



Response to Letter to the Editors regarding article entitled 'Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients'

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To the Editors

We are grateful to Finsterer and Mehri for their valuable comments [1] on our article entitled 'Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients' that was recently published in the Polish Journal of Neurology and Neurosurgery [2].

However, we believe that all the points raised in their recent Letter to the Editors were in fact covered in detail within the 'limitations' section of our paper [2].

Firstly, we admit that the ambiguity exists regarding what is perceived as a 'brain fog' in COVID-19 research. However, for the purposes of the current study, we used the meaning proposed by the National Institute for Health and Care Excellence and the Centres for Disease Control and Prevention that underlined difficulty in thinking [3] and other cognitive problems, including loss of concentration and memory [4]. All of these aspects were covered by our

detailed questionnaire that was created based on the experience of 70 healthcare professionals who were afflicted by SARS-CoV-2 infection [5]. Furthermore, the development and validation process of the BF-COVID questionnaire included a standardised methodology, i.e. item generation, validation of content, face validation, and psychometric analysis [6]. Noteworthy, exploratory factor analysis with varimax rotation and reliability testing showed good content validity and acceptable internal consistency (Kaiser-Meyer-Olkin value 0.796, Bartlett's test of sphericity $\chi^2 = 943$; $df = 36$, p -value < 0.001 , and Cronbach's alpha of 0.740) [6].

Secondly, as we mentioned in the limitations section of our article, our research was based on patient-reported data only and, given that the anonymous questionnaires were completed retrospectively, our results inherently reflect largely subjective aspects of brain fog. However, we did not rely solely on electronic versions of questionnaires, because individuals who attended the ambulatory clinic for

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post-COVID patients in the University Hospital in Krakow were also asked to participate in the study [2]. It is also noteworthy that patient-reported outcomes are increasingly being used among COVID-19 survivors [7]. Furthermore, although neuropsychological examination remains an important and valuable assessment tool, it may actually be less sensitive in detecting subtle cognitive changes during recovery after SARS-CoV-2 infection [8].

Thirdly, only 19% of participants were vaccinated against COVID-19; however, most of them underwent this procedure after their diagnosis of SARS-CoV-2 infection [2]. Indeed, as the authors of the Letter to the Editors suggest, although vaccination against COVID-19 might reduce the risk of persistent problems after initial infection, nonetheless, in individuals with existing long COVID symptoms, including brain fog, the role played by subsequent vaccination remains uncertain, as some studies have suggested improvement while others have not [9].

Fourthly, as specifically stated in the limitations section of our paper, no data on comorbidities, including neurological and psychiatric conditions such as depression, were collected during the course of our study [2]. Therefore, their influence on the responses given by the patients cannot be excluded. On the other hand, using self-reported screening questionnaires might not be helpful in depression, and can even result in its overestimation [10]. Thus, face-to-face interviews would be the preferable method for both brain fog and depression assessment, but this would require studies with diverse methodologies and designs.

Finally, we are aware of the uneven sex distribution in our cohort [2]. However, post hoc power calculation remained satisfactory [2].

In summary, the limitations of our study are important when interpreting the results. Nevertheless, the use of a previously validated questionnaire allowed us to show significant differences in the course of brain fog between women and men [2]. Although consistent with previous research regarding the role of female sex in the risk of developing post-COVID brain fog, future studies are essential to confirm the results and conclusions set out in our paper.

Conflicts of interest: None.

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