Neurol Ther
https://doi.org/10.1007/s40120-022-00424-x

LETTER

Response Letter to Vink et al. 'Neurological Study Does Not Provide Any Evidence that Long COVID is Psychosomatic'

Mark Stettner · Michael Fleischer · Eva-Maria Skoda · Martin Teufel · Christoph Kleinschnitz

Received: October 19, 2022 / Accepted: November 7, 2022

Keywords: COVID-19; Fatigue; Long COVID; Neurological deficits; Neuropsychological assessment; Post-COVID; Somatization

To the Editors

We thank Vink and colleagues [1] for their critical appraisal of our study [2].

The authors allege that our study would have labelled all patients with post-COVID-19 syndrome as 'psychosomatic' since the neurological workup was normal. Unfortunately, however, this claim is a misrepresentation of our conclusions. Rather, we suggested that psychosomatic factors *should be taken into account* since we were widely unable to objectify neurological impairment in our cohort. We regard this approach as state-of-the-art in modern medicine. It is best medical practice and in line with current guidelines—including post-COVID-19 guidelines [3]—to consider psychological and social factors in disease states without obvious organ damage. Even further, physicians would be acting negligently and potentially withholding patients from effective therapies, such as psychotherapy, if psychosomatic origin was not taken into account under such a constellation. The authors summarize their view as 'absence of evidence is no evidence of absence'. This rather general statement does not add anything specific to the current debate but in fact could be directed to any scientific finding. We have not claimed causality from our data and are fully aware of the fact that it is never possible to finally 'prove' absence of a specific condition.

Moreover, the authors suggest that our study exclusively focussed on neurological testing, which, however, is incorrect. In addition to our extensive neurological workup, we also evaluated pulmonary function, blood oxygen saturation and a range of laboratory parameters, including parameters of inflammation—all of which were normal in the vast majority of our patients. Furthermore, as neuroscientists, we of course focussed on neurological signs of post-COVID-19 syndrome, particularly in the light of the fact that

This reply refers to the comment available at DOI https://doi.org/10.1007/s40120-022-00426-9

M. Stettner · M. Fleischer · C. Kleinschnitz (✉)
Department of Neurology, Essen University Hospital, University Duisburg-Essen, Essen, Germany
e-mail: Christoph.Kleinschnitz@uk-essen.de

E.-M. Skoda · M. Teufel
Clinic for Psychosomatic Medicine, and Psychotherapy, LVR Essen University Hospital, University of Duisburg-Essen, 45147 Essen, Germany

M. Stettner · M. Fleischer · E.-M. Skoda · M. Teufel · C. Kleinschnitz
Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University of Duisburg-Essen, Essen, Germany

Published online: 12 December 2022

neurological complaints rank most common and most severe among patients with post-COVID-19 syndrome [4, 5]. In addition, we anything but ignored articles suggesting organ-specific alterations (immunological, vascular) in people with post-COVID-19 syndrome. Instead, we extensively discussed such references throughout various sections of our manuscript. We also disagree with the statement that our study design was not truly prospective. In contrast to a retrospective design, the key characteristic of a prospective study is that data are collected *after* subjects have been enrolled [6]. This is exactly the methodology followed in our study. It appears as if the authors mingled the terms 'prospective' and 'longitudinal'. However, longitudinal collection of data, i.e. at different time points, is not a requirement to label a study as 'prospective'. Moreover, the term 'cohort' is not exclusively used to describe studies that compare two different groups, as suggested by the authors [7].

Vink et al. [1] further call into question the validity of our results by claiming that we did not conduct all diagnostic tests in each and every single study participant. In fact, we transparently indicated the frequency and type of diagnostic tests performed in the manuscript and discussed this limitation in detail. In line with good clinical practice, diagnostics were performed according to the main neurological complaints and, for ethical reasons and due to contraindications, it was simply not possible to conduct the complete panel of examinations (e.g. lumbar puncture, magnetic resonance imaging [MRI]) in every patient. Nevertheless, given the range and the large number of tests used, we are convinced that our neurological workup was indeed comprehensive enough to state that the neurological status was normal in most of our patients. Of note, we have in the meantime examined more than 1000 people with post-COVID-19 syndrome in our post-COVID outpatient center, and the diagnostic results gathered so far are very similar to those published here.

Moreover, the authors might not be fully familiar with the technique of neurological ultrasound. The 'Doppler scan' is of course a routine part of the duplex ultrasound examination of the extra- and intracranial arteries. As detailed in the manuscript, findings from this ultrasound examination were largely normal, thereby excluding significant atherosclerosis as potential cause of the (unspecific) cognitive deficits described.

Exertional intolerance was not regularly mentioned by the majority of our patients during the structured interviews, probably due to the fact that our study focussed on neuropsychiatric complaints rather than internistic symptoms. Therefore, there was simply no rationale to assess exertional intolerance or other cardio-pulmonary parameters more extensively. Again, this bias towards a more 'neurological' population was transparently captured in the Discussion, as was the fact that our diagnostic workup was restricted towards established neurological tests, which, however, are highly sensitive, rather than experimental examinations (e.g. brain single photon emission computed tomography [SPECT]/positron emission tomography [PET]), which in most of the cases still lack external validation.

