **Overall** | | | | | 0.03 [ -0.01, 0.07] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 98.88\%$, $H^2 = 89.54$

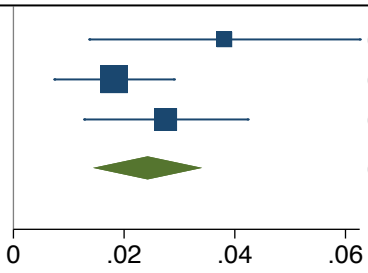



Random-effects REML model

## Reported symptom: earache or ringing in ears

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Roge | 9 | 227 | 0 | 142 | 0.04 [ 0.01, 0.06] | 14.58 |
| Stephenson | 191 | 2,874 | 165 | 3,574 | 0.02 [ 0.01, 0.03] | 51.77 |
| Zavala | 13 | 459 | 0 | 387 | 0.03 [ 0.01, 0.04] | 33.65 |
| **Overall** | | | | | 0.02 [ 0.01, 0.03] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 22.89\%$, $H^2 = 1.30$

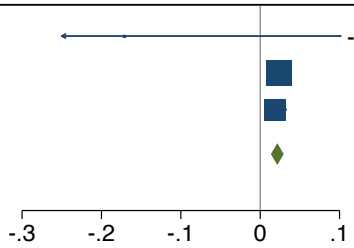



Random-effects REML model

## Reported symptom: eye soreness

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Molteni | 33 | 44 | 9 | 6 | -0.17 [ -0.44, 0.10] | 0.08 |
| Stephenson | 182 | 2,883 | 134 | 3,605 | 0.02 [ 0.01, 0.03] | 59.01 |
| Zavala | 9 | 463 | 0 | 387 | 0.02 [ 0.01, 0.03] | 40.90 |
| **Overall** | | | | | 0.02 [ 0.01, 0.03] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

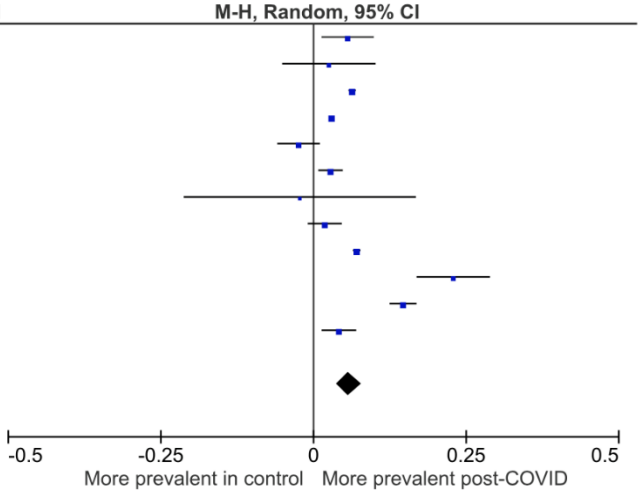



Random-effects REML model

## Reported symptom: fatigue

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bergia 2022 | 39 | 451 | 3 | 98 | 7.6% | 0.06 [0.01, 0.10] |
| Blankenberg 2021 | 71 | 178 | 496 | 1327 | 4.4% | 0.03 [-0.05, 0.10] |
| Borch 2022 | 1578 | 14883 | 654 | 15234 | 11.2% | 0.06 [0.06, 0.07] |
| Ewan Donnachie 2022 | 3211 | 43903 | 3226 | 73873 | 11.3% | 0.03 [0.03, 0.03] |
| Kikkenborg Berg 2022a | 19 | 242 | 542 | 5261 | 8.5% | -0.02 [-0.06, 0.01] |
| Kikkenborg Berg 2022b | 12 | 333 | 78 | 9408 | 10.2% | 0.03 [0.01, 0.05] |
| Molteni 2021 | 65 | 77 | 13 | 15 | 1.1% | -0.02 [-0.21, 0.17] |
| Radtke 2021 | 2 | 109 | 0 | 1246 | 9.4% | 0.02 [-0.01, 0.05] |
| Roessler 2021 | 1503 | 11950 | 3292 | 59750 | 11.2% | 0.07 [0.06, 0.08] |
| Roge 2021 | 59 | 236 | 3 | 142 | 5.7% | 0.23 [0.17, 0.29] |
| Stephenson 2021 | 1196 | 3065 | 911 | 3739 | 10.0% | 0.15 [0.12, 0.17] |
| Zavala 2021 | 33 | 472 | 11 | 387 | 9.3% | 0.04 [0.01, 0.07] |
| **Total (95% CI)** | | **75899** | | **170480** | **100.0%** | **0.06 [0.04, 0.08]** |
| Total events | 7788 | | 9229 | | | |

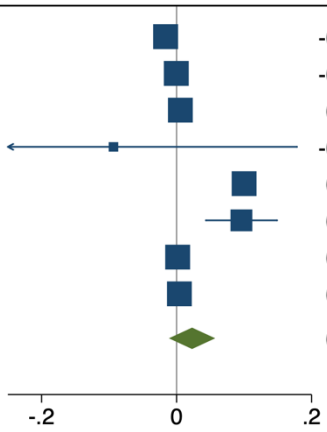
Heterogeneity: Tau² = 0.00; Chi² = 372.72, df = 11 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.50 (P < 0.00001)




## Reported symptom: fever

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 84 | 14,799 | 333 | 14,901 | -0.02 [ -0.02, -0.01] | 14.67 |
| Kikkkenborg Berg A | 0 | 242 | 2 | 5,259 | -0.00 [ -0.00, 0.00] | 14.68 |
| Kikkkenborg Berg B | 2 | 331 | 4 | 9,404 | 0.01 [ -0.00, 0.01] | 14.56 |
| Molteni | 39 | 38 | 9 | 6 | -0.09 [ -0.37, 0.18] | 1.42 |
| Roessler | 3,327 | 8,623 | 10,659 | 49,091 | 0.10 [ 0.09, 0.11] | 14.55 |
| Roge | 31 | 205 | 5 | 137 | 0.10 [ 0.04, 0.15] | 10.87 |
| Stephenson | 50 | 3,015 | 55 | 3,684 | 0.00 [ -0.00, 0.01] | 14.62 |
| Zavala | 2 | 470 | 0 | 387 | 0.00 [ -0.00, 0.01] | 14.62 |
| **Overall** | | | | | 0.02 [ -0.01, 0.06] | |

