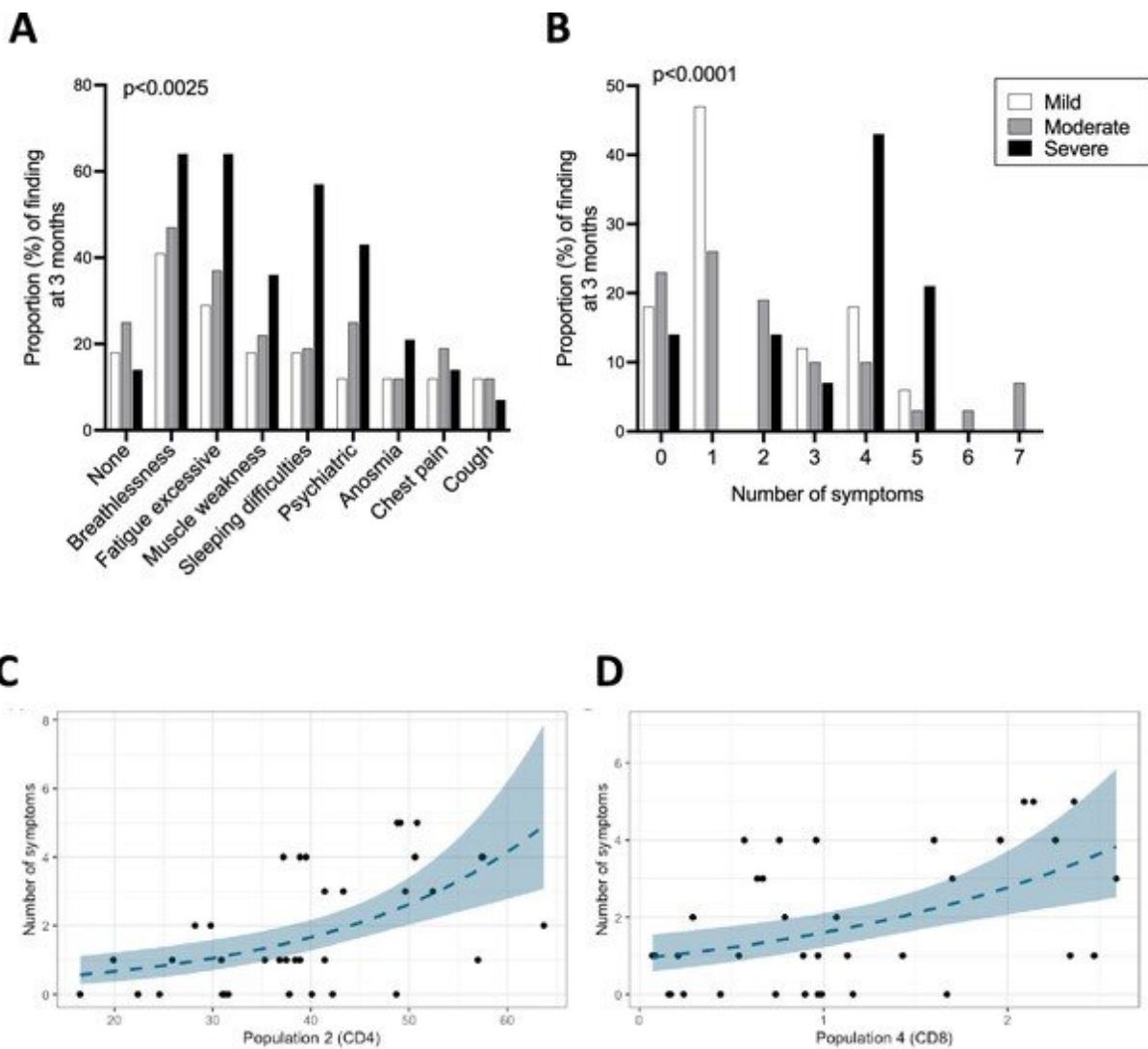


# Long COVID not caused by COVID-19 immune inflammatory response, new research finds

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Ongoing symptoms at three months and associations with immune profiles. (A,

