

# Long COVID includes breathing and reproductive problems and has a range of risk factors

A large cohort of non-hospitalized adults with confirmed SARS-CoV-2 infection and matched controls were studied to investigate the symptoms of long COVID. SARS-CoV-2 infection was associated with 62 symptoms (three clusters) that persisted beyond 12 weeks, and with a range of risk factors.

## This is a summary of:

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## The problem

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, the cause of coronavirus disease 2019 (COVID-19), is frequently associated with a wide range of long-term symptoms, referred to as 'post-COVID-19 condition' or 'long COVID'. Long COVID is now estimated to affect almost 3% of the UK population<sup>1</sup>. It is currently unclear which symptoms can be specifically attributed to the long-term effects of COVID-19. Previous studies have described symptoms reported by individuals with a history of COVID-19<sup>2</sup>. However, most studies reported on a limited number of symptoms, did not include a comparable control group or were undertaken in hospitalized cohorts that may not be generalizable to patients managed in the community. It is also unclear how symptoms associated with long COVID cluster together, and whether the condition can be classified into distinct symptom-based phenotypes. Finally, there is a need to identify predisposing risk factors for persistent symptoms after SARS-CoV-2 infection.

## The observation

We undertook a large retrospective cohort study using data from general practices in England that contribute to the Clinical Practice Research Datalink Aurum database. We included 486,149 adults with confirmed SARS-CoV-2 infection and statistically matched them to 1,944,580 individuals with no previous evidence of infection on a comprehensive range of factors, including demographic characteristics, clinical risk factors (such as smoking), comorbidities and previous symptom reporting. We used Cox proportional hazards models to estimate the association between SARS-CoV-2 infection and the reporting of a comprehensive array of 115 symptoms to primary care at least 12 weeks from the date of infection, while accounting for demographic and clinical confounding factors. Among individuals with confirmed SARS-CoV-2 infection, we also assessed the associations between various risk factors and long COVID defined as reporting persistent symptoms as included in the WHO (World Health Organization) case definition at least 12 weeks from the onset of COVID-19<sup>3</sup>. Finally, using latent class analysis (a statistical clustering method), we aimed to identify symptom-based long COVID phenotypes.

We found that 62 symptoms were significantly more likely to be reported in patients with confirmed SARS-CoV-2 infection than in the comparator group of patients with no documented evidence of infection.

Persistent symptoms with the largest associations with confirmed SARS-CoV-2 infection were anosmia (loss of sense of smell), hair loss, sneezing, ejaculation difficulty, reduced libido, shortness of breath, fatigue, pleuritic chest pain, hoarse voice and fever (Fig. 1). Among individuals with confirmed SARS-CoV-2 infection, the risk of reporting persistent symptoms increased with decreasing age, female sex, belonging to an ethnic minority group, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities, such as chronic obstructive pulmonary disease. We identified three symptom clusters, which were characterized as a broad spectrum of general symptoms, symptoms pertaining to mental health and cognitive problems, and respiratory symptoms.

## The implications

Previous infection with SARS-CoV-2 in non-hospitalized adults was independently associated with the presentation of a wide range of persistent symptoms to primary care services, even after accounting for other explanatory factors, such as pre-existing comorbidities. Thus, primary care services need tools to comprehensively capture the patient experience of long COVID and adequately assess the breadth of symptoms. Certain population groups, such as women, are at increased risk of developing long COVID, which requires consideration when stratifying risk to support clinical management. There are at least three main clusters of long COVID symptoms presenting to primary care, which may require different treatment approaches.

Our analysis relied on coded data in primary care records, which are unlikely to fully capture the symptoms experienced by individuals with long COVID. Thus, we were unable to estimate the absolute prevalence of these symptoms and could only estimate the relative differences in symptom reporting between individuals with confirmed SARS-CoV-2 infection and matched controls. We were also unable to evaluate the effect of SARS-CoV-2 vaccinations on reporting of persistent symptoms, owing to the limited follow-up of vaccinated individuals.