Heterogeneity: $\tau^2$ = 0.00, $I^2$ = 99.80%, $H^2$ = 503.45

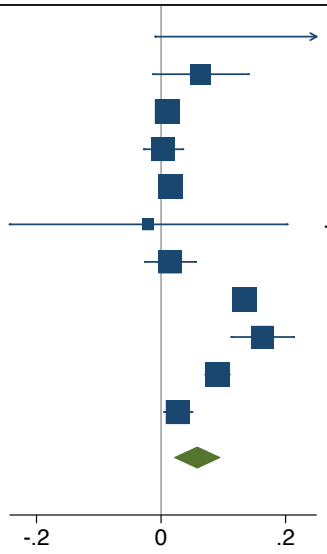



Random-effects REML model

## Reported symptom: headache

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 31 | 18 | 5 | 9 | 0.28 [ -0.01, 0.56] | 1.53 |
| Blankenburg | 109 | 69 | 728 | 598 | 0.06 [ -0.01, 0.14] | 7.91 |
| Borch | 1,033 | 13,850 | 911 | 14,323 | 0.01 [ 0.00, 0.02] | 11.67 |
| Kikkkenborg Berg A | 15 | 227 | 309 | 4,952 | 0.00 [ -0.03, 0.03] | 10.84 |
| Kikkkenborg Berg B | 7 | 326 | 49 | 9,359 | 0.02 [ 0.00, 0.03] | 11.47 |
| Molteni | 60 | 17 | 12 | 3 | -0.02 [ -0.24, 0.20] | 2.31 |
| Radtke | 5 | 104 | 39 | 1,207 | 0.01 [ -0.03, 0.06] | 10.31 |
| Roessler | 4,382 | 7,568 | 13,886 | 45,864 | 0.13 [ 0.13, 0.14] | 11.62 |
| Roge | 40 | 196 | 1 | 141 | 0.16 [ 0.11, 0.21] | 9.72 |
| Stephenson | 710 | 2,355 | 530 | 3,209 | 0.09 [ 0.07, 0.11] | 11.37 |
| Zavala | 20 | 452 | 6 | 381 | 0.03 [ 0.00, 0.05] | 11.25 |
| **Overall** | | | | | 0.06 [ 0.02, 0.10] | |

Heterogeneity: $\tau^2$ = 0.00, $I^2$ = 97.60%, $H^2$ = 41.75

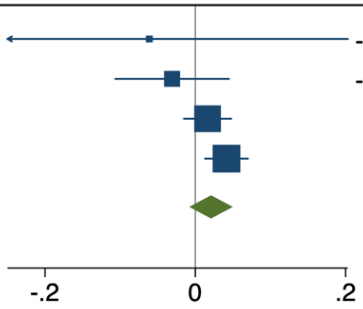



Random-effects REML model

## Reported symptom: insomnia

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 11 | 38 | 4 | 10 | -0.06 [ -0.33, 0.20] | 1.18 |
| Blankenburg | 112 | 66 | 874 | 450 | -0.03 [ -0.11, 0.04] | 12.36 |
| Radtke | 3 | 106 | 14 | 1,232 | 0.02 [ -0.01, 0.05] | 41.28 |
| Zavala | 33 | 439 | 11 | 376 | 0.04 [ 0.01, 0.07] | 45.19 |
| **Overall** | | | | | 0.02 [ -0.01, 0.05] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 32.41\%$, $H^2 = 1.48$

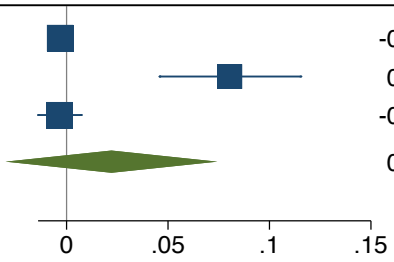



Random-effects REML model

## Reported symptom: joint pain or swelling

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 220 | 14,663 | 274 | 14,960 | -0.00 [ -0.01, -0.00] | 35.04 |
| Roge | 19 | 217 | 0 | 142 | 0.08 [ 0.05, 0.12] | 30.37 |
| Zavala | 2 | 470 | 3 | 384 | -0.00 [ -0.01, 0.01] | 34.59 |
| **Overall** | | | | | 0.02 [ -0.03, 0.07] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 98.62\%$, $H^2 = 72.29$



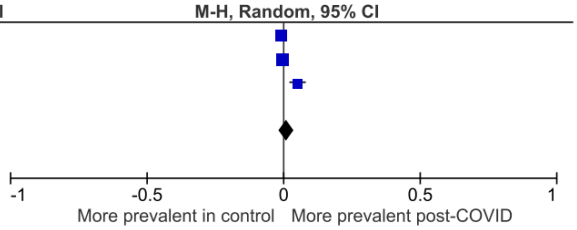

Random-effects REML model

## Reported symptom: light sensitivity

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Kikkenborg Berg 2022a | 5 | 242 | 152 | 5261 | 33.7% | -0.01 [-0.03, 0.01] |
| Kikkenborg Berg 2022b | 0 | 333 | 33 | 9408 | 38.8% | -0.00 [-0.01, 0.00] |
| Roge 2021 | 12 | 236 | 0 | 142 | 27.5% | 0.05 [0.02, 0.08] |
| **Total (95% CI)** | | **811** | | **14811** | **100.0%** | **0.01 [-0.02, 0.04]** |
| Total events | 17 | | 185 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 18.22, df = 2 (P = 0.0001); I² = 89%

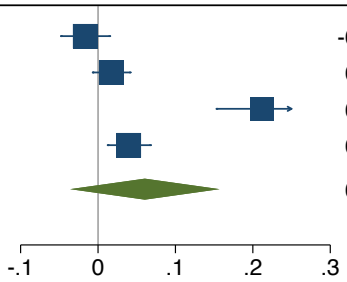
Test for overall effect: Z = 0.67 (P = 0.50)




## Reported symptom: mood swings

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Kikkkenborg Berg A | 15 | 227 | 414 | 4,847 | -0.02 [ -0.05, 0.01] | 25.29 |
| Kikkkenborg Berg B | 17 | 316 | 320 | 9,088 | 0.02 [ -0.01, 0.04] | 25.57 |
| Roge | 55 | 181 | 3 | 139 | 0.21 [ 0.15, 0.27] | 23.69 |
| Zavala | 31 | 441 | 10 | 377 | 0.04 [ 0.01, 0.07] | 25.45 |
| **Overall** | | | | | 0.06 [ -0.04, 0.16] | |

Heterogeneity: $\tau^2 = 0.01$, $I^2 = 97.32\%$, $H^2 = 37.32$

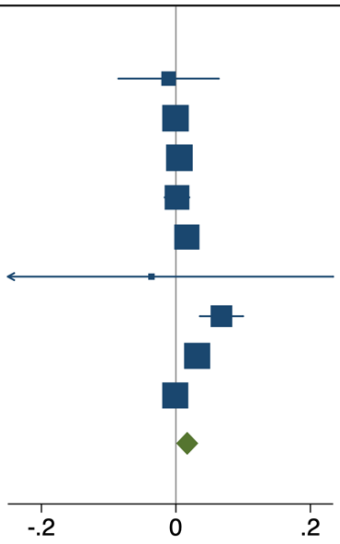



Random-effects REML model

## Reported symptom: myalgia

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 27 | 22 | 1 | 13 | 0.48 [ 0.29, 0.67] | 0.68 |
| Blankenburg | 62 | 116 | 477 | 851 | -0.01 [ -0.09, 0.06] | 3.64 |
| Borch | 330 | 14,553 | 346 | 14,888 | -0.00 [ -0.00, 0.00] | 15.17 |
| Ewan | 688 | 43,215 | 774 | 73,099 | 0.01 [ 0.00, 0.01] | 15.25 |
| Kikkkenborg Berg A | 5 | 237 | 100 | 5,161 | 0.00 [ -0.02, 0.02] | 12.80 |
| Kikkkenborg Berg B | 7 | 326 | 44 | 9,364 | 0.02 [ 0.00, 0.03] | 13.42 |
| Molteni | 28 | 49 | 6 | 9 | -0.04 [ -0.31, 0.23] | 0.36 |
| Roge | 16 | 220 | 0 | 142 | 0.07 [ 0.04, 0.10] | 9.60 |
| Stephenson | 165 | 2,900 | 83 | 3,656 | 0.03 [ 0.02, 0.04] | 14.55 |
| Zavala | 2 | 470 | 2 | 385 | -0.00 [ -0.01, 0.01] | 14.55 |
| **Overall** | | | | | 0.02 [ 0.00, 0.03] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 97.56\%$, $H^2 = 41.00$

