

Physical and cognitive stressors exacerbate symptoms in long COVID: more evidence triggering new research and therapeutic needs

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Post-exertional malaise is not a new symptom, but the incidence has increased dramatically in recent years. A well-known symptom of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, post-exertional malaise occurs when exercise elicits profound, lasting fatigue in affected individuals. Now, we are seeing troves of individuals with post-exertional symptoms, an unfortunate and lasting reminder of the impact of the COVID pandemic. The symptoms of long COVID, including post-exertional malaise, fluctuate and vary markedly between individuals. These symptoms have not previously been systematically measured, limiting clinicians' ability to diagnose diseases characterized by post-exertional malaise, and impacting patients' opportunity to receive care or research interventions.

That has changed now, thanks to a paper published in *The Lancet Regional Health—Europe* by Greenwood and colleagues who systematically characterized timing, severity, and nature of long COVID symptom fluctuations in response to effortful physical, social and cognitive activities, using Ecological Momentary Assessments.¹ They recorded activity, effort, and severity of 8 core symptoms (fatigue, pain or discomfort, dizziness, palpitations, cognitive dysfunction, anxiety and depression) every 3 h for up to 24 days in a cohort of 376 participants with long COVID, making this study the largest and most rigorous to characterize post-exertional symptoms in long COVID. Importantly, the authors demonstrated that not only physical efforts, but also cognitive, social and self-care activities all can trigger increased severity across every symptom. In particular, fatigue severity scores increased by 1.8/10 (95% CI: 1.6–1.9) following the highest physical exertions and by 1.5 (1.4–1.7) following cognitive efforts. For the most part, symptoms escalated shortly after

exertion (usually by 30 min), however, in some cases, symptoms could escalate days after the activity. And not unexpectedly, the greater the effort, the worse the symptom exacerbation.

This study has important implications. First, it validates the fluctuating nature of the symptoms seen in long COVID. People with long COVID, similar to those with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, suffer stigma due to the under recognition of their conditions from both healthcare professionals and the society, as their symptoms are frequently labeled as “functional”.^{2,3} While many COVID symptoms like fatigue are considered non-specific, Greenwood's study reinforces the concept that the increase/worsening of fatigue, and other symptoms, after even minor physical or cognitive efforts, is the key diagnostic clue to suspect long COVID, therefore supporting clinicians' ability to recognize and appropriately refer patients. Of note, these fluctuations of symptoms after minor efforts are also reported in children and adolescents.⁴

Secondly, Greenwood's study bears strong implications from a research perspective. Most of the long COVID studies are based on surveys capturing symptoms reported in days prior to survey administration,⁵ when individuals may have been self-regulating stimuli to minimize symptoms. As a result, most studies report no or only minor differences in persisting symptoms between long COVID patients and controls, thus fueling the erroneous concept that long COVID may be extremely rare. Greenwood's study demonstrates that studies need to take into account symptoms fluctuations and potential triggers. This raises the question: should outcomes in long COVID studies be measured at rest/baseline or after cognitive or physical exertion? Important to the success of Greenwood's study, the group benefited from input from people affected by long COVID; future studies should also elicit patient input to optimize feasibility and capture meaningful endpoints. Additionally, the observation that cognitive efforts may worsen physical and neuropsychiatric symptoms bolsters concern that the central nervous system is directly impacted by long COVID pathobiology.⁶

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The findings from Greenwood and colleagues have strong implications for daily lives of people with long COVID as well. To avoid isolation, loss of employment, and social and educational setbacks, we advocate for patients to adapt timelines and schedules, although these recommendations can be met with skepticism and resistance by employers and schools. This study provides strong evidence that any kind of efforts may trigger clinical worsening to patients with long COVID,¹ supporting our requests for adapted schedules. In fact, Greenwood and colleagues mention that their results are consistent with current recommendations.⁷

Research is urgently needed to define physical conditioning and limitations around long COVID, and ultimately to find effective therapeutic strategies. Avoidance of activities and daytime resting periods hold people back from fully engaging in things that they previously enjoyed, consequentially shifting career and educational goals with substantial long-term implications. With millions of people affected by long COVID, and evidence of thromboinflammation, immune dysregulation, T-cell infiltration, autoantibodies, mitochondrial dysfunction, viral persistence,^{8,9} well designed, ambitious interventional trials are needed now. Otherwise, patients with long COVID will continue to suffer in silence against skepticism and hold back from mental and physical exertion.

Contributors

DB and LMY both conceptualized, drafted and approved the final version of the manuscript.

Declaration of interests

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