# Examining well-being and cognitive function in people with long Covid and ME/CFS, and age-matched healthy controls: A Case-Case-Control Study

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## Authorship contributions according to the CRediT taxonomy

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## **Conflict of interest statement**

The submitted work was not carried out in the presence of any personal, professional, or financial relationships that could potentially be construed as a conflict of interest.

#### To the Editor:

We thank Dr. Finsterer for their letter to the editor expressing interest in our work<sup>1</sup>.

Regarding Dr. Finsterer's first concern about use of electronic questionnaires, participants in our laboratory testing sessions reported elsewhere<sup>2345</sup> were provided with a secure URL to complete questionnaires. This was to reduce participant burden, as people with ME/CFS and long COVID exhibit post-exertional malaise<sup>67</sup>. We see no motivation for someone other than the participant to complete questionnaires on participants' behalf.

Online questionnaires were administered for inclusivity and accessibility for varying levels of ME/CFS and long COVID, given NICE reports 25% of individuals with ME/CFS are housebound<sup>8</sup>. Furthermore, Dr. Finsterer questions the use of a validated questionnaire to assess neurological symptoms<sup>9</sup>, suggesting it be replaced with a neurological examination. However, such examinations may lack validity and reliability due to human error, and indeed the Edinburgh Neurosymptoms Questionnaire (ENS) is reportedly capable of reliably excluding patients diagnosed by neurologists as not having a functional disorder. We therefore suggest Dr. Finsterer's suggestion that neurological involvement should not be assessed via the ENS lacks substantial evidence and fails to recognise the globally accepted nature of the validated questionnaire. Ultimately, we used the ENS as a research tool (which has been validated), and not for diagnostic assessment of a functional neurological disorder.

Concerning clinical manifestations of the conditions, this was not the aim of our paper. Given the self-reporting nature of our study, we were interested in participants' well-being (i.e. self-reported outcomes) and cognitive function, as expressed in the hypotheses.

The third point questions vaccination status of participants with long COVID and ME/CFS. We are aware that vaccine status may influence long COVID symptomology<sup>10</sup>, but our work identified vaccine status broadly did not influence number, severity or frequency of symptoms, mood, or impact on work or study in a Scottish cohort<sup>1112</sup>. Thus, available evidence is not conclusive regarding this point.

The fourth point regarding sample size was already given in our limitations section ('this study acknowledges specific limitations .... Firstly, the sample size was relatively small, and was not powered to detect changes in all outcomes at the P < .05 level.').

Regarding the fifth point about current medication and comorbidities, these factors have been previously reported within this sample in other papers <sup>13141516</sup>, so we avoided self-plagiarism. Medications for long COVID and ME/CFS to treat individual symptoms, may of course influence symptomology, as may co-morbidities and lifestyle factors, and socioeconomic status (as we have previously reported<sup>1718</sup>.

Participant groups were matched for age and sex; however, some control participants did not complete the questionnaires. This is a common occurrence in research which we accept as a limitation.

In conclusion, concerns raised by Dr. Finsterer are justifiable from a diagnostic standpoint (i.e. in clinical practice), but our study was conducted outside of routine care. Therefore, we believe our article remains valuable for the knowledge economy and is evidence-informed and

supported by background literature, whilst citations were notably absent from Dr. Finsterer's correspondence.

<sup>1</sup> Sanal-Hayes, N. E., Mclaughlin, M., Hayes, L. D., Berry, E. C., & Sculthorpe, N. F. (2024). Examining wellbeing and cognitive function in people with long Covid and ME/CFS, and age-matched healthy controls: A Case-Case-Control Study. *The American Journal of Medicine*. Available at: https://doi.org/10.1016/j.amjmed.2024.04.041

<sup>2</sup> Hayes, L.D. *et al.* (2023) 'People with Long Covid and ME/CFS Exhibit Similarly Impaired Balance and Physical Capacity: A Case-Case-Control Study', *The American Journal of Medicine*, pp. S0002-9343(23)00465–5. Available at: https://doi.org/10.1016/j.amjmed.2023.06.028.