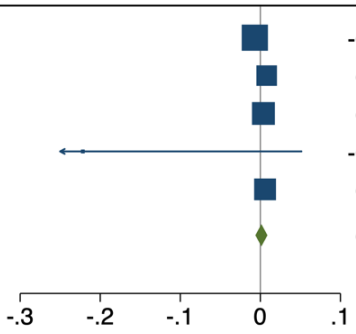



Random-effects REML model

## Reported symptom: nausea

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 243 | 14,640 | 354 | 14,880 | -0.01 [ -0.01, -0.00] | 33.55 |
| Kikkkenborg Berg A | 2 | 240 | 2 | 5,259 | 0.01 [ -0.00, 0.02] | 19.44 |
| Kikkkenborg Berg B | 2 | 331 | 20 | 9,388 | 0.00 [ -0.00, 0.01] | 24.66 |
| Molteni | 24 | 53 | 8 | 7 | -0.22 [ -0.49, 0.05] | 0.07 |
| Zavala | 4 | 468 | 1 | 386 | 0.01 [ -0.00, 0.02] | 22.27 |
| **Overall** | | | | | 0.00 [ -0.01, 0.01] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 68.04\%$, $H^2 = 3.13$

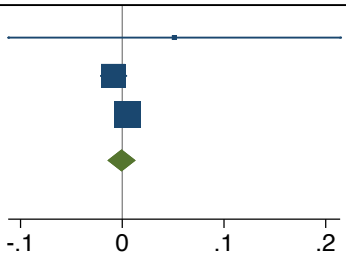



Random-effects REML model

## Reported symptom: palpitations

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 6 | 43 | 1 | 13 | 0.05 [ -0.11, 0.21] | 0.72 |
| Kikkkenborg Berg A | 2 | 240 | 91 | 5,170 | -0.01 [ -0.02, 0.00] | 45.02 |
| Kikkkenborg Berg B | 2 | 331 | 5 | 9,403 | 0.01 [ -0.00, 0.01] | 54.25 |
| **Overall** | | | | | -0.00 [ -0.01, 0.01] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 57.90\%$, $H^2 = 2.38$

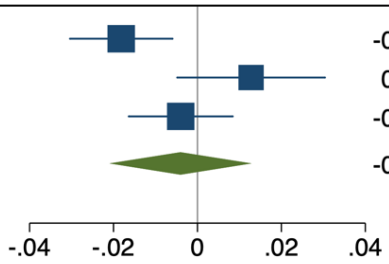



Random-effects REML model

## Reported symptom: rash

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Kikkkenborg Berg A | 2 | 240 | 139 | 5,122 | -0.02 [ -0.03, -0.01] | 35.34 |
| Kikkkenborg Berg B | 9 | 324 | 134 | 9,274 | 0.01 [ -0.00, 0.03] | 29.50 |
| Zavala | 3 | 469 | 4 | 383 | -0.00 [ -0.02, 0.01] | 35.16 |
| **Overall** | | | | | -0.00 [ -0.02, 0.01] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 77.68\%$, $H^2 = 4.48$

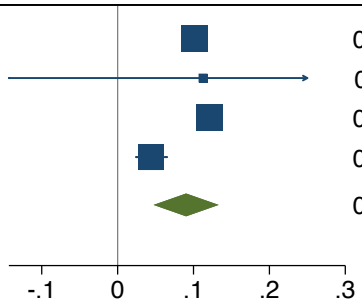



Random-effects REML model

## Reported symptom: altered smell

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Borch | 1,529 | 13,354 | 19 | 15,215 | 0.10 [ 0.10, 0.11] | 33.42 |
| Molteni | 60 | 17 | 10 | 5 | 0.11 [ -0.14, 0.37] | 2.60 |
| Stephenson | 414 | 2,651 | 51 | 3,688 | 0.12 [ 0.11, 0.13] | 32.62 |
| Zavala | 22 | 450 | 1 | 386 | 0.04 [ 0.02, 0.06] | 31.36 |
| **Overall** | | | | | 0.09 [ 0.05, 0.13] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 96.54\%$, $H^2 = 28.88$

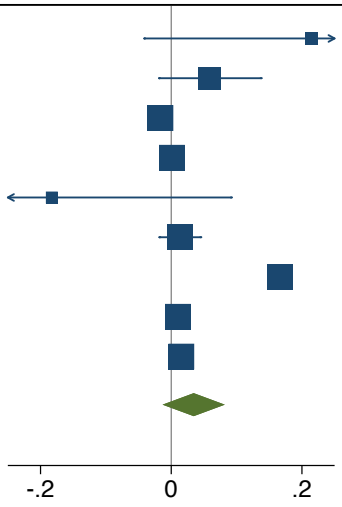



Random-effects REML model

## Reported symptom: stomach-ache

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Bergia | 21 | 28 | 3 | 11 | 0.21 [ -0.04, 0.47] | 2.79 |
| Blankenburg | 82 | 96 | 533 | 794 | 0.06 [ -0.02, 0.14] | 10.35 |
| Kikkkenborg Berg A | 0 | 242 | 87 | 5,174 | -0.02 [ -0.02, -0.01] | 14.28 |
| Kikkkenborg Berg B | 4 | 329 | 102 | 9,306 | 0.00 [ -0.01, 0.01] | 14.16 |
| Molteni | 27 | 50 | 8 | 7 | -0.18 [ -0.46, 0.09] | 2.50 |
| Radtke | 3 | 106 | 18 | 1,228 | 0.01 [ -0.02, 0.04] | 13.45 |
| Roessler | 6,446 | 5,504 | 22,293 | 37,457 | 0.17 [ 0.16, 0.18] | 14.20 |
| Stephenson | 119 | 2,946 | 107 | 3,632 | 0.01 [ 0.00, 0.02] | 14.22 |
| Zavala | 11 | 461 | 3 | 384 | 0.02 [ -0.00, 0.03] | 14.05 |
| **Overall** | | | | | 0.03 [ -0.01, 0.08] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 99.14\%$, $H^2 = 116.63$

