

# Response to advocating for rigorous and multifactorial analyses in post-COVID cognitive research

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We agreed with Professor Zeng for advocating for rigorous and multifactorial analyses in post-COVID cognitive research, who emphasized that some important variables were need to be considered in the analyses, including cognitive function of COVID-19 survivors prior to their infection, sociodemographic factors, multiple COVID-19 infections and vaccination.<sup>1</sup>

Paralleled with Professor Zeng's idea, understanding the baseline cognitive state of COVID-19 survivors before infection is crucial to explore the association between cognitive function and COVID-19 infection. Despite the lack of cognitive state before infection, to minimize potential sources of bias, the healthy control participants were recruited from the same community as survivors to match the age range, sex proportion, and education level. Moreover, no difference of some factors related to cognitive function before infection like history of physical diseases or mental disorders between survivors and healthy control group was found, which can suggest that two groups were comparable in the baseline cognitive state before infection to a great extent.

Our results indicated that our participants were either employed or retired, and the differences of employment between COVID survivors and healthy controls were not observed ( $p = 0.075$ ). Despite the lack of income data, we matched control groups for education level which was associated with incomes. In brief, the risk of these sociodemographic factors confounding our results was relatively low.

Due to strict prevention and control measures conducted by the Chinese government, it is unlikely for our participants to experience multiple COVID-19 infections before and during the enrollment of our research. Moreover, we are grateful for Professor Zeng to provide the argument about considering the effect of vaccination on prognosis after COVID-19 infection in the research. And we failed to conduct subgroup analyses due to the limit of sample size. However, we found that there was no significant difference of vaccination between survivors of mild-moderate acute symptoms group and severe-critical group (mild-moderate vs. severe-critical:  $p = 0.349$ ), but both the rates of vaccination in two survivor groups were lower than those in the control group (mild-moderate vs. healthy control:  $p = 0.014$ ; severe-critical vs. healthy control:  $p = 0.003$ ), which indicates that besides COVID-19 infection, the relatively lower rates of vaccination in survivors may contribute to unfavorable prognosis after infection [severe-critical: 66.67% (multiple doses), 22.22% (single dose), 11.11% (never) vs. mild-moderate: 76.00%, 8.00%, 16.00% vs. healthy control: 97.14%, 10.34%, 8.05%,  $p = 0.005$ ]. Therefore, we should advocate for getting vaccination according to national recommendations in order to prevent infection and improve prognosis.

As Professor Zeng has provided, some studies suggested that cognitive impairments may be partly the result of psychiatric conditions like depression, insomnia, PTSD and so on.<sup>2</sup> Moreover, the COVID-19 pandemic may worsen the mental health of people



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reporting subjective cognitive decline and therefore their clinical prognosis.<sup>3</sup> These means that there may be bidirectional relationship between psychiatric conditions and cognitive impairment during the COVID-19 pandemic. Although we didn't explore the potential causal relationships between these conditions including cognitive complaints, psychiatric, and neurological symptoms, and COVID-19 infection in this research, our team is doing some analyses to investigate whether cognitive problems are a direct result of COVID-19 virus or secondary to psychiatric conditions induced or exacerbated by the pandemic consequences.

In conclusion, our study revealed that COVID-19 survivors commonly experienced psychiatric symptoms, neurological symptoms and cognitive complaints even 2 years after recovery.<sup>4,5</sup> The rs-fMRI results indicated that the changes in brain function in regions such as the putamen, temporal lobe, and superior parietal gyrus may contribute to cognitive complaints in individuals with long COVID even after 2-year infection<sup>5</sup> However, further rigorous and multifactorial analyses, and long-term follow up studies are warranted to confirm the effects of COVID-19 infection on cognitive function.

#### Contributors

Yanping Bao and Lin Lu proposed the topic and main idea; Yimiao Zhao wrote the initial draft of the manuscript; Yimiao Zhao, Peng Li, Xiujun Zhang, Yanping Bao, and Lin Lu commented on and revised the manuscript; Yanping Bao and Lin Lu finalized the manuscript.

All authors have read and agreed to the published version of the manuscript.

#### Declaration of interests

We declare no conflict of interest for this study.

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#### References

- 1 Zeng Q, Shan D. Beyond initial findings: advocating for rigorous and multifactorial analyses in PostCOVID cognitive research. *Lancet Reg Health West Pac.* 2024.
- 2 Santangelo G, Baldassarre I, Barbaro A, et al. Subjective cognitive failures and their psychological correlates in a large Italian sample during quarantine/self-isolation for COVID-19. *Neurol Sci.* 2021;42(7):2625–2635.
- 3 Liu L, Ni SY, Yan W, et al. Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: a systematic review, meta-analysis and call for action. *eClinicalMedicine.* 2021;40:101111.
- 4 Zhao Y, Shi L, Jiang Z, et al. The phenotype and prediction of long-term physical, mental and cognitive COVID-19 sequelae 20 months after recovery, a community-based cohort study in China. *Mol Psychiatry.* 2023;28(4):1793–1801.
- 5 Zhao YM, Liang QD, Jiang ZD, et al. Brain abnormalities in survivors of COVID-19 after 2-year recovery: a functional MRI study. *Lancet Reg Health West Pac.* 2024;47:101086. <https://doi.org/10.1016/j.lanwpc.2024.101086>.