STUDY PROTOCOL

REVISED What are the long-term symptoms and complications of COVID-19: a protocol for a living systematic review [version 2; peer review: 2 approved]

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Abstract

Although the majority of people with Covid-19 will experience mild to moderate symptoms and will recover fully, there is now increasing evidence that a significant proportion will experience persistent symptoms for months after the acute phase of the illness. These symptoms include, among others, fatigue, problems breathing, lack of smell and taste, headaches, and depression and anxiety. It is also clear the virus has lasting fluctuating multiorgan sequelae, including affecting not only the respiratory system but also the heart, liver, and nervous system.

We present a protocol for a living systematic review that aims to synthesize the evidence on the prevalence and characteristics of post-acute COVID-19.

The living systematic review will be updated regularly, approximately

Open Peer Review

Reviewer Status ✓ ✓

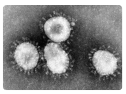
	Invited Reviewers	
	1	**2**
version 2 (revision) 27 Aug 2021	✓ report	✓ report
version 1 14 Dec 2020	? report	✗ report

1. **Johannes Siegrist**, University of

every 6 months, as new evidence emerges. We will include studies that follow up at least 100 people with Covid-19 at 12 or more weeks post Covid-19 onset, with no restrictions regarding country, setting, or language.
We will use descriptive statistics and, for outcomes reported in two or more studies, we will use meta-analyses to estimate prevalence with 95% confidence intervals (CIs) using the exact method. Heterogeneity between estimates will be assessed using the I2 statistic. Our findings will also be presented as infographics to facilitate transcription to lay audiences. Ultimately, we aim to support the work of policy makers, practitioners, and patients when planning rehabilitation for those recovering from Covid-19.
The protocol has been registered with PROSPERO (CRD42020211131, 25/09/2020).

Keywords
Living systematic review, COVID-19, long covid, lasting effects

This article is included in the Emerging Diseases and Outbreaks gateway.



This article is included in the Coronavirus collection.

This article is included in the Living Evidence collection.

Duesseldorf, Duesseldorf, Germany

2. **Madelon van Wely**, University of Amsterdam, Amsterdam, The Netherlands

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Charitini Stavropoulou (C.Stavropoulou@city.ac.uk)

Author roles: Michelen M: Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Cheng V**: Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Manoharan L**: Data Curation, Formal Analysis, Methodology, Validation, Writing – Review & Editing; **Elkheir N**: Data Curation, Investigation, Methodology, Validation, Writing – Review & Editing; **Dagens D**: Data Curation, Investigation, Methodology, Writing – Review & Editing; **Hastie C**: Investigation, Validation, Writing – Review & Editing; **O'Hara M**: Investigation, Validation, Writing – Review & Editing; **Suett JC**: Investigation, Methodology, Validation, Writing – Review & Editing; **Dahmash D**: Data Curation, Formal Analysis, Validation, Writing – Review & Editing; **Bugaeva P**: Data Curation, Formal Analysis, Validation, Writing – Review & Editing; **Rigby I**: Data Curation, Formal Analysis, Validation, Writing – Review & Editing; **Munblit D**: Formal Analysis, Validation, Writing – Review & Editing; **Harriss E**: Data Curation, Writing – Review & Editing; **Burls A**: Investigation, Validation, Writing – Review & Editing; **Foote C**: Investigation, Validation, Writing – Review & Editing; **Scott J**: Writing – Review & Editing; **Carson G**: Funding Acquisition, Validation, Writing – Review & Editing; **Olliaro P**: Funding Acquisition, Validation, Writing – Review & Editing; **Sigfrid L**: Funding Acquisition, Methodology, Validation, Writing – Review & Editing; **Stavropoulou C**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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First published: 14 Dec 2020, **9**:1455 https://doi.org/10.12688/f1000research.27284.1

REVISED **Amendments from Version 1**

In the updated version, we have taken into consideration every point that each reviewer has made and responded to them in detail.