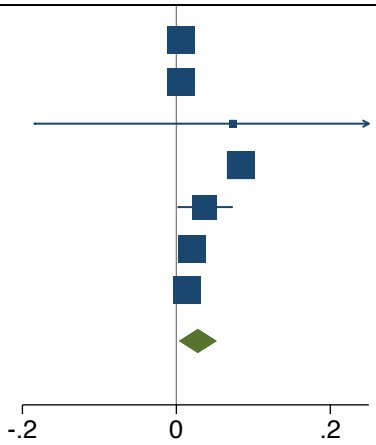



Random-effects REML model

## Reported symptom: sore throat

| Study | Post-COVID Yes | Post-COVID No | Control Yes | Control No | Risk Difference with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Kikkkenborg Berg A | 2 | 240 | 13 | 5,248 | 0.01 [ -0.01, 0.02] | 17.11 |
| Kikkkenborg Berg B | 2 | 331 | 0 | 9,408 | 0.01 [ -0.00, 0.01] | 17.42 |
| Molteni | 57 | 20 | 10 | 5 | 0.07 [ -0.18, 0.33] | 0.87 |
| Roessler | 2,391 | 9,559 | 6,967 | 52,783 | 0.08 [ 0.08, 0.09] | 17.48 |
| Roge | 12 | 224 | 2 | 140 | 0.04 [ 0.00, 0.07] | 13.26 |
| Stephenson | 291 | 2,774 | 281 | 3,458 | 0.02 [ 0.01, 0.03] | 16.89 |
| Zavala | 8 | 464 | 1 | 386 | 0.01 [ 0.00, 0.03] | 16.97 |
| **Overall** | | | | | 0.03 [ 0.00, 0.05] | |

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 95.77\%$, $H^2 = 23.63$

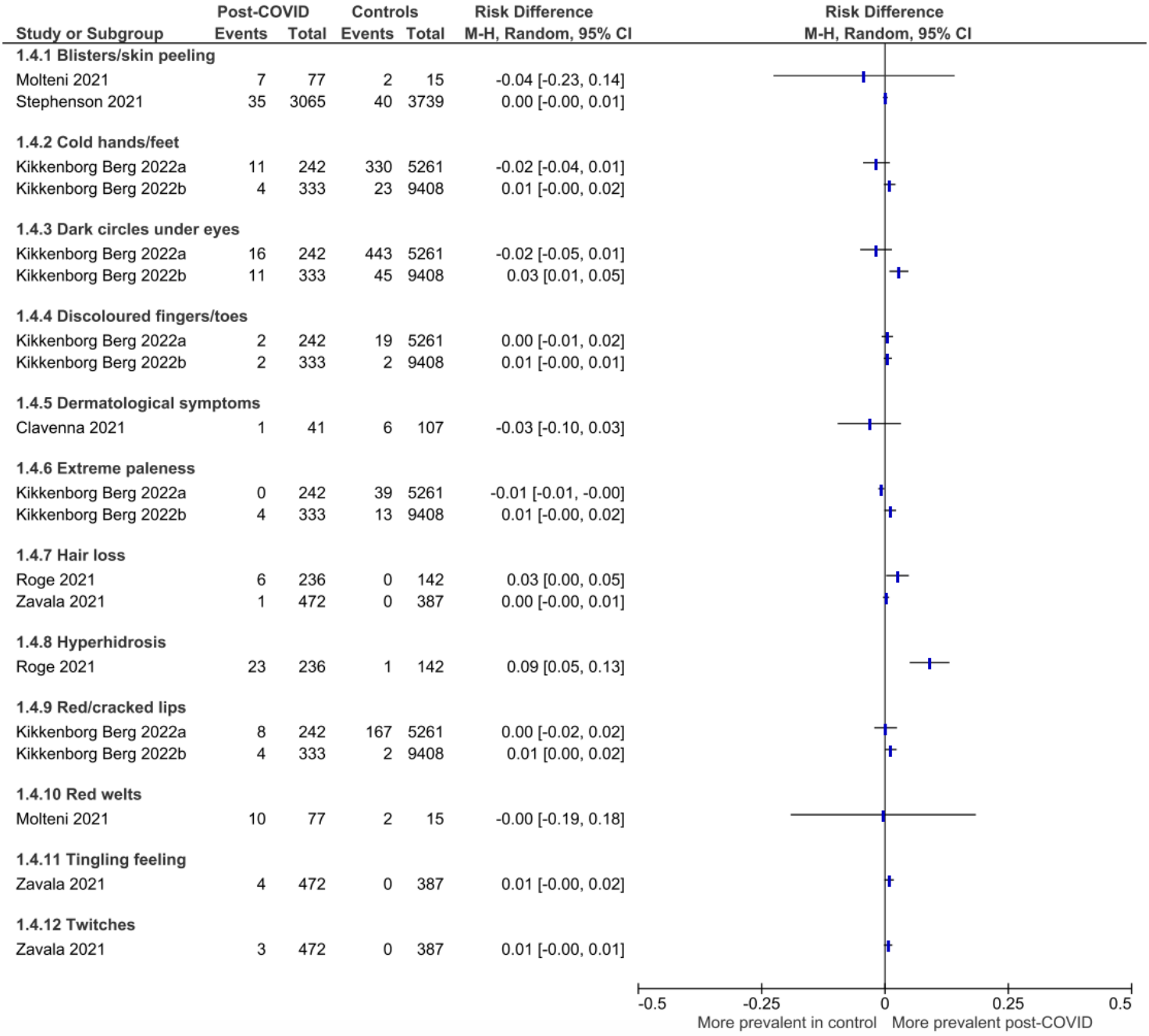



Random-effects REML model

Figure 3: Forest Plots of persistent symptoms reported by <3 controlled studies

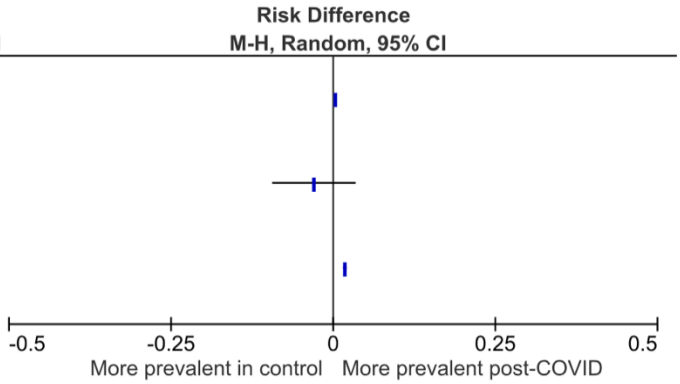
## Individual Symptoms (by body area/function)

## Dermatological:



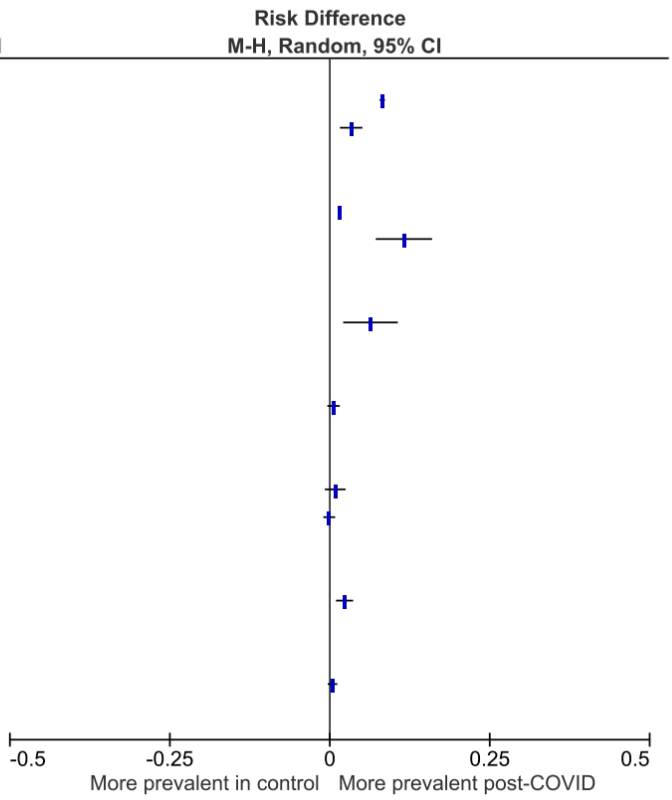
## Fatigue/Weakness:

