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Letter to the Editor Regarding Fleischer et al. Neurological Study Does Not Provide Any Evidence that Long COVID is Psychosomatic

Mark Vink · Tilman Grande · Matthias Kohl

Dear editor

We read the study by Fleischer et al. [1] with interest. The authors conclude that post-COVID-19 syndrome, also known as long Covid, might be psychosomatic without providing any evidence supporting this conclusion. Their line of logic seems to be that if neurological tests are normal then the condition under study is psychosomatic. However, first of all, absence of evidence is not evidence of absence. Secondly, the authors themselves note that "the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can affect multiple organs" so then it is illogical to rely on neurological testing only. Moreover, they ignore the increasing number of articles which have found immunological, vascular and other abnormalities in patients with long Covid [2].

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M. Vink (✉)
Independent Researcher, Amsterdam, The Netherlands
e-mail: markvink.md@outlook.com

T. Grande
Private Practice, Heidelberg, Germany

M. Kohl
Institute of Precision Medicine, Furtwangen University, Furtwangen im Schwarzwald, Germany

We suggest that there are also a number of other issues with this study, including the following.

The authors state that they conducted a prospective cohort study; however, although their study was not prospective, it was also not a prospective cohort study because then they should have followed a group of individuals who are alike in many ways but differ by a certain characteristic, for example, female nurses who smoke and those who do not smoke, and compare them for a particular outcome, such as lung cancer; however, this was not done [3].

The authors claim to have performed a comprehensive neurological assessment of patients with post-COVID-19 syndrome. However, ultrasound examination of the extra- and intracranial head and neck arteries was only performed in 76 patients, brain magnetic resonance imaging in only 41 patients and a lumbar puncture in only nine patients, even though 171 patients were enrolled in the study. The study did not include positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) scans of the brain nor did it include cerebral Doppler scans to see if there was objective evidence for the cognitive problems of patients. In this context, it should be noted that the cerebral Doppler scan study of Van Campen et al., which was published in December 2021, found a reduction in cerebral blood flow in response to tilt testing

in long COVID-19 patients, similar to that observed in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which was not seen in healthy controls [4].

The study also did not enquire about exertional intolerance even though many long COVID patients suffer from that. Objective evidence for exertional intolerance in long COVID-19 patients was provided by Singh et al. using invasive cardiopulmonary exercise testing [5].

Yet, interestingly enough, 146 of the 171 patients underwent structured neuropsychological testing by trained personnel because according to the authors there is an "importance of psychosomatic factors in the emergence and perpetuation of post-COVID-19 syndrome" which according to them is "supported by similarities between post-COVID-19 syndrome and the presentation of posttraumatic distress syndrome, depression, anxiety disorder, or poorly defined disease entities such as...ME/CFS." We would like to point out that, first of all, the two references used by Fleischer et al. for this are an evaluation study of a new post-traumatic stress disorder (PTSD) questionnaire related to the COVID-19 pandemic and a systemic review into the overlap in symptomatology of long COVID and Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [6, 7]. It is therefore unclear on which evidence Fleischer et al. base their claim that there are similarities in the presentation of long COVID, ME/CFS, PTSD, depression and anxiety. It is also unclear why the authors do not mention that ME/CFS has been classified as a neurological disease by the World Health Organisation since 1969 [8]. Nor is it clear why they do not mention that the prestigious American Institute of Medicine (now the National Academy of Medicine), the Dutch Health Council and the British National Institute for Health and Care Excellence (NICE) have all concluded after extensive reviews of the literature in 2015, 2018 and 2021 [9–11], respectively, that ME/CFS is a debilitating chronic multisystem disease and not a psychological, psychiatric or psychosomatic disease. Moreover, NICE also concluded that cognitive behavioural

therapy (CBT) and graded exercise therapy (GET) are not effective treatments for ME/CFS, that GET is harmful and should not be used and that CBT should only be used for patients with ME/CFS as an adjunctive therapy for a secondary depression or anxiety disorder or if patients have difficulty coping with this debilitating disease.

The statement on the psychosomatic background is also based on the Patient Health Questionnaire 15 (PHQ15), i.e. on a questionnaire with 15 items. Of these 15 items, 13 ask about various pains and other physical symptoms, such as dizziness, tachycardia and gastrointestinal problems, the two other questions are about sleep disorders and fatigue. It is clear that patients with long Covid will answer many of these questions in the affirmative. In order to evaluate this finding, one must again make it clear that this is not a prospective study, but that all data are collected at a single examination time, on average approximately 4 months after infection. The authors use the PHQ15 as if it could be used to capture a kind of somatoform personality that persists regardless of current sensitivities. This also means that the instrument captures what it is supposed to explain, i.e. it does not depict a disposition independent of the long Covid symptoms.

On top of this, there are a number of issues with the statistics used in the paper; for example, the authors write that "influencing factors on somatization (PHQ-15) and cognitive dimensions were identified with linear regression calculation with the method enter." Yet it is known that such stepwise regression analyses have weaknesses from a statistical point of view. In particular, one must assume that the p-values and standard errors are too small and confidence intervals too short [12]. Furthermore, the clustering approach is insufficiently described. It is not clear which information (variables) was used, nor whether underlying distributional assumptions were verified and known limitations, such as order dependence, were adequately addressed. In addition, p-values are not reported to two or three decimal places as requested by standard statistical guidelines, and the problem of multiple testing is not even

mentioned. Overall, there is a high probability of multiple false positives [13].

In conclusion, the study by Fleischer et al. [1] does not provide any evidence that long Covid is or might be psychosomatic and ignores all evidence to the contrary.

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