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Briefing Paper

Long COVID

An update on research, management and other developments

Enquiry No. 2022/767

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Abstract

This briefing paper provides an update to a previous paper provided in respect of long COVID (Enquiry No. 2022/26). It provides details of the management of long COVID at national level, as well as presenting research that is indicative of the nature of the emerging scientific investigation being undertaken in respect of long COVID.

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Contents

Introduction 2
Background 2
Management of long COVID at national level 2
An Interim Model of Care 3
Research and data 5
International research on long COVID 8
Context/Limitations 8
Cause 8
Prevalence 9
Omicron and prevalence of long COVID 14
Vaccination – protective effects against long COVID 15
Emerging concerns/issues in respect of long COVID 18
More commonly reported in women 18
Reinfection is potentially a long COVID risk 19
Increased focus of neurological features 20
Impacts of long COVID on the labour force 22
Estimating the 'burden of disease' associated with long COVID 23
Future developments 26
Methodological concerns 27

Introduction

This briefing paper provides an update to a previous paper provided in respect of long COVID requested from the L&RS (Enquiry No. 2022/26). It provides details of management of long COVID at national level, as well as presenting research that is indicative of the nature of the emerging scientific investigation being undertaken in the realm of long COVID.

Background

The most recent summary of evidence published by the HSE National Health Library and Knowledge Service's Evidence Team in respect of long COVID addresses the varying understanding and interpretations as follows:

> *The designation "long COVID" has its origins in social media as COVID-19 survivors shared narratives of persisting symptoms after recovery from the acute phase of illness. Post-COVID conditions are being referred to by a wide range of names, including long COVID, post-acute COVID-19, long-term effects of COVID, post-acute COVID syndrome, chronic COVID, long-haul COVID, late sequelae, and others, as well as the research term "post-acute sequelae of SARS-COV-2 infection (PASC)." Although standardized case definitions are still being developed, in the broadest sense, post-COVID conditions can be considered a lack of return to a usual state of health following acute COVID-19 illness. Post-COVID conditions might also include development of new or recurrent symptoms that occur after the symptoms of acute illness have resolved.*[1]

This summary of evidence further notes that, clinically speaking, the mid- and long-term effects of long COVID remain unclear, with studies published to date having "significant methodologic limitations" (e.g. lack of a control population, selection and reporting bias, lack of standardised assessment protocols). A key point from this summary evidence is that:

> *Research to date is methodologically limited and more research is needed to establish a clear understanding of the mid- and long-term effects of COVID-19.*[2]

Nonetheless, it observes that:

> *However, it is apparent that persistent physical symptoms following acute COVID-19 are common, and typically include fatigue, dyspnea, chest pain, and cough. Patients recovering from COVID-19 may also have additional psychological (anxiety, depression, post-traumatic stress disorder) and cognitive (poor memory and concentration) symptoms, similar to the syndrome experienced by patients recovering from other critical illnesses known as Post-Intensive Care Syndrome (PICS).*[3]

Management of long COVID at national level

According to the HSE, long COVID can be understood as follows:

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[1] What is the latest national and international evidence about the existence of long COVID or post-COVID and its persistence for COVID-19 survivors? - HLI (Health Library Ireland) (hselibrary.ie), 28 April 2022

[2] ibid

[3] ibid

> *COVID-19 is a new disease so information on the disease, its features, incidence and disease course are still emerging. The natural history, clinical course and consequences of COVID-19 are still not completely understood. It is recognised that most people with Covid-19 return to baseline after acute infection, however a proportion will experience persistent and prolonged symptoms. There are many terms used to describe this post-acute sequelae, the most commonly used terms are Post COVID-19 Condition or Long COVID. Common symptoms include fatigue, shortness of breath and cognitive dysfunction which can have a significant impact on everyday functioning. Symptoms may be of new onset, following initial recovery from an acute COVID-19 episode, or may persist from the initial illness. The condition usually presents with clusters of symptoms, often overlapping, which may change over time and can affect any system in the body.*[4]

In respect of incidence of long COVID, Minister Donnelly stated at the end of June that:

> *The number of people that are affected with longer term sequelae after acute COVID-19 remains unknown, but published reports indicate that approximately 10– 20% of COVID-19 patients experience lingering symptoms for weeks to months following acute SARS-CoV-2 infection. Patients with persistent symptoms following COVID-19 infection may be followed up by their GP or in hospital settings as clinically appropriate.*[5]

An Interim Model of Care

At the end of March, Minister Donnelly advised that:

