Dear Prof. Kern,

We want to thank you for your patience as we worked to get this reviewed; please accept our apologies for any delay in the process. We sincerely appreciate you sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Timothy Feeney MD MS MPH
Research Editor
The BMJ
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**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Navjoyt Ladher (chair), Jamie Kirkham (statistical editor), Tim Feeney, John Fletcher, Joseph Ross, Tiago Villanueva, Di Wang, Wim Weber; Sophie Cook (editor in chief, BMJ Medicine), Emma Rourke (clinical editor, BMJ Medicine)

Decision: Put points

Detailed comments from the meeting:
First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee: We are very interested in this topic because it has important implications for physicians, patients and society at large when making decisions about personal and societal risk regarding COVID. Nevertheless we recognize that this study has serious limitations related to specific response and recall biases that might alter the interpretation of the estimates presented here. We suggest that instead of solely focusing on the proportion of those with COVID and long COVID, the focus shift slightly to concentrate on the types of symptoms present and how they cluster. Our reasoning is that while there are selection and recall biases that can bias the proportion of all COVID patients with long COVID, the response pattern and symptom clusters might be more informative overall. Presenting the estimates as you have them now is fine as long as limitations of prevalence are strongly worded and honest, and as long as the focus is shifted as suggested above. We have more specific comments below, and reviewers also raised many important points that need to be addressed.

- Please be direct about the potential for bias to affect the magnitude of the associations is substantial.

1) Selection bias
   This is highlighted in the low response rate. People are invited to participate about symptoms and COVID, and it is possible that those with symptoms are more likely to participate than those without. Again, the low response rate means the magnitude of this bias could be large.

2) Recall bias
   Participants are asked about symptoms before, during and after COVID infection, all of which are at varying times in the past. Recall is likely to be affected by previous events and experience and the effects could be large.

3) Lack of a comparator
   Only those with a positive test were invited. a) It is possible that tying symptoms to an event will heighten reporting. There should be a control group recruited around an alternative event. b) It is possible that societal changes at the same time were associated with symptoms and this seems plausible for psychological symptoms such as anxiety and mild fatigue. Again these are potentially large effects.

- Please be more specific about missing data. Please highlight how that was evaluated and addressed.

- Can the authors offer a a sense of how representative the sample was.

- Cluster analysis is a valid technique, but it is unclear how clusters were chosen. More detail is needed. The linkage approach to clusters and general health and working capacity was also unclear. How was this done?

- Only 3.5% were hospitalized. Does this indicate a group with predominately mild disease.

- Can the authors offer any clear time frame for "pre-Covid" period?

- Can you provide more information about how clusters were developed? It is not quite clear why some symptoms were lumped to form a cluster while others were not.
- We are not sure table S2 shows “determinants” (indicating causal link) of the 13 symptom clusters, as other confounders might exist. Can the authors clarify this?

- There is no information of variants and vaccination status, and their impact on the outcomes. Can the authors provide this linkage?

- Please make sure to include a required dissemination statement in the end matter. This statement should describe any plans to promote your research and findings. This can include posts on social media. You can even offer information on the pre-print.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
It is an interesting and well designed work that deserves publication, in my opinion, both because it is based on a large number of cases and because it introduces some new elements, such as symptom clusters.
It may be useful to ask the authors for two further insights:
1) highlight any treatment performed, provided that it has been included in the questionnaire (see pag. 10 third line);
2) given that the study covers the period in which anti-covid vaccination was offered regularly, the percentage of vaccinated patients and any differences between the two groups (vaccinated vs unvaccinated).

Additional Questions:
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Please enter your name: Marcello Tavio

Job Title: Director

Institution: Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona
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A fee for organising education?: No

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Reviewer: 2

Comments:
Dr. Peter and colleagues report about a large retrospective cohort study conducted in Southern Germany that assessed symptoms and symptom clusters of Long Covid. The study was carefully designed, conducted and reported. It provides timely evidence on Long Covid when the wild type of SARS-CoV-2 was still prevalent. Particular strengths are the population-based set up, the use of standardized questionnaires, the large sample size (important to have enough power to assess specific risk factors like specific pre-existing conditions), the detailness of symptoms assessment and the follow-up of up to 12 months. The following comments may be considered to further improve the paper and facilitate interpretation of its results:

- It was difficult to find the study on the DRKS study registry and it would be useful to have access to the protocol for some details. For example: How were participants...
informed about the purpose of the study? Was there specific reference to Long Covid or was it frame more generally as a cohort study that aims to address several questions around SARS-CoV-2? This is quite key since self selection into a study may have substantial impact on the results. Generally, studies that explicitly refer to Long Covid (or similar terms) have higher prevalence and also sometimes different associations because there is some self-selection of persons into a study who may be more affected by Long Covid as compared to population based studies that also had different aims and do not focus entirely on Long Covid.