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.3.1 Chronic fatigue syndrome** | | | | | |
| Ewan Donnachie 2022 | 189 | 43903 | 72 | 73873 | 0.00 [0.00, 0.00] |
| **1.3.2 Listlessness** | | | | | |
| Blankenberg 2021 | 139 | 178 | 1075 | 1326 | -0.03 [-0.09, 0.03] |
| **1.3.3 Muscle weakness** | | | | | |
| Borch 2022 | 373 | 14883 | 108 | 15234 | 0.02 [0.02, 0.02] |



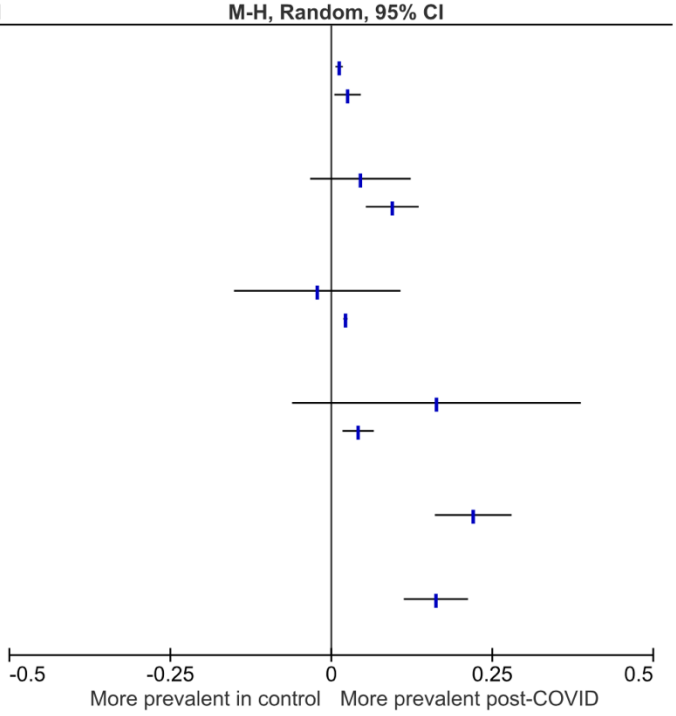

## Gastrointestinal:

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.5.1 Altered taste** | | | | | |
| Borch 2022 | 1236 | 14883 | 16 | 15234 | 0.08 [0.08, 0.09] |
| Zavala 2021 | 17 | 472 | 1 | 387 | 0.03 [0.02, 0.05] |
| **1.5.2 Anosmia/ageusia or Parosmia/euosmia** | | | | | |
| Ewan Donnachie 2022 | 839 | 43903 | 244 | 73873 | 0.02 [0.01, 0.02] |
| Roge 2021 | 29 | 236 | 1 | 142 | 0.12 [0.07, 0.16] |
| **1.5.3 Body weight changes** | | | | | |
| Roge 2021 | 20 | 236 | 3 | 142 | 0.06 [0.02, 0.11] |
| **1.5.4 Constipation** | | | | | |
| Zavala 2021 | 4 | 472 | 1 | 387 | 0.01 [-0.00, 0.02] |
| **1.5.5 Problem swallowing** | | | | | |
| Roge 2021 | 2 | 236 | 0 | 142 | 0.01 [-0.01, 0.02] |
| Zavala 2021 | 2 | 472 | 2 | 387 | -0.00 [-0.01, 0.01] |
| **1.5.6 Skipping meals** | | | | | |
| Stephenson 2021 | 296 | 3065 | 275 | 3739 | 0.02 [0.01, 0.04] |
| **1.5.7 Vomiting** | | | | | |
| Zavala 2021 | 2 | 472 | 0 | 387 | 0.00 [-0.00, 0.01] |



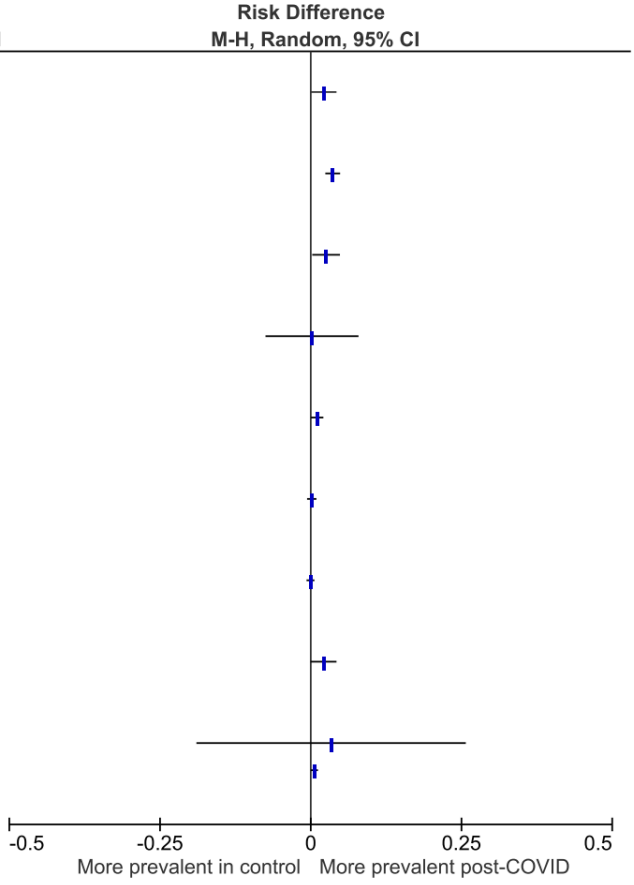
## Mental Health:

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.6.1 Depression** | | | | | |
| Roessler 2021 | 1140 | 11950 | 4971 | 59750 | 0.01 [0.01, 0.02] |
| Zavala 2021 | 18 | 472 | 5 | 387 | 0.03 [0.00, 0.05] |
| **1.6.2 Memory impairment** | | | | | |
| Blankenberg 2021 | 91 | 178 | 619 | 1328 | 0.05 [-0.03, 0.12] |
| Roge 2021 | 24 | 236 | 1 | 142 | 0.09 [0.05, 0.14] |
| **1.6.3 Psychiatric symptoms** | | | | | |
| Clavenna 2021 | 6 | 41 | 18 | 107 | -0.02 [-0.15, 0.11] |
| Ewan Donnachie 2022 | 4109 | 43903 | 5288 | 73873 | 0.02 [0.02, 0.03] |
| **1.6.4 Sadness** | | | | | |
| Bergia 2022 | 15 | 49 | 2 | 14 | 0.16 [-0.06, 0.39] |
| Zavala 2021 | 27 | 472 | 6 | 387 | 0.04 [0.02, 0.07] |
| **1.6.5 Unexplained irritability** | | | | | |
| Roge 2021 | 57 | 236 | 3 | 142 | 0.22 [0.16, 0.28] |
| **1.6.6 Impaired attention** | | | | | |
| Roge 2021 (1) | 40 | 236 | 1 | 142 | 0.16 [0.11, 0.21] |