> *My Department, and the HSE, continue to review new evidence, research and data on all aspects of COVID19 including Long COVID, as it emerges, internationally and nationally, to ensure care is in place for all who need it.*[6]

At that point, the Minister noted that the HSE had developed and was implementing an "interim Model of Care" to provide long COVID services nationally, with the initial priority being to establish Post-Acute[7] and Long COVID clinics[8] (which he indicated was underway).[9] In mid-June, Minister Donnelly indicated a similar approach to management of long COVID, updating it as follows:

> *The HSE has developed and is implementing an interim Model of Care to provide Long COVID services nationally. This builds on existing service provision to further develop the necessary services across a number of health care settings including GP, community services and acute hospitals. The first priority is to ensure there are Long COVID and Post-Acute COVID clinics operating within each Hospital Group to ensure a national service. This involves expanding the resources at existing clinics where required and development of new clinics in line with the Model of Care. Anyone concerned about Long COVID is advised to engage with their GP in the first instance.*[10]

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[4] PQ 23742/22 (hse.ie), 24 May 2022

[5] Covid-19 Pandemic – Tuesday, 28 Jun 2022 – Parliamentary Questions (33rd Dáil) – Houses of the Oireachtas

[6] Covid-19 Pandemic – Thursday, 31 Mar 2022 – Parliamentary Questions (33rd Dáil) – Houses of the Oireachtas

[7] Managing patients between 4-12 weeks after initial onset of infection.

[8] Managing patients 12 weeks post onset of infection.

[9] Covid-19 Pandemic – Thursday, 31 Mar 2022 – Parliamentary Questions (33rd Dáil) – Houses of the Oireachtas

[10] Covid-19 Pandemic – Tuesday, 14 Jun 2022 – PQs (33rd Dáil) – Houses of the Oireachtas

Further, he advised that:

> *COVID-19 is a new diseases (sic) and information on it, its features, incidence and course are still emerging. My Department and the HSE, continue to review new evidence, research and data on all aspects of COVID19 including Long COVID, as it emerges to ensure care is in place for all who need it.*[11]

Recently (late June), Minister Donnelly again indicated that the HSE is developing and implementing an interim Model of Care and further advised that:

> *The first priority is to ensure there are Long COVID and Post-Acute COVID clinics operating within each Hospital Group to ensure a national service. This involves expanding the resources at existing clinics where required and development of new clinics in line with the Model of Care.*[12]

Providing further details in respect of the implementation of this Model of Care, he indicated that:

> *A HSE National Implementation Team has been established to lead the implementation of the Model of Care and clinical leads representing the areas of respiratory medicine, infectious diseases, neurology, mental health, allied health professionals, community services and general practice have been appointed. In some incidences, clinics have been established on an interim basis within existing resources until staffing provided through the model of care becomes available. The objective is to provide a full national service to ensure those who need care have access to it.*[13]

According to the HSE, an Interim Model of Care for long COVID was finalised in September 2021, which aims to "provide a national approach to provision of services and supports for patients experiencing prolonged symptoms of Covid-19". This Interim Model recommended the development of 8 Post-Acute Clinics and 6 Long COVID clinics[14], with the distribution of clinics informed on the basis of "access to diagnostics and the availability of specialties such as infectious disease and respiratory services". Regional areas were selected to ensure hospital groups had access to both types of Clinics with a view to "geographical equality" (see Table 1 below).[15]

Table 1 Location of Post-Acute and Long COVID Clinics under Interim Model of Care

Post-Acute Clinics	Long COVID Clinics
Connolly Hospital Blanchardstown	St. James University Hospital
Mater University Hospital	Cork University Hospital
Tallaght University Hospital	University Hospital Galway
St. James University Hospital	University Hospital Limerick
Cork University Hospital	Beaumont University Hospital
University Hospital Galway	St. Vincent's University Hospital
University Hospital Limerick	
Letterkenny University Hospital	

[11] ibid
[12] Covid-19 Pandemic – Tuesday, 28 Jun 2022 – PQs (33rd Dáil) – Houses of the Oireachtas
[13] ibid
[14] PQ 22706/22 (hse.ie), 24 May 2022
[15] PQ 22707/22 (hse.ie), 12 April 2022

Post-Acute Clinics will be led by respiratory consultants, whilst Long COVID clinics will be led by infectious disease consultants.[16] The HSE advises that over 70 new posts will be funded as part of the Interim Model across these sites, with recruitment having commenced.[17] Recruitment will include consultants in the area of infectious diseases, respiratory medicine, neurology, as well as additional multi-disciplinary staff to support the work of these clinics.[18] In a PQ response at the end of May, the HSE noted that, in some incidences, the designated sites are providing clinics on an interim basis whilst recruitment of full staffing as per the Interim Model.[19]