The main changes are as follows. We now explicitly state the primary and secondary outcomes we are interested in, the specific inclusion/exclusion criteria and the data that we will extract. In addition, we now clarify that the analysis will go beyond descriptive statistics and when possible, it will include a meta-analysis. The choice of groups for our subgroup analysis will depend on discussions with our clinical experts, patient advocates and by reviewing the literature. In addition, we further justify the choice of Hoy et al risk of bias assessment checklist, a validated tool for assessing risk of bias in prevalence studies, which can also be used with cohort studies. Finally, we clarify issues that relate to how we dealt with different languages and how often we will be updating the review. Given the fast increasing literature on Long Covid, we have had to add more co-authors to the paper to allow us to cope with the continuous updates of the living systematic review.

Any further responses from the reviewers can be found at the end of the article

Background

The range of documented Covid-19 infections vary from asymptomatic to severe, but the vast majority of patients experience mild to moderate symptoms and do not require hospitalisation[1]. We have previously conducted a rapid review of the literature to identify which symptoms and signs might differentiate mild and moderate from severe Covid-19[2]. Since then, and as more data are being gathered, there is increasing evidence of a "long-tail" of Covid-19 illness, but limited information about the range and duration of symptoms experienced[3] or longer term health complications. A community app developed at King's College London, which tracks self-reported symptoms, has shown that about one in ten will be sick for three weeks or more (https://covid.joinzoe.com/post/covid-long-term). Some individuals with Covid-19 have reported "fatigue, headaches and tingling nerves" that lasted months after symptom onset[4]. A recent longitudinal cohort of 143 patients followed after hospitalisation from Covid-19 in Italy reported that 87% had at least one ongoing symptom, most (55%) reporting three or more, at 60 day follow up. Fatigue (53%), dyspnoea (43%), joint pain (27%) and chest pain (22%) were the most common ongoing symptoms[5], but there is a variety of other symptoms and complications that have been reported including neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption, thromboembolic conditions and mental health conditions[6]. A prolonged course of illness has also been reported among people with mild Covid-19 who did not require hospitalisation[3,7,8].

The evidence to date remains fragmented as to the onset of symptoms and clinical features, how long symptoms may last, how this relates to the severity of the initial illness, and further lasting impacts to health. A better understanding of patients' projected recovery from Covid-19 is helpful to patients, healthcare professionals, policymakers and commissioners. The clinical management of persisting symptoms of Covid-19 has started to be addressed in the clinical literature[6] and NHS England has issued guidance for the multisystem needs of patients recovering from Covid-19[9]. Our findings could help identify people requiring additional rehabilitation services and, where necessary, specialist referral to establish a secondary cause of their symptoms. Our findings will also be relevant to organisations such as NHS England, which have recently launched an online Covid-19 rehab service supporting patients suffering long-term effects of the disease (https://www.yourcovidrecovery.nhs.uk/) or the British Society of Immunologists, which recently released a briefing note recommending research into the long-term immunological health consequences of Covid-19[10].

The aim of this review is to synthesize and continually update the evidence on the characteristics, including prevalence and duration of symptoms and clinical features of post-acute COVID-19, as well as risk factors for developing Long Covid. This will inform clinical and public health management, prevention, and rehabilitation policies.

Methods

To address the aim of this study we will conduct a living systematic review (LSR). LSRs are used in areas where research evidence is emerging rapidly, current evidence is uncertain, and new research may influence policy or practice decisions[11]. These are all features of Covid-19 research, where much about the long-term effects of the disease are still unknown and policy makers are calling for more evidence. The review will be updated approximately every six months, with update cycles under continuous review as the pace of new evidence generated develops through the pandemic. We aim to continue to update the review for up to two years. Our study methodology has been developed and strengthened through consultation with Long Covid Support (a patient support network).

Inclusion/exclusion criteria

We will include studies that meet the follow criteria:

- Studies following up with at least 100 people with suspected, laboratory confirmed, and/or clinically diagnosed Covid-19
- Studies assessing symptoms or outcomes at 12 or more weeks post Covid-19 onset
- Peer reviewed articles published since 1 January 2020
- No restriction regarding country, setting, or language

We will exclude:

- Studies that focus only on acute Covid-19
- Editorials and opinion papers

Search strategy

A search of the following databases will be conducted: Pubmed and CINAHL through the EBSCO database host for

general health peer-reviewed articles and Global Health for global peer-reviewed articles through the Ovid database host. In addition, we will search Google Scholar for grey literature. We will also conduct complementary searches using the WHO Global Research Database on Covid-19 and LitCOVID as two databases that bring together evidence on Covid-19 from a worldwide dataset. A 'backwards' snowball search will be conducted for the references of systematic reviews. Finally, we will contact experts in the field and use social media to identify relevant studies.