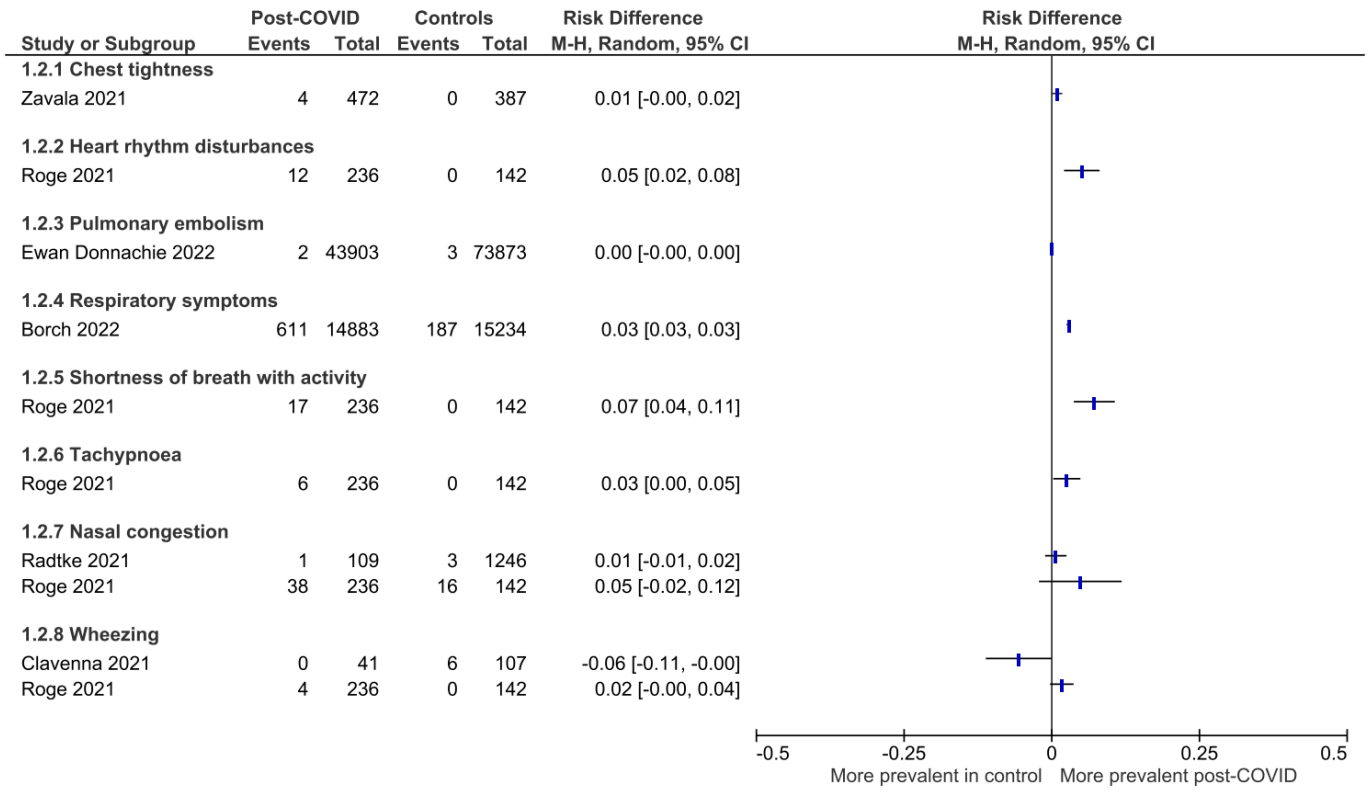



## Neurological/Other:

| Study or Subgroup | Post-COVID Events | Post-COVID Total | Controls Events | Controls Total | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|
| **1.7.1 Change in menstruation** | | | | | |
| Roge 2021 | 5 | 236 | 0 | 142 | 0.02 [-0.00, 0.04] |
| **1.7.2 Chills** | | | | | |
| Stephenson 2021 | 269 | 3065 | 192 | 3739 | 0.04 [0.02, 0.05] |
| **1.7.3 Enlarged lymph nodes** | | | | | |
| Roge 2021 | 6 | 236 | 0 | 142 | 0.03 [0.00, 0.05] |
| **1.7.4 Neurological symptoms** | | | | | |
| Clavenna 2021 | 2 | 41 | 5 | 107 | 0.00 [-0.08, 0.08] |
| **1.7.5 Problems seeing/blurred vision** | | | | | |
| Zavala 2021 | 5 | 472 | 0 | 387 | 0.01 [0.00, 0.02] |
| **1.7.6 Problem speaking/communicating** | | | | | |
| Zavala 2021 | 2 | 472 | 1 | 387 | 0.00 [-0.01, 0.01] |
| **1.7.7 Seizures/fits** | | | | | |
| Zavala 2021 | 1 | 472 | 1 | 387 | -0.00 [-0.01, 0.01] |
| **1.7.8 Stiffness** | | | | | |
| Roge 2021 | 5 | 236 | 0 | 142 | 0.02 [-0.00, 0.04] |
| **1.7.9 Hoarse voice** | | | | | |
| Molteni 2021 | 18 | 77 | 3 | 15 | 0.03 [-0.19, 0.26] |
| Stephenson 2021 | 56 | 3065 | 46 | 3739 | 0.01 [0.00, 0.01] |