Further research is needed to obtain rich patient-reported data on symptom burden associated with long COVID, as well as effects on quality of life and work capability. There is an ongoing need to study the natural history of these symptoms over time in population-representative cohorts and matched control population.

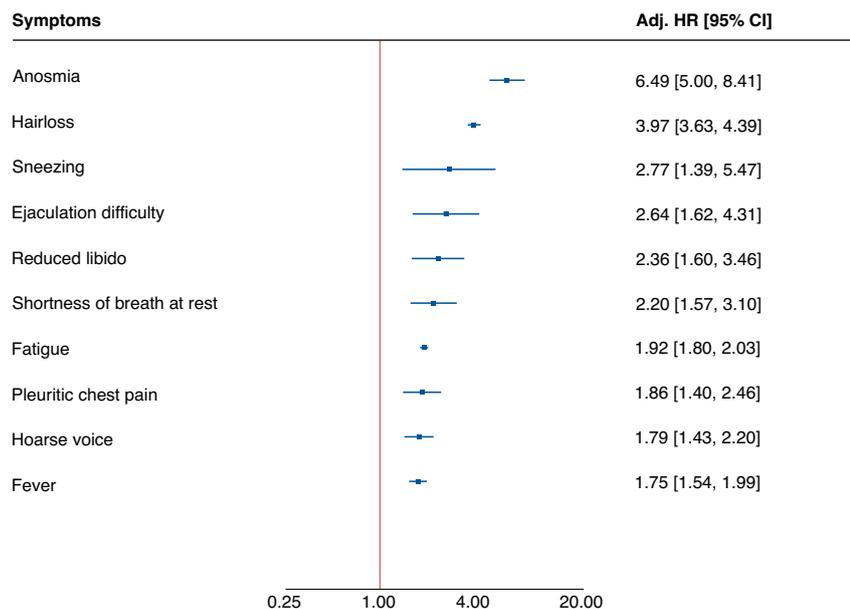
**Shamil Haroon and Anuradha Subramanian, The University of Birmingham, Birmingham, UK.**

## EXPERT OPINION

**||** The paper shows the value of using existing, large datasets from primary care in analyzing new disease entities. Although such data cannot provide true prevalence of symptoms, they can identify unexpected symptoms of

a new disease. A limitation is that patients with COVID-19 may be more likely to mention incidental symptoms of unrelated causes to their doctors than patients without this new disease.” **Nina Langeland, University of Bergen, Bergen, Norway.**

## FIGURE



**Fig. 1 | Persistent symptoms with the largest associations with confirmed SARS-CoV-2 infection.** Adjusted hazard ratios (Adj. HR) are reported. Hazard ratios are adjusted for age, sex, body mass index, ethnicity, smoking status, deprivation status and symptom of interest at baseline. CI, confidence interval. Cohort of patients with SARS-CoV-2 infection: 384,137; comparator cohort: 1,501,689. © 2022, Subramanian, A. et al., CC BY 4.0.

## BEHIND THE PAPER

We had previously undertaken extensive work to understand the symptom burden experienced by adults with long COVID as part of the Therapies for Long COVID (TLC) study<sup>4</sup>. Such work included a systematic review of long COVID symptoms and complications<sup>4</sup>, interviews with individuals with long COVID and surveys of clinicians with expertise in the management of long COVID. These studies culminated in the development of a draft questionnaire

of patient-reported outcome measures assessing the symptom burden of long COVID (the Symptom Burden Questionnaire for Long COVID), which was validated in a field test of 274 adults with long COVID<sup>5</sup>. We used this questionnaire to determine the list of symptoms we evaluated in the current study. A team of clinicians developed code lists for these symptoms, enabling the data to be extracted for this detailed analysis. **S.H. and A.S.**

## REFERENCES

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## FROM THE EDITOR

**||** The long-term consequences of post-acute COVID-19 are poorly understood, yet long COVID is poised to be a major public health challenge after the SARS-CoV-2 pandemic. This study provides a comprehensive analysis of symptoms and risk factors associated with long COVID presenting in primary care. These data have the potential to further our understanding of this heterogeneous condition for improved prevention and clinical management strategies.” **Editorial Team, Nature Medicine**