We will search using controlled subject headings and keywords of the following concepts: Terms related to 1) COVID-19 OR COVID OR SARS-CoV-2; 2) symptoms OR clinical features OR signs OR characteristics OR sequelae OR complications; 3) long-term OR post-acute OR long-tail OR persistent OR chronic COVID OR long COVID OR post discharge OR prolonged symptoms OR long haul. The search terms were piloted on Pubmed and CINAHL through the EBSCO database host the week starting 14th September 2020 to ensure that high profile research articles on long covid were included. No important studies were missed.

An example is shown below:

MEDLINE Search (16/3/2021)	
S1. COVID-19 OR OR covid OR SARS-CoV-2. ab	
S2. symptom* OR "clinical features" OR signs OR characteristic* OR sequelae OR complication*.ab	
S3. "long-term Covid" OR long-term N2 consequence* OR "long-term impact" OR "long-term effect" OR "post-acute" OR long-tail OR persist* OR "chronic-COVID" OR "long-COVID" OR post-discharge OR postdischarge OR "prolonged symptom" OR "long-haul" .ab	
S4. S1 AND S2 AND S3	1952

Screening

Search results will be managed and screened using a review online platform, Rayyan[12]. Initial screening of titles and abstracts as well as full text screening against the inclusion criteria will be done by two reviewers independently. Non-English articles will be translated using Google Translate or reviewed by a reviewer with good knowledge of the language. Disagreements for inclusion will be resolved by consensus. Where disagreements cannot be resolved, a third researcher will review the papers to make the final decision.

Risk of bias

We will be using the Hoy *et al.* checklist[13] to critically appraise the studies included in the review, a validated tool for assessing risk of bias in prevalence studies.

Data extraction

The following information will be extracted from each study based on an extraction form informed by a previous review[2]: study aim, country of study, setting, method, study design, population size and characteristics, types and frequency of symptoms reported, onset and duration of symptoms, treatment and possible risk factors. Data extraction will be performed by one reviewer and checked by a second reviewer. Disagreements will be resolved through discussion and consensus.

Outcomes

The primary outcome is to characterise the prevalence of symptoms and complications of long term Covid-19 in different populations. Secondary outcomes include diagnostics and risk factors for developing different sequelae.

Data analysis

We will use descriptive analysis, and present proportion of symptoms and estimate their 95% confidence intervals (CIs) using the exact method. When more than two studies provide information on a symptom, we will perform a meta-analysis using a random intercept logistic regression model. Heterogeneity between estimates will be assessed using the I^2 statistic.

Where data is available, we will explore key factors that affect prevalence estimates, e.g. hospitalisation, settings, location of the study, sex and follow-up timing using subgroup analysis and meta-regression analysis. We will identify these factors by discussing with our clinical experts and patient advocates and by reviewing the literature. The division for key factors used in subgroup analysis will depend on the availability of reported data across studies. We will align the division with the literature and expert opinions to form exploratory analysis and to help the interpretation.

We will also conduct sensitivity analysis to examine the impact of high risk of bias studies and conventional statistical methods on the prevalence estimates, e.g. Freeman-Tukey Double arcsine transformation using inverse variance meta-analysis. All analysis and data presentation will be performed using meta and ggplot2 in R (version 4.0.5 or above) via RStudio (version 1.3.1093 or above).

We will work with patient advocates to present the data to facilitate transcription to lay audiences.

Protocol registration

This protocol report is structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines[14], was registered with PROSPERO (CRD42020211131, 25 September 2020). The protocol will be updated as we progress with the living review as and if needed. CS is the guarantor for this study.

Data availability

Underlying data

No underlying data are associated with this article.