Budget-wise, the overall costing for the Interim Model is calculated as €6.6 million annually, with €2.2 million allocated for 2022.[20]

In a PQ response at the end of May, the HSE further advised of its intention to develop a minimum data set to estimate population need, as well as capture demand and activity levels in respect of Post-Acute and Long COVID Clinics:

> *To further assist in estimating population need for Post-Acute and Long COVID Clinics and resource requirements, the HSE will be endeavouring to capture demand and activity levels of each clinic. The HSE is currently developing a minimum data set to capture this information. This will include the waiting list for each clinic, the number of patients referred to each clinic on a monthly basis and the number of patients who attended each clinic on a monthly basis. Collation of this data will be key to informing current and future service provision and resource requirements.*[21]

Research and data

A number of research projects have been conducted in respect of COVID at a national level[22], with long COVID a feature of some of these. For instance, the HRB-funded follow-up study[23] on COVID set out to determine the baseline characteristics and care outcomes of COVID patients presenting to/attending the Infectious Disease Department at the Mater Hospital.[24] An article published in the *International Journal of Infectious Diseases* reported that one quarter of patients attending the Mater's COVID follow-up clinic met the definition of 'Post Covid-19 Syndrome' one year after initial diagnosis[25], with these patients having a significant reduction in their physical wellbeing, as demonstrated using Health-related Quality of Life Questionnaires. A total of 107 (72%) patients had ongoing symptoms at Timepoint 1 (2-4 months post-COVID), with the most common symptoms being shortness of breath (n = 51 [48%]), fatigue (n = 44 [41%]), and chest pain (n = 16). At Timepoint 2 (7-14 months post-COVID), a quarter of participants had long COVID (n = 24),

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[16] PQ 22706/22 (hse.ie), 24 May 2022
[17] PQ 23742/22 (hse.ie), 24 May 2022
[18] PQ 22834/22 (hse.ie), 16 April 2022
[19] PQ 22706/22 (hse.ie), 24 May 2022
[20] PQ 22834/22 (hse.ie), 16 April 2022
[21] PQ 23742/22 (hse.ie), 24 May 2022
[22] Details of research funded by Health Research Board can be found at: Covid-19 Pandemic – Tuesday, 31 May 2022 – Parliamentary Questions (33rd Dáil) – Houses of the Oireachtas
[23] The study protocol for their study can be found at: Anticipate study protocol: Baseline profile and... | HRB Open Research.
[24] Anticipate study protocol: Baseline profile and... | HRB Open Research, 18 January 2021
[25] Hospitalised and non-hospitalised patients were seen at a dedicated post-COVID clinic at a 2-4-month (Timepoint 1) and 7-14-month follow-up (Timepoint 2). A total of 155 patients were enrolled, 105 (68%) were female aged 43.3 (31-52) years.

with neurological issues including headache, anosmia, tinnitus, numbness, and paraesthesia present in 10 (37.5%) patients, with fatigue and difficulties with concentration also common. Further, of these 24 patients with long COVID, symptoms tended to persist from the time of acute illness.

> *The symptomatic profile of patients with PoCS also changed over time from having predominately SOB and fatigue to fatigue and neurological sequelae, including difficulties concentrating. This highlights the nature of long COVID and that symptomatology is not dominated by single organ dysfunction ... Fatigue was the most consistent symptom across both Timepoints 1 and 2* [26]

Of note also is that this research found that a lower physical composite score and a higher baseline heart rate at clinic review approximately 3 months post COVID helped predict those at risk of long COVID at 1 year. However, there were a number of limitations associated with this research including that the study had a small sample size from a single centre, the small cohort of 155 may not have been representative of all patients after acute infection with COVID-19, and the cohort may have been over-representative of patients with persistent symptoms.[27] Additional publications from this study include one which examined predictors and outcomes for COVID re-admissions[28] and another which investigated psychiatric symptoms and problematic alcohol use among long COVID patients[29].