Surprisingly, one specific criticism of Vink and colleagues [1] was that our manuscript did not contain a range of topics related to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This is due to the fact that our study was about post-COVID-19 syndrome rather than ME/CFS. Consequently, we refrained from adding references on ME/CFS, such as the European (treatment) guidelines or World Health Organization (WHO) disease definitions, since these would have been beyond the scope of our paper. In fact, we briefly mentioned ME/CFS only twice, once in the Introduction and once in the Discussion in order to highlight potential similarities between post-COVID-19 and ME/CFS regarding the underlying pathomechanisms and symptomatology. According to the latest literature, those similarities might indeed exist [8], although independent confirmation from other groups is still pending, and the recognition of ME/CFS as distinct disease entity is not broadly accepted in the medical community, at least not in Germany [9].

Vink and colleagues also falsely suggest that the Patient Health Questionnaire-15 (PHQ15) lacks sensitivity and only 'captures what it is supposed to explain'. Rather, the PHQ15 is widely accepted as a valid instrument to assess the severity of somatic symptoms [10].

Finally, several issues related to our statistical analysis were raised. The authors assume 'a high probability of multiple false positives'. The rationale behind this conclusion remains unclear. They claim that for the stepwise regression analyses '*p*-values and standard errors are too small and confidence intervals too short'. This statement is inherently linked to the stepwise regression approach and is not a specific limitation of our study. As a matter of fact, the results stand as they are and were confirmed by the statistical tests described in the Methods section. Moreover, our manuscript underwent extensive peer review, including statistics and editorial review, prior to publication. Also, the reporting of statistical findings was in full accordance with the Journal's submission guidelines, which do not require reporting of *p*-values to two or three decimal places [11]. Regarding the clustering approach, categorical variables of complaints were used in a two-step algorithm, which is accepted as a robust test. For the multinomial distribution of the variants, the log-likelihood measure of distance was performed. We can confirm the verification of underlying distributional assumptions with the chosen variables' independence by using the χ^2-test. In addition, order dependence was fully considered during the statistical analysis by clustering the variables multiple times in different orders.

In conclusion, our study provides evidence that the nervous system is only rarely affected in people with post-COVID-19 syndrome. Since long-lasting damage of other organs also appears to be rare [12], categorical denial of psychosomatic disease modifiers ignores common medical and scientific standards and could potentially exclude post-COVID-19 patients from essential diagnostics and effective treatments.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Funding. No funding or sponsorship was received for this letter or publication of this article. The Rapid Service Fee was funded by the authors.

Author Contributions. Christoph Kleinschnitz drafted the first version of the letter. Mark Stettner, Eva-Maria Skoda, Martin Teufel and Michael Fleischer carried out critical intellectual revision. All authors read and approved the final manuscript.

Disclosures. Mark Stettner, Michael Fleischer, Eva-Maria Skoda, Martin Teufel and Christoph Kleinschnitz declare that they have no competing interest in connection with the letter.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Vink M, Grande T, Kohl M. Neurological study does not provide any evidence that long COVID is psychosomatic. Response to Fleischer et al. Neurol Ther. 2022;

2. Fleischer M, Szepanowski F, Tovar M, Herchert K, Dinse H, Schweda A, et al. Post-COVID-19 syndrome is rarely associated with damage of the nervous system: findings from a prospective observational cohort study in 171 patients. Neurol Ther. 2022;11:1637–57.

3. Berlit P, Bösel J, Gahn G, Isenmann S, Franke C, Meuth S, et al. Neurologische Manifestationen bei COVID-19, S2k-Leitlinie, Leitlinien für Diagnostik und Therapie in der Neurologie. Dtsch Ges Neurol (Hrsg). 2022;5:197–209.

4. Hayes LD, Ingram J, Sculthorpe NF. More than 100 persistent symptoms of SARS-CoV-2 (long COVID): a scoping review. Front Med. 2021;1(8):750378.

5. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. BMJ Glob Health. 2021;6(9):e005427.

6. Ranganathan P, Aggarwal R. Study designs: part 1—an overview and classification. Perspect Clin Res. 2018;9(4):184–6.

7. Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol. 2020;19(4):317–25.

8. Kedor C, Freitag H, Meyer-Arndt L, Wittke K, Hanitsch LG, Zoller T, et al. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat Commun. 2022;13(1):5104.

9. Rollnik JD. Chronic fatigue syndrome: a critical review. Fortschr Neurol Psychiatr. 2017;85(2):79–85.

10. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002;64(2):258–66.

11. Springer. Neurology and Therapy. Instructions for author. Submission guidelines https://www.springer.com/journal/40120/submission-guidelines. Accessed 12 Oct 2022.

12. Sneller MC, Liang CJ, Marques AR, Chung JY, Shanbhag SM, Fontana JR, et al. A longitudinal study of COVID-19 sequelae and immunity: baseline findings. Ann Intern Med. 2022;175(7):969–79.