Reporting guidelines

Figshare: PRISMA-P checklist for "What are the long-term symptoms and complications of COVID-19: a protocol for a living systematic review". https://doi.org/10.25383/city.13187456.v1[15].

References

1. CDC: **Coronavirus Disease 2019 (COVID-19).** Cent Dis Control Prev. 2020; (accessed 6 Aug 2020).
Reference Source
2. Michelen M, Jones N, Stavropoulou C: **In patients of COVID-19, what are the symptoms and clinical features of mild and moderate cases?** (accessed 6 Aug 2020).
Reference Source
3. Rayner C, Lokugamage AU, Molokhia M: **Covid-19: Prolonged and relapsing course of illness has implications for returning workers**. 2020; (accessed 6 Aug 2020).
Reference Source
4. Garner P: **Paul Garner: Covid-19 at 14 weeks—phantom speed cameras, unknown limits, and harsh penalties.** *The BMJ.* (accessed 6 Aug 2020).
Reference Source
5. Carfì A, Bernabei R, Landi F, *et al.*: **Persistent Symptoms in Patients After Acute COVID-19.** *JAMA.* 2020; **324**(6): 603–5.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Greenhalgh T, Knight M, A'Court C, *et al.*: **Management of post-acute covid-19 in primary care.** *BMJ.* 2020; **370**: m3026.
PubMed Abstract | Publisher Full Text
7. Tenforde MW: **Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020.** *MMWR Morb Mortal Wkly Rep.* 2020; **69**: 993–998.
Publisher Full Text
8. Sigfrid L, Cevik M, Jesudason E, *et al.*: **What is the recovery rate and risk of long-term consequences following a diagnosis of COVID-19? - A harmonised, global longitudinal observational study.** *medRxiv.* 2020.
Publisher Full Text
9. NHS England and NHS Improvement: **After-care needs of inpatients recovering from COVID-19**. 2020; (accessed 24 Sep 2020).
Reference Source
10. British Society for Immunology: **COVID-19 immunology briefing note: What we know about long-term health consequences and priorities for research.** *Immunology.* 2020.
Reference Source
11. Elliott JH, Synnot A, Turner T, *et al.*: **Living systematic review: 1. Introduction-the why, what, when, and how.** *J Clin Epidemiol.* 2017; **91**: 23–30.
PubMed Abstract | Publisher Full Text
12. Ouzzani M, Hammady H, Fedorowicz Z, *et al.*: **Rayyan-a web and mobile app for systematic reviews.** *Syst Rev.* 2016; **5**(1): 210.
PubMed Abstract | Publisher Full Text | Free Full Text
13. Hoy D, Brooks P, Woolf A, *et al.*: **Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement.** *J Clin Epidemiol.* 2012; **65**(9): 934–9.
PubMed Abstract | Publisher Full Text
14. Moher D, Shamseer L, Clarke M, *et al.*: **Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.** *Syst Rev.* 2015; **4**(1): 1.
PubMed Abstract | Publisher Full Text | Free Full Text
15. Michelen M, Sigfrid L, Manoharan L, *et al.*: **What are the long-term symptoms and complications of COVID-19: a protocol for a living systematic review.** City, University of London. Journal contribution. 2020.
http://www.doi.org/10.25383/city.13187456.v1

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 22 September 2021

https://doi.org/10.5256/f1000research.58402.r92984

✔ **Madelon van Wely**
Centre for Reproductive Medicine, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

In my view all queries were answered and adequately addressed, the protocol quality has improved and I am content with the present version. I wish the authors good luck with their review.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, meta-analyses, Obstetrics and Gynaecology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 31 August 2021

https://doi.org/10.5256/f1000research.58402.r92985

✔ **Johannes Siegrist**
Senior Professorship on Work Stress Research, University of Duesseldorf, Duesseldorf, Germany

I have read the revision of the manuscript and approve the publication of this manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Social epidemiology systematic reviews

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 22 March 2021

https://doi.org/10.5256/f1000research.30148.r80913

Madelon van Wely
Centre for Reproductive Medicine, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

No doubt this is an important LSR that needs to be performed. I am in favor of getting this protocol published, however, at present many details are lacking. In my view in LSRs it is crucial to decide beforehand what the authors plan to do. Though it may seem annoying now, it will be helpful in the end.