Earlier this month, Professor Jack Lambert, Consultant in Infectious Diseases at the Mater Hospital and a co-author of the above study, gave evidence to the Joint Committee on Health[30] in respect of long COVID. In terms of prevalence, he noted that:

> *Our studies at one year showed that 30% of people were still not right. I would say that 1% were unable to work, function or get out of bed, so they were unable to return to work. Looking at the number of cases in Ireland, which is approximately 5 million because some people have had the virus two or three times, each time you get Covid, you are at risk of long Covid. If you calculate conservatively that 1% will be disabled by long Covid, that is 1% of 5 million. Looking at people impacted by long Covid, lots of staff tell me that they got mild Covid three months earlier and that their brain is not working right. They cannot remember their PIN or names at work. It has a subtle effect on many people, and that is the 30% I was reporting from the studies that we did at the Mater.* [31]

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[26] Assessing the impact of COVID-19 at 1-year using the SF-12 questionnaire: Data from the Anticipate longitudinal cohort study - International Journal of Infectious Diseases (ijidonline.com), 14 March 2022

[27] ibid

[28] Predictors and Outcomes for COVID-19 Re-Admissions in the Anticipate Cohort – Irish Medical Journal (imj.ie), 25 May 2022

[29] Mental health and alcohol use among patients... | HRB Open Research, 3 March 2022; see also: Long Covid study finds high levels of depression (rte.ie)

[30] The Committee considered the effects of long COVID and the provision of long COVID care in Ireland at its meeting of 6 July 2022. The debate of this meeting is available on the Oireachtas website here, with Professor Lambert's opening statement available here. In addition, various reports of this meeting are available, including: Impact of long Covid on the brain 'underestimated' and not included in HSE treatment plan, warns leading doctor - Independent.ie, Up to 5% of long Covid patients 'disabled' a year on (rte.ie), Hospital consultant says people with Long Covid have been accused of exaggerating illness (thejournal.ie), and One-in-five Long COVID patients suffer anxiety, depression, and PTSD, Oireachtas Committee hears (ucd.ie)

[31] Effects of Long Covid and Provision of Long Covid Care: Engagement with Dr. John Lambert, Joint Committee on Health, 6 July 2022

In terms of the management of long COVID, Professor Lambert advised that:

> *.. the time the HSE's draft long Covid guidelines were drawn up a year ago the "goal posts" had shifted.*
>
> *"The plan focuses on early post Covid-19 follow up with a group of eight pulmonary specialists and a cadre of dieticians and podiatrists with no mention of psychologists.*
>
> *"However, for those of us managing patients in hospital the accumulating evidence at that time was that the lungs were healing, the heart was healing but the brain was not healing."*[32]

Specifically, he noted that a multidisciplinary team is required to manage long COVID and proposed the following:

> *What we propose at the Mater is a centre for neurorehabilitation with national network to support GPs, as there are so many patients throughout the country with long Covid and many of them cannot travel, as they are too ill.*
>
> *This neurorehabilitation centre will focus on 'brain rehabilitation' as patients with long Covid act very much like patients who have experienced 'closed head injuries'.*
>
> *A group of neuro-rehab specialists, neurologists, ID physicians, psychologists/psychiatrists, and neuro physiotherapists need to be the 'primary' team managing these patients, as the central nervous system is the problem with our patients with long Covid.*[33]

Irish research is also investigating the causes of long COVID, with a study[34] from APC Microbiome Ireland (UCC) finding that biomarkers of immune system activation were linked with impaired metabolism in Long COVID patients. Specifically, it found that the levels of multiple biomarkers were altered in serum from patients with Long COVID, even nine months after the initial infection with SARS-CoV-2. The implications of this were described as follows:

> *These differences indicate an ongoing activation of the immune system, which were coupled with differences in molecules generated during metabolism. These differences in metabolism (e.g. decreased serotonin levels) give us some hints at what might be underpinning long term symptoms such as fatigue and brain fog. Overall the study findings identify novel mechanistic and potential diagnostic markers as well as potential therapeutic targets in Long COVID patients.*[35]

Further, according to Professor Liam O' Mahony, a Principal Investigator in APC Microbiome Ireland and a Professor of Immunology at UCC's Dept of Medicine and School of Microbiology:

> *.. this study provides further evidence that SARS-CoV-2 infection can impact immune and metabolic systems for a long time following elimination of the virus. These new findings provide us with definitive targets to be further examined in helping us better understand why some people get Long COVID, and represent a first step in developing potential new targets for diagnosis and therapy.*[36]

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[32] Impact of long Covid on the brain 'underestimated' and not included in HSE treatment plan, warns leading doctor - Independent.ie, 6 July 2022

[33] Prof Jack Lambert: 'Brain fog' the most persistent symptom of long Covid (irishexaminer.com), 7 July 2022

[34] This study was published in *Allergy* and can be found here.

