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# Brain, Behavior, & Immunity - Health

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## The possibility of circadian rhythm disruption in long COVID

Dear Editor

We read with great interest the recent review of circadian rhythm disruption in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and the implications for the post-acute sequelae of COVID-19 (PASC) (McCarthy, 2022), also known as “long COVID”. In this review, McCarthy discusses the possibility that immune and inflammatory responses following viral infection could contribute to circadian disruption and drive ME/CFS symptoms (McCarthy, 2022). This in turn suggests that circadian-based treatments could offer some therapeutic benefits to people suffering from these disorders. Emerging research supports this, as morning bright light treatment which phase advances (shifts earlier) and stabilizes circadian timing, has been found to be beneficial in reducing depressive symptoms, fatigue, pain and in improving sleep quality in a variety of disorders from breast cancer to fibromyalgia (Burgess et al., 2017; Ancoli-Israel et al., 2012). These early results are promising, but require further investigation in larger samples.

Due to the potential conversion to ME/CFS, the role of circadian disruption in long COVID merits investigation. Long COVID, defined as symptoms that arise  $\geq 3$  months after SARS-CoV-2 infection, and last for at least 2 months without other explanation, is typically marked by fatigue, shortness of breath, cognitive dysfunction, and other symptoms that result in daytime dysfunction (<https://www.who.int/publications/i/item/-WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1>, 2019). Sleep disturbance has been widely reported, but to our understanding, circadian disruption has rarely been considered as a possible contributor to long COVID symptoms. We recently surveyed 314 adults (164 males, 150 females; mean age  $34.4 \pm 11.07$  years) who had tested positive for SARS-CoV-2 infection at least 3 months ago (approved by University of Michigan Institutional Review Board). Most (92%) had tested positive prior to vaccination. Seventy-nine percent of the sample reported at least 1 new symptom of at least moderate severity (rated  $\geq 5$  on a 10-point scale), that could not be explained by a current health condition, and we categorized them as a “long COVID” group. Notably, the majority of the long COVID group reported 2 or more such symptoms (88%). People with long COVID were more likely to have been hospitalized (55% vs 29%, Chi-square  $p = 0.002$ ), but were not more likely to have received mechanical ventilation ( $p > 0.40$ ). The most common new symptoms in the long COVID group were fatigue (81%), poor concentration (72%) and poor memory (69%). Compared to those without long COVID, participants in the long COVID group reported significantly greater difficulty falling asleep at their desired bedtime (Wilcoxon signed-rank sum tests  $p < 0.001$ ) and waking up at their desired wake time ( $p < 0.001$ ) and were more likely to report that this difficulty had significantly worsened since COVID infection ( $p < 0.0001$ ). This difficulty in falling asleep and waking up at a desired time

is characteristic of a circadian rhythm disorder known as delayed sleep-wake phase disorder (The International Classification of Sleep, 2014). The delay in sleep-wake timing after infection suggest an association between long COVID symptoms and possible circadian-related sleep difficulties, and supports McCarthy’s suggestion that circadian disruption be considered in the treatment approaches for long COVID.

### Declaration of competing interest

Dr. Burgess serves on the scientific advisory board for Natrol, LLC, and Moving Mindz, Pty Ltd, and is a consultant for F. Hoffmann-La Roche Ltd. Dr. Goldstein is the part inventor of a circadian rhythm mobile application licensed to Arcascope, LLC, on the medical advisory boards of Huxley Medical, Inc. and eviCore, and receives royalties from UpToDate. All other authors report no relevant financial or non-financial disclosures.

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<https://doi.org/10.1016/j.bbih.2022.100476>

Received 20 May 2022; Received in revised form 26 May 2022; Accepted 30 May 2022

Available online 31 May 2022

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