## Respiratory:



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# Appendix

## Appendix 1: Detailed search strategy for Ovid MEDLINE (R) database

| # | Searches |
|---|---|
| 1 | ((longterm or long) adj4 (covid* or corona or coronavirus*)).ti,ab,kf. |
| 2 | (chronic adj3 (covid* or corona or coronavirus*)).ti,ab,kf. |
| 3 | (persist* adj3 (covid* or corona or coronavirus*)).ti,ab,kf. |
| 4 | (sustain* adj3 (covid* or corona or coronavirus*)).ti,ab,kf. |
| 5 | (history adj3 (covid* or corona or coronavirus*)).ti,ab,kf. |
| 6 | ((postcovid* or post covid* or postcoronavirus* or postcorona* virus* or post coronavirus* or post corona* virus* or postcoronovirus* or postcorono* virus* or post coronovirus* or post corono* virus* or postcoronavirinae* or postcorona* virinae* or post coronavirinae* or post corona* virinae* or postCov or post Cov or postsars* or post sars* or "post severe acute respiratory syndrome*" or postncov* or post ncov* or posthcov* or post hcov*) adj3 (syndrome* or disorder* or illness* or sickness* or disease* or condition* or symptom* or sign* or prognos* or followup* or "follow up*" or feature* or comorbid* or "co morbid*" or multimorbid* or "multi morbid*" or survivor* or survival* or risk* or care* or convalescen* or recuperat* or aftercare* or ambulatory* or outpatient* or "out patient*")).ti,ab,kf. |
| 7 | ("long sars*" or "Covid* syndrome" or "post- acute sequelae of COVID*" or "late sequelae covid*or post acute COVID*" or "Covid* syndrome" or "post-acute sequelae SARS-CoV-2 infection").ti,ab,kf. |
| 8 | or/1-7 |
| 9 | exp Child/ |
| 10 | exp infant/ |
| 11 | Adolescent/ |
| 12 | Pediatrics/ |
| 13 | (paediatri* or pediatri*).ti,ab,kf. |
| 14 | (baby or babies).ti,ab,kf. |
| 15 | toddler*.ti,ab,kf. |
| 16 | neonate*.ti,ab,kf. |
| 17 | (girl* or boy*).ti,ab,kf. |
| 18 | (newborn* or new born*).ti,ab,kf. |
| 19 | (kindergarten* or school* or preschool*).ti,ab,kf. |
| 20 | (youth* or juvenile* or minor* or teen*).ti,ab,kf. |
| 21 | (young adj (person or people)).ti,ab,kf. |
| 22 | or/9-21 |
| 23 | exp Coronavirinae/ |
| 24 | (Betacoronavirus* or Corona Virus* or Coronavirus* or Coronovirus* or CoV or CoV2 or COVID or COVID19 or COVID-19 or HCoV-19 or nCoV or SARS CoV 2 or SARS2 or SARSCoV or SARS-CoV or SARS-CoV-2 or 2019nCoV).mp. |
| 25 | exp Coronavirus infection/ |
| 26 | ((novel or new or nouveau) adj2 (CoV or Pandemi*2)).mp. |

| | |
|---|---|
| 27 | (covid* or coronavirus* or "corona* virus*" or coronovirus* or "corono* virus*" or coronavirinae* or "corona* virinae*" or Cov or "2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARSCoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARSCov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or "severe acute respiratory syndrome*").ti. |
| 28 | exp pneumonia/ and (wuhan or hubei or huanan).mp. |
| 29 | or/23-28 |
| 30 | ((longterm or long term) adj3 (complication* or infect* or symptom* or syndrome* or consequence* or outcome* or impact* or suffer* or effect* or debilit*)).ti,ab,kf. |
| 31 | (("long* term*" or longterm* or "long* haul*" or longhaul* or "long* tail*" or longtail* or longduration* or "long duration*" or longlast* or "long last*" or longstanding* or "long standing*" or "medium* term*" or mediumterm*) adj3 (covid* or coronavirus* or corona* virus* or coronovirus* or corono* virus* or coronavirinae* or corona* virinae* or Cov or "2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARScoronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or "severe acute respiratory syndrome*")).ti,ab. |
| 32 | ((chronic or persist* or prolong* or sustain* or continu*) adj3 (complication* or infect* or symptom* or syndrome* or consequence* or outcome* or impact* or suffer* or effect* or debilit*)).ti,ab,kf. |
| 33 | ((after or following) adj infect*).ti,ab,kf. |
| 34 | ((post or postvir* or postacute) adj4 (complication* or infect* or symptom* or syndrome* or consequence* or outcome* or impact* or suffer* or effect* or debilit*)).ti,ab,kf. |
| 35 | ((post or postvir* or postacute) adj4 (complication* or infect* or symptom* or syndrome* or consequence* or outcome* or impact* or suffer* or effect* or debilit*)).ti,ab,kf. |

| | |
|---|---|
| 36 | ((ongoing* or endur* or long* or legacy* or slow* or gradual* or protract* or lengthy* or chronic* or persist* or relaps* or remit* or remission* or residual* or delay* or prolong* or extend* or linger* or permanent* or fluctuat* or multisystem* or "multi system*" or nonrecover* or "non recover*" or subacute* or "sub acute*" or lasting* or continuous* or continual* or continuing* or postacute* or "post acute*" or postdischarg* or "post discharg*" or postinfect* or "post infect*" or postviral* or "post viral*" or postvirus* or "post virus*" or "medium* term*" or mediumterm* or adverse* or dangerous* or harmful* or indirect* or injurious* or secondary* or side effect* or undesirable* or sequela* or complication* or consequence* or effect* or event* or impact* or outcome* or reaction* or complexit* or aftercare* or impair* or problem* or issue* or rehab* or function* or perform*) adj10 ((daily* or everyday* or day* or normal* or usual*) adj1 (activit* or living* or life* or lives* or job* or work* or employ* or occupation* or hobby* or hobbies* or leisure*)) adj10 (covid* or coronavirus* or corona* virus* or coronovirus* or corono* virus* or coronavirinae* or corona* virinae* or Cov or "2019-nCoV*" or 2019nCoV* or "19- nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARScoronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or "severe acute respiratory syndrome*")).ti,ab. |
| 37 | (sequala* or sequela*).ti,ab,kf. |
| 38 | or/30-37 |
| 39 | 29 and 38 |
| 40 | 8 or 39 |
| 41 | 40 and 22 |
| 42 | exp animals/ not humans/ |
| 43 | 41 not 42 |
| 44 | limit 43 to ed=Date-Date |

# Annex 3: Global distribution of participants and their characteristics

| Last name | First name | Country | WHO Region* |
|---|---|---|---|
| Abbas | Qalab | Pakistan | EMR |
| Apiyo | Mirriam | Uganda | AFR |
| Asadi-Pooya | Ali | Iran (Islamic Republic of) | EMR |
| Buonsenso | Danilo | Italy | EUR |
| Casasbuenas | Olga Lucia | Colombia | AMR |
| Dalwai | Samir Hasan | India | SEAR |
| Fernandez | Gabriela | Argentina | AMR |
| Funk | Anna | Canada | AMR |
| Fwoloshi | Sombo | Zambia | AFR |
| Gupta | Dhiren | India | SEAR |
| Koh Cheng | Thoon | Singapore | WPR |
| Lu | Chun-Yi | Taiwan, China | WPR |
| Malone | Laura | United States | AMR |
| McDowall | Susan | New Zealand | WPR |
| McFarland | Sammie | United Kingdom | EUR |
| Perera | Bede Ananda | Sri Lanka | SEAR |
| Pretorius | Resia | South Africa | AFR |
| Putri | Nina Dwi | Indonesia | SEAR |
| Rahman | Mujibur | Bangladesh | SEAR |
| Salih | Aso Faeq | Iraq | EMR |
| Scheidt-Nave | Christa | Germany | EUR |
| Semper | Elizabeth | Spain | EUR |
| Smane | Liene | Latvia | EUR |
| de Sousa Marques | Heloisa | Brazil | AMR |
| Triki | Chahnez Charfi | Tunisia | EMR |
| Turkalj | Mirjana | Croatia | EUR |
| Zulu | James Exnobert | Zambia | AFR |

* AFR: African Region; AMR: Region of the Americas; EMD: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asia Region; WPR: Western Pacific Region.