1. The outcomes. You performed a rapid review so you will know what main outcomes you are looking for. The outcomes are not stated in the Prospero protocol either.

2. It would also be advisable to have list of inclusion criteria and data you want to extract like risk factors and demographics. You could combine these with outcomes and present them in one table.

3. Data analysis: descriptive analysis sub grouped by age, sex, comorbidities? As the idea is to provide proportions from different studies I think you will be able to pool these, stratified by age etc. You could for instance summarise proportions (maybe use Freeman-Tukey transformation to stabilise variances in case of studies with zero events?), provide 95% CIs and predictive intervals to report on the precision of estimates. (meta-analysis of proportions)

4. About the subgrouping. How are you planning to do so? Are the age groups pre-specified or will they be dichotomised of subgrouped on basis of distribution of the data?

5. The duration is very important, how do you intend to present time? As grouped or continuous variable? When you have adequate data you could present the prevalence estimates over time.

6. Besides prevalence studies you might also include cohorts in which case you may want

to assess the risk of bias using the Newcastle Ottawa Scale for comparative cohorts or another such checklist.

7. Search: I would also search specifically for the expected outcomes

8. I do advise to clarify when you consider a symptom to be persistent? You write: persistent mild, moderate or severe symptoms as defined by the article authors. I suppose post-discharge is T0.

9. How often do you at this moment intend to update and publish the results?

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
No

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, meta-analyses, Obstetrics and Gynaecology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Jul 2021

Charitini Stavropoulou, City, University of London, London, UK

Thank you for your thorough review, please find an outline of the response to the comments raised.

1. The outcomes. You performed a rapid review so you will know what main outcomes you are looking for. The outcomes are not stated in the Prospero protocol either.

Response: *Thanks for highlighting, we have updated the text in the methodology section to highlight that the primary outcome is to characterise the prevalence of symptoms and complications of long term Covid-19 in different populations. Secondary outcomes include diagnostics and risk factors for developing different sequelae. This is now stated on page 7 of the revised protocol.*

1. It would also be advisable to have list of inclusion criteria and data you want to extract like risk factors and demographics. You could combine these with outcomes and present them in one table.

Response: *We have provided further details in the methods, regarding the inclusion/exclusion criteria. We have also expanded on the data extraction section to show the clarify the data we will be extracting. Please see page 7 of the revised protocol.*

1. Data analysis: descriptive analysis sub grouped by age, sex, comorbidities? As the idea is to provide proportions from different studies I think you will be able to pool these, stratified by age etc. You could for instance summarise proportions (maybe use Freeman-Tukey transformation to stabilise variances in case of studies with zero events?), provide 95% CIs and predictive intervals to report on the precision of estimates. (meta-analysis of proportions)

Response *We have provided further information in our analysis section to clarify that the analysis will go beyond descriptive statistics and that we will perform meta-analysis wherever this is possible, i.e. when there are more than two studies providing information on a symptom. Please see pages 7 and 8 of the revised protocol.*

1. About the subgrouping. How are you planning to do so? Are the age groups pre-specified or will they be dichotomised of subgrouped on basis of distribution of the data?

Response: *We plan to conduct subgroup analysis to explore the influence of key factors, e.g. age, on the estimates of prevalence. We will identify these key factors by discussing with our clinical experts, patient advocates and by reviewing the literature. We will try to align the division for subgroups with the literature to help inform the analysis and results. However, the methods will heavily depend on the availability and distribution of data. We have updated the methodology section accordingly.*

1. The duration is very important, how do you intend to present time? As grouped or continuous variable? When you have adequate data you could present the prevalence estimates over time.

Response: *We now clarify in the methods section that a subgroup analysis will be performed on follow up timing as indeed this is an important parameter as a group variable.*

1. Besides prevalence studies you might also include cohorts in which case you may want to assess the risk of bias using the Newcastle Ottawa Scale for comparative cohorts or another such checklist.