[35] New APC research helps us to better understand Long COVID (sfi.ie)

[36] ibid

International research on long COVID

Context/Limitations

This section provides details of international research on long COVID. This research is indicative of the nature of emerging scientific investigation being undertaken in respect of long COVID, giving a sense of the nature of the research that is currently available, as well pointing to some of the most recently published/newly available data (including research awaiting peer review[37]). It should be noted, however, that research in respect of long COVID remains at an early point and cannot be regarded as 'settled', with a lack of consensus across a range of matters (e.g. cause, prevalence), as well as a lack of methodologically robust and sound research studies and pre-prints[38] presenting early data which have not yet undergone peer review. This is an important context to this paper and much of the research presented here should be read/interpreted in the context of these caveats. Further, the limitations associated with individual studies are not necessarily explicitly referenced – instead, the research presented below should be read within the overall context of the above caveats.

Cause

Researchers are attempting to understand the cause(s) of long COVID. However, this work remains in the exploratory phase. For instance, a recent US National Institutes of Health (NIH) study sought to identify people with symptoms of long COVID, most of whom had recovered from mild to moderate COVID. However, whilst more than half had signs of long COVID, researchers were "unable to pinpoint any underlying cause" of these symptoms in most cases.[39]

One hypothesis is that "the virus is able to find a safe haven in the body from which it can bide its time and potentially re-emerge — a viral reservoir", with researchers finding evidence of SARS-CoV-2 in a number of organs (including the digestive system) months after the infection appears to have cleared from the respiration system. Whilst this remains at the level of a hypothesis, commentators in *Nature* note that:

> *Although there is still a long way to go before the reservoir hypothesis can be confirmed, these data provide compelling new support for the theory.*[40]

Other avenues are also being explored. For instance, a study published in the *Endocrine Journal* reported on research on hormonal trends in patients with long COVID symptoms, with depression and fatigue scores positively correlated with serum levels of cortisol and free thyroxin (FT4), respectively, whilst patients suffering from general fatigue had lower levels of serum growth hormone and higher levels of serum FT4. This led the researches to conclude that hormonal changes seem to be (partially) involved in persistent long COVID symptoms.[41]

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[37] Peer-reviewed journal articles have gone through an evaluation process in which editors and other expert scholars critically assess the quality and scientific merit of the article and its research. For further details on peer review, please see here.

[38] For further details on unreferred preprints, please see here.

[39] Using AI to Advance Understanding of Long COVID Syndrome – NIH Director's Blog, 7 June 2022

[40] Coronapod: 'viral ghosts' support idea that SARS-CoV-2 reservoirs could be behind long COVID (nature.com), 13 May 2022

[41] Hormonal trends in patients suffering from long COVID symptoms (jst.go.jp), 28 April 2022

A feature in *Science* considered three potentials "clues" to the cause(s) of long COVID: miniscule clots, lingering virus, and immune abnormalities. Further, researchers observe that "solo operators are unlikely", with lingering virus potentially attacking the circulatory system, which in turn triggers blood clots or chronic inflammation.[42]

> *.. untangling the complex syndrome, with a still-evolving definition, is a laborious, step-wise process. First, [researchers] must show that a possible contributor—such as minuscule clots, lingering virus, or immune abnormalities—crops up disproportionately in people with Long Covid. Then comes the hard part: proving that each of these traits, alone or in combination, explains why the coronavirus has rendered millions of people shadows of their former selves ..*[43]

Other considerations in respect of studying long COVID have also been posited. For instance, researchers of the Norwegian Mother, Father and Child Cohort Study (MoBa) found clusters of symptoms following infection and suggested that these clusters might be due to different mechanisms, thereby questioning if it is "meaningful' to conceptualise long COVID as a single syndrome.[44]

Prevalence

A range of prevalence figures have been proffered in respect of long COVID, with a range of study types (e.g. international, national, multi-centre, single centre) undertaken in a range of contexts (e.g. pre-/post-vaccination, pre-/post-variants). Earlier this Spring, a meta-analysis and systematic review of the global prevalence of long COVID was published in *The Journal of Infectious Diseases*[45], with an estimated global prevalence of long COVID of 43%. All told, prevalence of long COVID at 1 month was 37%, whilst it was 25% at 2 months and 32% at 3 months. The most common symptoms were fatigue (23%), memory problems (14%), shortness of breath (13%), sleep problems (11%) and join pain (10%). This meta-analysis found a higher proportion of women reporting long COVID than men (49% versus 37% respectively).[46] The authors concluded that:

> *With an estimated 200 million individuals affected, post-COVID-19 condition's impact on population health and the labor force is enormous. It is imperative that those affected are provided proper health, social, and economic protections.*[47]