**B)** The percentage of patients with mild (N=17), moderate (N=32), and severe (N=14) coronavirus disease-19 (COVID-19) who reported the indicated symptom (**A**) or number of symptoms (**B**) at three months are indicated with white, grey, and black bars, respectively. Statistics were calculated using a Chi-square test. (**C, D**) Graphs depicting the association between number of symptoms and uniform manifold approximation and projection (UMAP) T-cells clusters in Poisson models, specifically CD4<sup>+</sup> T-cell cluster 2 (**C**) and CD8<sup>+</sup> T-cell cluster 4 (**D**). Credit: *eLife* (2023). DOI: 10.7554/eLife.85009

Long COVID, which affects nearly two-million people in the UK, is not caused by an immune inflammatory reaction to COVID-19, University of Bristol-led research finds. Emerging data demonstrates that immune activation may persist for months after COVID-19.

In this new study, published in *eLife*, researchers wanted to find out whether persistent immune activation and ongoing inflammation response could be the underlying cause of long COVID.

To investigate this, the Bristol team collected and analyzed immune responses in blood samples from 63 patients hospitalized with mild, moderate or severe COVID-19 at the start of the pandemic and before vaccines were available.

The team then tested patients' immune responses at three months and again at eight and 12 months post hospital admission. Of these patients, 79% (82%, 75%, and 86% of mild, moderate, and severe patients, respectively) reported at least one ongoing symptom with breathlessness and excessive fatigue being the most common.

Dr. Laura Rivino, Senior Lecturer in Bristol's School of Cellular and Molecular Medicine and the study's lead author, explained, "Long COVID occurs in one out of 10 COVID-19 cases, but we still don't

understand what causes it. Several theories proposed include whether it might be triggered by an inflammatory immune response towards the virus that is still persisting in our body, sending our immune system into overdrive or the reactivation of latent viruses such as human cytomegalovirus (CMV) and Epstein Barr virus (EBV)."

The team found patients' immune responses at three months with [severe symptoms](#) displayed significant dysfunction in their T-cell profiles indicating that inflammation may persist for months even after they have recovered from the virus. Reassuringly, results showed that even in severe cases inflammation in these patients resolved in time. At 12 months, both the immune profiles and inflammatory levels of patients with severe disease were similar to those of mild and moderate patients.

Patients with severe COVID-19 were found to display a higher number of long COVID symptoms compared to mild and moderate patients. However, further analysis by the team revealed no direct association between long COVID symptoms and immune inflammatory responses, for the markers that were measured, in any of the patients after adjusting for age, sex and disease severity.

Importantly, there was no rapid increase in [immune cells](#) targeting SARS-CoV-2 at three months, but T-cells targeting the persistent and dormant Cytomegalovirus (CMV)—a common virus that is usually harmless but can stay in your body for life once infected with it— did show an increase at low levels.

This indicates that the prolonged T-cell activation observed at three months in severe patients may not be driven by SARS-CoV-2 but instead may be "bystander driven" i.e. driven by cytokines.

Dr. Rivino added, "Our findings suggest that prolonged immune activation and long COVID may correlate independently with severe

COVID-19. Larger studies should be conducted looking at both a larger number of patients, including if possible vaccinated and non-vaccinated COVID-19 patients, and measuring a larger range of markers and cytokines.

"Understanding whether inflammation and [immune activation](#) associate with long COVID would allow us to understand whether targeting these factors may be a useful therapy for this debilitating condition."

**More information:** Marianna Santopaolo et al, Prolonged T-cell activation and long COVID symptoms independently associate with severe COVID-19 at 3 months, *eLife* (2023). [DOI: 10.7554/eLife.85009](https://doi.org/10.7554/eLife.85009)

Provided by University of Bristol

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