Response: *We will include any study design including cohort studies with symptom prevalence. We have chosen to use the Hoy et al risk of bias assessment checklist, a validated tool for assessing risk of bias in prevalence studies, which does not prevent us from using it with cohort studies.*

1. Search: I would also search specifically for the expected outcomes

Thank you for your suggestion. We have conducted pilot searches and noticed considerable diversity in the reported outcomes. The inclusion of key terms for the expected outcomes in search strings generated excessive hits and contributed to low precision, aka a low percentage of useful publications found in the search results. It also limits searches by "expected" outcomes and loses the opportunities finding new types of long covid symptoms and risk factors. Therefore, we used a search strategy using simple search strings focusing on describing long covid and complement the searches by backwards snowball searches in the references of relevant publications and consulting experts.

1. I do advise to clarify when you consider a symptom to be persistent? You write: persistent mild, moderate or severe symptoms as defined by the article authors. I

suppose post-discharge is T0.

Response. *Thanks for highlighting. We have provided further clarification in the inclusion criteria (page 5). In light of the new definitions issued by the Office for National Statistics (ONS), we clarify we will be including studies assessing symptoms or outcomes at 12 or more weeks post Covid-19 onset.*

1. How often do you at this moment intend to update and publish the results?

Response: *We will update the review every 6 months, as now clarified on page 5 of the methods section.*

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 February 2021

https://doi.org/10.5256/f1000research.30148.r78755

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Johannes Siegrist
Senior Professorship on Work Stress Research, University of Duesseldorf, Duesseldorf, Germany

This protocol paper describes the aims and methods of conducting a living systematic review (LSR) on findings from studies following COVID-19 patients with long-terms symptoms. The LSR is planned to be updated at 2-months intervals up to 2 years. The paper offers information on search strategy with key terms, data management procedure, screening with critical appraisal, data extraction, and strategies of data analysis. Overall, the approach is in line with the PRISMA guidelines of performing systematic reviews and meta-analyses. Moreover, the protocol was registered in PROSPERO. Critical appraisal was proposed according to Hoy *et al.* 2012, and authors are expected to ensure that relevant criteria of risk of bias can be assessed by this tool.

In summary, while the indexing of the paper is endorsed, several minor queries still need to be addressed, as detailed below.

Search strategy:
Authors claim that their search will not be restricted by country and language. However, it is unrealistic to identify and analyse written materials in more than 3 or 4 main languages, and these languages (English plus...) should be explicitly mentioned in the study protocol.

Data extraction:
I wonder why no data on treatment (therapy of COVID-19 symptoms) are included in the data extraction matrix. This information is crucial if aspects such as symptom severity and duration are being evaluated.

Data analysis:

This section is not well elaborated. Basic descriptive statistics only are mentioned. However, systematized data from respective publications will probably allow additional, more informative ways of synthesizing the data.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Social epidemiology systematic reviews

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Jul 2021

Charitini Stavropoulou, City, University of London, London, UK

Thank you for your thorough review of our protocol, please find the response to the comments made outlined below.

Search strategy:
Authors claim that their search will not be restricted by country and language. However, it is unrealistic to identify and analyse written materials in more than 3 or 4 main languages, and these languages (English plus...) should be explicitly mentioned in the study protocol.

Response: *The main search will be performed in English, articles identified in non-English languages will be translated using Google translate and assessed by a reviewer with good knowledge of the language. This is now stated on page 7 of the revised protocol.*

Data extraction:
I wonder why no data on treatment (therapy of COVID-19 symptoms) are included in the data extraction matrix. This information is crucial if aspects such as symptom severity and duration are being evaluated.

Response: *Thank you for the comment. This is part of the information included in the characteristics of population and is now explicitly mentioned in the protocol. Where data is*

available and synthesizable, we plan to assess the association between acute treatment and symptom severity and duration.

Data analysis:
This section is not well elaborated. Basic descriptive statistics only are mentioned. However, systematized data from respective publications will probably allow additional, more informative ways of synthesizing the data.

Response: *Thank you for your comments. We have amended the data analysis section to clarify that the analysis will go beyond descriptive statistics and, when possible, we will perform a meta-analysis. Please see pages 7 and 8 of the revised protocol.*

Competing Interests: No competing interests were disclosed.