A large-scale international study used electronic health record (EHR) data[48] from 277 international hospitals[49] representing 414,602 patients with COVID-19, 2.3 million control patients without COVID-19 in the inpatient and outpatient settings, and over 221 million diagnosis codes to

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[42] Clues to long COVID (science.org), 17 June 2022

[43] ibid

[44] Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort - PMC (nih.gov), 25 February 2022

[45] Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review | The Journal of Infectious Diseases, 16 April 2022

[46] Global data reveal half may have long COVID 4 months on | CIDRAP (umn.edu), 18 April 2022

[47] Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review | The Journal of Infectious Diseases, 16 April 2022

[48] This data derived from an international cohort of patients from the healthcare systems participating in the Consortium for Clinical Characterization of COVID-19 by EHR (4CE). Further details can be found at: Members - 4CE (covidclinical.net)

[49] This involved the following geographical distribution: 42 in France, 1 in Germany, 4 in Italy, 1 in Singapore, and 228 in the US.

systematically identify new-onset conditions among patients with COVID during the post-acute period. Compared to inpatient controls, inpatient COVID cases were at significant risk for angina pectoris, heart failure, cognitive dysfunctions, and fatigue. Relative to outpatient controls, outpatient COVID cases were at risk for pulmonary embolism, venous embolism, atrial fibrillation, type 2 diabetes and vitamin D deficiency. Outpatient COVID cases were also at risk for loss of smell and taste, inflammatory neuropathy, and cognitive dysfunction. According to the researchers, this study "systematically identified robust conditions associated with PASC [post-acute sequelae SARS-CoV-2 infection] compared to control groups, underscoring the multifaceted cardiovascular and neurological phenotype profiles of PASC".[50]

> *Our results indicate a possible high burden of long-term sequelae in patients recovering from SARS-CoV-2 infection. We observed a wide spectrum of PASC-related conditions not only in inpatient COVID-19 cases but also in outpatient cases. This supports the emerging evidence that even patients who did not experience severe disease requiring hospitalization during the acute period may experience long-term complications. The similar PASC profiles between both the inpatient and outpatient COVID-19 cohorts suggest common underlying etiologic pathways in the development of PASC.*[51]

There were a range of limitations associated with this research, however, including that:

- among the participating healthcare systems, only two non-U.S. sites could contribute control data; and
- the study could not control for patient-level variables potentially confounding analysis through the introduction of bias (e.g. comorbidities, medications, and other societal and environmental factors).[52]

To that end, the researchers cautioned against "strong inferences from this study" on the basis that it can identify association but not mechanism nor assess causality. Further, they asserted that additional studies accounting for viral variants and vaccination status are needed to study trends in long COVID incidence over different waves of the pandemic.[53]

At a national level, the UK Office for National Statistics estimates the prevalence of self-reported long COVID[54] and associated activity limitation using UK Coronavirus (COVID-19) Infection Survey data[55]. The first iteration of the series was released in April 2021, with the current estimates released on 7 July 2022 (next release date: 4 August 2022). An estimated 2 million people living in private households in the UK (3% of the population) were experiencing self-reported long COVID as of 4 June 2022.[56] Figure 1 overleaf presents the prevalence of self-reported long COVID in UK households over four-week periods, beginning with a four-week period ending 2 May 2021 and continuing to a four-week period ending 4 June 2022.

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[50] International electronic health record-derived post-acute sequelae profiles of COVID-19 patients | npj Digital Medicine (nature.com), 29 June 2022