<sup>3</sup> Mclaughlin, M., Sanal-Hayes, N.E.M., *et al.* (2023) 'People with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Exhibit Similarly Impaired Vascular Function', *The American Journal of Medicine* [Preprint]. Available at: https://doi.org/10.1016/j.amjmed.2023.09.013.

<sup>4</sup> Sanal-Hayes, N.E.M. *et al.* (2023) 'Post-Traumatic Stress Disorder and Complex Post-Traumatic Stress Disorder in People with Long COVID, ME/CFS, and Controls', *The American Journal of Medicine* [Preprint]. Available at: https://doi.org/10.1016/j.amjmed.2023.12.006.

<sup>5</sup> Sanal-Hayes, N.E.M. *et al.* (2024) 'People with Long COVID and ME/CFS Exhibit Similarly Impaired Dexterity and Bimanual Coordination: A Case-Case-Control Study', *The American Journal of Medicine*, 0(0). Available at: https://doi.org/10.1016/j.amjmed.2024.02.003.

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<sup>8</sup> NICE (no date) Overview | Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management | Guidance | NICE. NICE. Available at: https://www.nice.org.uk/guidance/ng206 (Accessed: 22 August 2022).

<sup>9</sup> Shipston-Sharman, O. *et al.* (2019) 'Screening for functional neurological disorders by questionnaire', *Journal of Psychosomatic Research*, 119, pp. 65–73. Available at: https://doi.org/10.1016/j.jpsychores.2019.02.005.

<sup>10</sup> Trinh, N.T. *et al.* (2024) 'Effectiveness of COVID-19 vaccines to prevent long COVID: data from Norway', *The Lancet Respiratory Medicine*, 12(5), pp. e33–e34. Available at: https://doi.org/10.1016/S2213-2600(24)00082-1.

<sup>11</sup> Mclaughlin, M., Cerexhe, L., Macdonald, E., Ingram, J., Sanal-Hayes, N.E.M., Hayes, L.D., *et al.* (2023) 'A Cross-Sectional Study of Symptom Prevalence, Frequency, Severity, and Impact of Long COVID in Scotland: Part II', *The American Journal of Medicine*, pp. S0002-9343(23)00461–8. Available at: https://doi.org/10.1016/j.amjmed.2023.07.009.

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<sup>13</sup> Mclaughlin, M., Sanal-Hayes, N.E.M., *et al.* (2023) 'People with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Exhibit Similarly Impaired Vascular Function', *The American Journal of Medicine* [Preprint]. Available at: <u>https://doi.org/10.1016/j.amjmed.2023.09.013</u>.

<sup>14</sup> Hayes, L.D. *et al.* (2023) 'People with Long Covid and ME/CFS Exhibit Similarly Impaired Balance and Physical Capacity: A Case-Case-Control Study', *The American Journal of Medicine*, pp. S0002-9343(23)00465–5. Available at: https://doi.org/10.1016/j.amjmed.2023.06.028.

<sup>15</sup> Sanal-Hayes, N.E.M. *et al.* (2024) 'People with Long COVID and ME/CFS Exhibit Similarly Impaired Dexterity and Bimanual Coordination: A Case-Case-Control Study', *The American Journal of Medicine*, 0(0). Available at: <u>https://doi.org/10.1016/j.amjmed.2024.02.003</u>

<sup>16</sup> Sanal-Hayes, N.E.M. *et al.* (2023) 'Post-Traumatic Stress Disorder and Complex Post-Traumatic Stress Disorder in People with Long COVID, ME/CFS, and Controls', *The American Journal of Medicine* [Preprint]. Available at: <u>https://doi.org/10.1016/j.amjmed.2023.12.006</u>

<sup>17</sup> Mclaughlin, M., Cerexhe, L., Macdonald, E., Ingram, J., Sanal-Hayes, N.E.M., Hayes, L.D., *et al.* (2023) 'A Cross-Sectional Study of Symptom Prevalence, Frequency, Severity, and Impact of Long COVID in Scotland: Part II', *The American Journal of Medicine*, pp. S0002-9343(23)00461–8. Available at: https://doi.org/10.1016/j.amjmed.2023.07.009

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