STUDY PROTOCOL

What are the long-term symptoms and complications of COVID-19: a protocol for a living systematic review [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Although the majority of patients 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 weeks or months after the acute phase of the illness. These symptoms include, among others, fatigue, problems in breathing, lack of smell and taste, headaches, and also depression and anxiety. It has also become clear that the virus has lasting effects not only on the respiratory system but also on other parts of the body, including the heart, liver, and the nervous system.

In this paper we present a protocol for a living systematic review that aims to synthesize the evidence on the prevalence and duration of symptoms and clinical features of post-acute COVID-19 and its long-term complications.

The living systematic review will be updated regularly, initially monthly with update cycles under continuous review as the pace of new evidence generated develops through the pandemic. We will include studies that follow up with COVID-19 patients who have experienced persistent mild, moderate or severe symptoms, with no restrictions regarding country, setting, or language.

We will use descriptive statistics to analyse the data and our findings will be presented as infographics to facilitate transcription to lay audiences. Ultimately, we aim to support the work of policy makers,

Open Peer Review

Approval Status

	1	2
version 2		
(revision)
27 Aug 2021	view	view
version 1
14 Dec 2020	view	view

1. **Johannes Siegrist** , University of 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.

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 **Pathogens** gateway.

This article is included in the **Coronavirus** collection.

This article is included in the **Living Evidence** collection.

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Author roles: **Michelen M:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Sigfrid L:** Funding Acquisition, 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; **Hastie C:** Investigation, Validation, Writing – Review & Editing; **O'Hara M:** Investigation, Validation, Writing – Review & Editing; **Suett JC:** Investigation, Methodology, Validation, Writing – Review & Editing; **Cheng V:** Data Curation, Formal Analysis, Investigation, Methodology, Validation, Writing – Review & Editing; **Burls A:** Investigation, Validation, Writing – Review & Editing; **Footte C:** Investigation, 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

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Background

More than six months into the pandemic, our knowledge around COVID-19 continues to develop rapidly. 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 hospitalisation¹. We have previously conducted a rapid review of the literature to identify which symptoms and signs might differentiate mild and moderate from severe COVID-19². 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 experienced³ 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 onset⁴. 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 symptoms⁵, 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 conditions⁶. 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 literature⁶ and NHS England has issued guidance for the multisystem needs of patients recovering from COVID-19⁹. 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.your-covidrecovery.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-19¹⁰.

The aim of this review is to synthesize the evidence on the prevalence and duration of symptoms and clinical features of post-acute COVID-19 and its long-term complications. 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 decisions¹¹. 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 initially updated monthly, 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 of patients with COVID-19 who have persistent mild, moderate or severe symptoms as defined by the article authors
- Studies following up with COVID-19 patients
- Peer reviewed articles published since 1st 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 Cochrane for relevant systematic reviews and Google Scholar for grey literature including pre-prints. We will also look at the [WHO Global Research Database on COVID-19](#) and LitCOVID as two databases that bring together evidence on COVID-19 from a worldwide dataset. Finally, we will contact experts in the field and use social media to identify relevant studies.

Data will be managed using the review software Rayyan¹².

Key search terms

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

recent high profile research articles on long covid were included. No important studies were missed.

An example is shown below:

MEDLINE Search	
S1. COVID-19 OR OR covid OR SARS-CoV-2. ab	31,903
S2. symptom* OR "clinical features" OR signs OR characteristic* OR sequelae OR complication*.ab	188,243
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	25,598
S4. S1 AND S2 AND S3	309

Screening

Initial screening of titles and abstracts as well as full text screening against the inclusion criteria will be done by two reviewers. 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.

Critical appraisal checklist

We will be using the Hoy *et al.* checklist¹³ to critically appraise the studies included in the review.

Data extraction

The following information will be extracted from each study based on the extraction form used for our initial review²: study

aim, country of study, setting, method, study design and population size and characteristics, types and frequency of symptoms reported, onset and duration of symptoms. Data extraction will be performed by one reviewer and checked by a second reviewer. Disagreements will be resolved through discussion and consensus.

Data analysis

We will use descriptive statistics to summarise the types of symptoms, their frequency and duration. We will perform subgroup analysis on the basis of age, sex, comorbidities and severity of the disease. The data will be presented as infographics 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 guidelines¹⁴, 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.

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Version 1

Reviewer Report 22 March 2021

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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 or 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 or 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

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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.

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