[51] ibid

[52] ibid

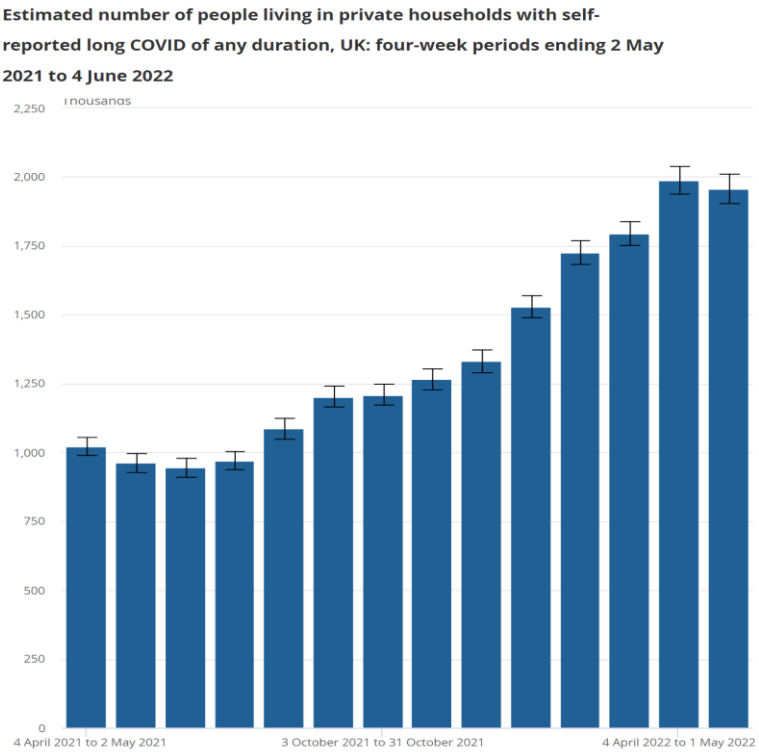
[53] ibid

[54] Characterised as symptoms continuing for more than 4 weeks after suspected COVID infection.

[55] Data based on 247,557 responses to UK Coronavirus (COVID-19) Infection Survey collected over the four-week period ending 4 June 2022, weighted to represent people aged two years and over living in private households in the UK.

[56] Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics (ons.gov.uk), 7 July 2022

Figure 1 Prevalence of self-reported long COVID, UK, as of 4 June 2022



Reproduced from UK Office for National Statistics[57]

Long COVID symptoms adversely affected the day-to-day activities of 1.4 million people (72% of those with self-reported long COVID) in the UK as of 4 June 2022, with 409,000 (21%) reporting that their ability to undertake their day-to-day activities had been "limited a lot". Fatigue was the most common symptom reported (56% of those with self-reported long COVID), followed by shortness of breath (31%), loss of smell (22%), and muscle ache (21%). As a proportion of the UK population, the prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, people living in more deprived areas, those working in social care, health care, or teaching and education, and those with another activity-limiting health condition or disability. Of people with self-reported long COVID, 570,000 (29%) first had (or suspected they had) COVID before Alpha became the main variant; this figure was 237,000 (12%) in the Alpha period, 394,000 (20%) in the Delta period, and 642,000 (33%) in the Omicron period.[58]

Data from the US Household Pulse Survey found that 14.7% of all US adults reported ever experiencing long COVID, with 34.3% of US adults who ever had COVID reporting this. Further, 7.6% of all US adults and 17.7% of those who ever had COVID reported experiencing long COVID symptoms at the time of data collection. Of note is that this survey found that older adults were less likely to report having long COVID than younger adults, with nearly three times as many adults aged 50-59 currently having long COVID as compared to those aged 80+.[59]

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[57] ibid *[interactive chart available at link]*

[58] Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics (ons.gov.uk), 7 July 2022

[59] Long COVID - Household Pulse Survey - COVID-19 (cdc.gov); Nearly One in Five American Adults Who Have Had COVID-19 Still Have "Long COVID" (cdc.gov)

Table 2 Experience of Long COVID, US data, 29 June 2022 - 11 July 2022

Age range	Ever experienced long COVID, % of all adults	Ever experienced long COVID, % of adults who ever had COVID	Currently experiencing long COVID, % of all adults	Currently experiencing long COVID, % of adults who ever had COVID
18-29 years	15.5%	30.9%	7.5%	15.1%
30-39 years	17.3%	33.7%	8.2%	16.0%
40-49 years	17.6%	36.5%	8.3%	17.2%
50-59 years	15.4%	35.6%	8.8%	20.2%
60-69 years	11.5%	33.9%	6.4%	19.0%
70-79 years	10.3%	37.7%	6.4%	23.3%
80+ years	7.3%	28.8%	4.0%	15.6%

Source of data: US Census Bureau, Household Pulse Survey 2022[60]

Beyond large-scale international and national studies such as those referenced above, a range of smaller scale studies have also been conducted, such as those referenced below.

- A recent study published in the *International Journal of Infectious Diseases* reported on the prevalence of long COVID in a population-wide study of Faroese individuals with a confirmed COVID diagnosis[61]. In this national cohort[62], 39% of people reported long COVID a medium of 168 days after the acute phase of COVID and 8% reported severe persistent symptoms up to 8 months after infection. Fatigue and taste/smell dysfunction were the most prevalent long COVID symptoms.[63]
- A longitudinal study of COVID sequelae recently reported its baseline findings. Symptoms consistent with long COVID were reported by 55% of the COVID-19 cohort[64] (n=189) and 13% of control participants[65] (n=120) on enrolment to the study. Increased risk for long COVID was noted in women and those with a history of anxiety disorder. The researchers concluded that:

  > *A high burden of persistent symptoms was observed in persons after COVID-19. Extensive diagnostic evaluation revealed no specific cause of reported symptoms in most cases.*[66] *Antibody levels were highly variable after COVID-19.*[67]

[60] Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)

[61] All Faroese individuals with confirmed COVID-19 diagnosis from August to December 2020 were invited to participate in this study (n = 297), with a total of 226 individuals participating at baseline (76% participation rate).