- When asking about symptoms, were participants specifically asked if they related the symptoms to the SARS-CoV-2 infection? Given the rather unspecific nature of most symptoms of Long Covid specifying whether the symptoms relate to the infection or not (and participants can usually distinguish quite well) is useful to narrow down the symptoms that are a consequence of an infection or were there before or occurred after (e.g. due to some other illness). The authors may have dealt with the issue by comparing pre- and post infection symptoms but it should be more clearly stated how specific symptoms were assessed.

- From the description of the statistical analysis it is not entirely clear if time since infection was considered in the models. Since symptoms do decline substantially over time (see also https://doi.org/10.1101/2022.05.26.22275532 ) it is important to adjust for time since infection because the follow-up differs across participants.

- The authors acknowledge the limitation of recall bias but also refer to self reports and no validation as limitation. I disagree that the latter two are a limitation since this is the only way to get the information. Self report per se is by no means a limitation and often, medical validation is a pseudo-validation based on the idea that such tests are more valid and reliable. But this is simply to based on evidence. Thus I suggest to remove the reference to self reports and no validation as limitation.

- Finally, the authors may want to point out the unique points of the study a bit more. Most results are not surprising and are in line with previous, but often smaller and less valid studies. Thus study substantially strengthens the evidence base which would be good to point out more.

Additional Questions:

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Job Title: Prof of Epidemiology
Institution: University of Zurich
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
Funds for a member of staff?: No
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Reviewer: 3

Comments:
Interesting work from a German group on PASC/Long Covid.
I have the following comments.
a. The paper would be strengthened considerably by the inclusion of a control group. The lack of control (e.g. people with no known infection) limits the interpretation of the findings significantly.
b. The methodology of polychoric factor analysis and co-occurrence network analyses are not well described. I found it hard to evaluate given paucity of description in methods. Also how and why is this meaningful? The authors should provide discussion on why this analysis is meaningful and how does it advance our understanding of Long Covid.

c. It is also unclear how "loss of general health" and working capacity are derived and estimated from these questionnaires? These are self-reported? How? What are the questions or sets of questions? Have the questions been validated? How do we know that these measure what we think they measure? Again, there is very little detail on this.

d. Percent missing is not provided for the main data points.

e. The response rate is quite low (24%) and it is unclear how this affects the results? The authors mention older adults and females had a higher response, and refer to table S4 (I looked for table S4, and it is not provided anywhere). Will this over or under represent people with LC? This should be discussed in greater detail, and if anything is known about the people who did not respond, it should be included. By the way (minor comment, the tables/figures are not ordered correctly, and it was very confusing for me to go through the supplemental file).

f. It is not clear to me how the symptom clusters in figure 3 were developed? How was this validated? Ideally, you would develop them in a dataset (or half the dataset) and validate them in a second dataset. Also co-occurrence is a function of underlying frequency. I think the approach should take into consideration natural frequency of 2 things happening together, and test whether covid result in excess co-occurrence or in some cases less co-occurrence. I think the lack of control limits your ability to develop this more.

g. The data visualization is not that clear, it should be optimized, and perhaps decluttered a bit. There is just too much data. Focus the story on the most relevant message and develop the visuals around it.

Additional Questions:
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Please enter your name: Ziyad Al-Aly, MD
Job Title: Chief Research and Development Service

Institution: VA Saint Louis Healthcare System

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

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Reviewer: 4

Comments:
The authors performed a retrospective study aimed at investigating the prevalence of sequelae at 6 to 12 months following SARS-COV2 infection in Germany. They conclude that the burden of self-reported post-acute symptoms and possible sequelae, notably fatigue and neurocognitive impairment, remains considerable after acute infection. The issue is relevant and contemporary. The sample size is large. The study has limitations inherent to the retrospective nature.

Comments:
1. A Table reporting the features of patients with >= 2 symptoms vs those with 1 symptom/no symptom could be added.
2. The limitation that over time changes of symptoms during follow-up were not captured should be included
3. The risk of inclusion bias should be specifically added in the limitations
4. Previous studies reporting the high prevalence of sequelae even at 1 year after COVID-19 (Bellan M, et al. Sci Rep 2021) could be included.

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Please enter your name: Giuseppe Patti

Job Title: Full Professor of Cardiology
Institution: University Of Eastern Piedmont
Reimbursement for attending a symposium?: Yes
A fee for speaking?: Yes
A fee for organising education?: No
Funds for research?: Yes
Funds for a member of staff?: No
Fees for consulting?: Yes
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Reviewer: 5

Comments:
I found this article well written, concise, and easy to follow. I believe it achieved its stated goals.

My only comments and questions are these:

Did the present study control well enough for pre-existing conditions and comorbidity? Perhaps the survey could be repeated by canvassing medical professionals dealing with such cases, which would be a good way to re-test the results.

The study is slanted to delineating differences between age and sex. However, it might be enlightening to include socio-economic and ethnicity as determinants. Depending on prevalence patterns of COVID-19 in Germany, this might be relevant.

The study does limit age of participants to 65 years. Since the thrust of the study is the ability to work, this is a valid restriction. However, it does limit the predictive value of the study to the population as a whole.

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Please enter your name: Bala Munipalli

Job Title: Physician

Institution: Mayo Clinic Florida

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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