**Characteristics of participants (n = 27)**

| Variable | Total number (%) |
|---|---|
| **Stakeholder group** | |
| Clinical researcher | 14 (51.9%) |
| Clinician | 5 (18.5%) |
| Patient/advocate | 3 (11.1%) |
| Researcher | 3 (11.1%) |
| Other | 2 (7.4%) |
| **Gender** | |
| Female | 16 (59%) |
| Female | 11 (41%) |
| Not specified | - |
| **WHO Region** | |
| African Region | 4 (14.8%) |
| Region of the Americas | 5 (18.5%) |
| South-East Asia | 5 (18.5%) |
| European | 6 (22.2%) |
| Eastern Mediterranean | 4 (14.8%) |
| Western Pacific | 3 (11.1%) |

# Annex 4: Impact analysis questionnaire

| Objectives of the case definition | | |
|---|---|---|
| | **Yes** | **No** |
| To have one name and definition that will simplify our global common understanding and communication. | | |
| Allow physicians, patients, caregivers, epidemiologists, ministers of health, policy-makers, governments to be aligned in their understanding and informed to make policy decisions. | | |
| Enable researchers to aggregate data in a consistent and reliable manner and to conduct interventional studies using common enrolment criteria, case record forms and core outcome sets. | | |

| | **Strongly disagree** | **Disagree** | **Neutral** | **Agree** | **Strongly agree** |
|---|---|---|---|---|---|
| **Overarching reasons for this case definition** | | | | | |
| The case definition for post COVID-19 condition for children and adolescents is **clear and easily applicable** for physicians, patients, caregivers, epidemiologists, ministers of health, policy-makers, governments. | | | | | |
| Applying and implementing this case definition will **improve our understanding and communication** of post COVID-19 condition in children and adolescents. | | | | | |
| Applying and implementing this case definition will allow physicians, patients, caregivers, epidemiologists, ministers of health, policy-makers, governments to be **aligned in their understanding** of post COVID-19 condition in children and adolescents and informed to make policy decisions. | | | | | |
| Applying and implementing this case definition will enable researchers to aggregate data in a **consistent and reliable manner** and to conduct interventional studies using common enrolment criteria, case record form and core outcome sets. | | | | | |
| **Global use of this case definition** | | | | | |
| This case definition will help health care professionals with the **clinical management and care** of children and adolescents with post COVID-19 condition. | | | | | |
| Applying this case definition will help **families**, **children and adolescents** with post COVID-19 condition. | | | | | |
| Applying this case definition will help **researchers** to study post COVID-19 condition in children and adolescents. | | | | | |
| **In your jurisdiction of work** | | | | | |
| Application of this case definition will *put pressure on/harm/negatively impact (e.g. clinically, financially, resources)* **children and adolescents** with post COVID-19 condition and their **families.** | | | | | |
| Application of this case definition will *pressure on/harm/negatively impact (e.g. clinically, financially, resources)* **health professionals** providing care to children and adolescents with post COVID-19 condition. | | | | | |
| Application of this case definition will *put pressure on/harm/negatively impact (e.g. clinically, financially, resources)* the **health system.** | | | | | |

## Annex 5: Conflict of interest assessment

| Name | Interest or conflict |
|---|---|
| **Qalab Abbas** | No conflict of interest declared or identified |
| **Mirriam Apiyo** | Participated in the development of the Uganda Ministry of Health Case definition for COVID-19 in children in 2021. I did not receive any payment for this work. As Medical Director of Case Hospital, I worked with MoH on regulation for COVID-19 care.<br>**Decision: no action needed.** |
| **Ali Asadi-Pooya** | No conflict of interest declared or identified |
| **Danilo Buonsenso** | Participation in a peer-to-peer programme on long COVID (peace programme) funded by Pfizer (2022). €1500 for speaking on long COVID: speaker at a Pfizer online meeting; speaker at ESPID 2022 on Covid vaccines, Pfizer supported/sponsored session; granted research project on long COVID by Pfizer non-competitive grants (€16 000).<br>**Decision: Danilo Buonsenso can attend this case definition but will not be part of the GDG for recommendations.** |
| **Olga Lucia Casasbuenas** | No conflict of interest declared or identified |
| **Samir Dalwai** | No conflict of interest declared or identified |
| **Gabriela Fernandez** | No conflict of interest declared or identified |
| **Anna Funk** | Research funding from "other" (non-commercial) organizations – Canadian Institute of Health Research (CIHR) governmental health agency. CIHR has an interest in COVID-19 research and health improvement related to COVID-19 (hence providing grants funding research on the topic). Collaborator with other academics/principal investigators. Approximately CAD 1 million. Ended in 2021 and 2022.<br>**Decision: no action needed.** |
| **Dhiren Gupta** | No conflict of interest declared or identified |
| **Sombo Fwoloshi** | No conflict of interest declared or identified |
| **Thoon Koh Cheng** | No conflict of interest declared or identified |
| **Chun-Yi Lu** | No conflict of interest declared or identified |
| **Laura Malone** | Research support for the Thomas Wilson Foundation, self/research unit (US$ 10 000), current.<br>Paediatric Covid Clinic grants for the PNC Charitable Trusts, self/research unit (US$ 50 000), current.<br>**Decision: no action needed.** |
| **Susan McDowall** | No conflict of interest declared or identified |
| **Sammie McFarland** | Personal benefit. I have a child with long COVID. I have close personal colleagues who have children with long COVID and I run a charity representing children and young people living with long COVID.<br>**Decision: no action needed.** |
| **Martin Offringa** | No conflict of interest declared or identified |

| | |
|---|---|
| **Bede Ananda Perera** | Consulting – MOBIO, Tech Co, free, current.<br>Research support – Independent Medical Practitioners Association, less than US$ 500, current.<br>Copyright – self, current.<br>Proprietary – self, current.<br>**Decision: no action needed.** |
| **Resia Pretorius** | Filed patent for the diagnosis of Long COVID4b: Research know-how: coagulation and inflammatory biomarkers in acute COVID-19 and long COVID, Stellenbosch University, no monetary value.<br>**Decision: no action needed.** |
| **Nina Dwi Putri** | Site investigator for COVID-19 vaccine trial (ZF-2001) in adults, Anhul Zifel Longcom Pte Ltd (research unit) – US$ 350/month, completed.<br>**Decision: Nina Dwi Putri can attend this case definition but will not be part of the GDG for recommendations.** |
| **Md Mujibar Rahman** | No conflict of interest declared or identified |
| **Aso Faeq Salih** | No conflict of interest declared or identified |
| **Christa Scheidt-Nave** | Grant on post COVID-19 incidence and ambulatory health care services provision, Federal Ministry of Health, Germany – €784 931, 2021–2023.<br>**Decision: no action needed.** |
| **Elizabeth Semper** | No conflict of interest declared or identified |
| **Liene Smane** | No conflict of interest declared or identified |
| **Heloisa de Sousa Marques** | No conflict of interest declared or identified |
| **Chahnez Charfi Triki** | No conflict of interest declared or identified |
| **Mirjana Turkalj** | No conflict of interest declared or identified |
| **James Exnobert Zulu** | No conflict of interest declared or identified |