[62] One limitation of this study was that there was no control group for comparative purposes, meaning that the potential effects of society measures (e.g. lockdowns) could not be considered.

[63] Prevalence of long COVID in a national cohort: longitudinal measures from disease onset until 8 months' follow-up - ScienceDirect, 6 July 2022

[64] This group comprised of self-referred adults with laboratory-documented SARS-CoV-2 infection who were at least 6 weeks from symptom onset. One cited limitation of this research was that prevalence was likely overestimated in the recruited cohort because individuals experiencing long COVID symptoms may be been more motivated to enrol in the study.

[65] This control group comprised persons with no history of COVID-19 or serologic evidence of SARS-CoV-2 infection.

[66] For instance, the study reported that: "Abnormal findings on physical examination and diagnostic testing were uncommon. Neutralizing antibody levels to spike protein were negative in 27% of the unvaccinated COVID-19 cohort and none of the vaccinated COVID-19 cohort. Exploratory studies found no evidence of persistent viral infection, autoimmunity, or abnormal immune activation in participants with PASC."

[67] A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings - PubMed (nih.gov), May 2022

However, the researchers noted that:

> *Despite the largely normal findings on objective testing, the presence of PASC had a significant effect on self-reported physical and mental health. Participants with PASC reported lower quality of life than either participants with COVID-19 without PASC or control participants, as measured by the mental and physical health components of the SF-36 Health Survey. Self-reported current anxiety, as measured by the GAD-2 questionnaire, was significantly associated with PASC. This finding suggests that reported anxiety after COVID-19 may reflect the uncertainty and worry felt by those experiencing persistent unexplained symptoms.*[68]

- A recently published, large-scale US study examined the symptom trajectory of long COVID in a representative sample of Americans[69] in the first year of the pandemic. This research found that approximately 23% of the sample experienced new-onset symptoms during infection which lasted for more than 12 weeks (i.e. can be considered as having long COVID), with the most common symptoms being headache (22%), runny or stuffy nose (19%), abdominal discomfort (18%), fatigue (17%), and diarrhoea (13%). Whilst long COVID was more likely among obese individuals, there was a lack of evidence relating risk to age, gender, race/ethnicity, education, current smoking status, or comorbid chronic conditions. However, long COVID was more likely in those who experienced hair loss, headache, and sore throat during infection. There were a number of limitations associated with this research, including the lack of new variants in the disease profile of those with COVID infections.[70]
- Long COVID risk factors were assessed across 10 UK longitudinal studies and electronic health records (EHR)[71], with proportions of presumed COVID-19 cases in longitudinal studies reporting any symptoms for 12+ weeks ranging from 7.8% and 17% (with 1.2 to 4.8% reporting debilitating symptoms). Factors associated with prolonged symptoms in both longitudinal study and EHR data, included increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/obesity, and asthma.[72] Thus, the researchers asserted that:

> *Although causal inferences cannot be drawn from these data, our findings justify further investigations into the role of sex difference, age related change, and/or immunity and respiratory health in development of long COVID. Older working individuals, with high levels of comorbidity, may particularly require support.*[73]

- A US study[74] examined post–COVID conditions among adult COVID survivors across two age cohorts (18-64 years and ≥65 Years). Among patients aged ≥65 years, the risks were higher among case-

[68] ibid

[69] This sample was drawn from the Understanding America Study COVID-19 Survey, which surveyed around 8,000 respondents bi-weekly from March 2020 to March 2021. The final sample in this study included 308 infected individuals who were interviewed one month before, around the time of, and 12 weeks after infection.

[70] Long COVID and symptom trajectory in a representative sample of Americans in the first year of the pandemic | Scientific Reports (nature.com), 8 July 2022

[71] Analysis of survey data from 6,907 individuals with self-reported COVID-19 from 10 UK longitudinal study samples and 1.1 million individuals with COVID-19 diagnostic codes in EHR collected by spring 2021.

[72] Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records | Nature Communications, 28 June 2022

[73] ibid

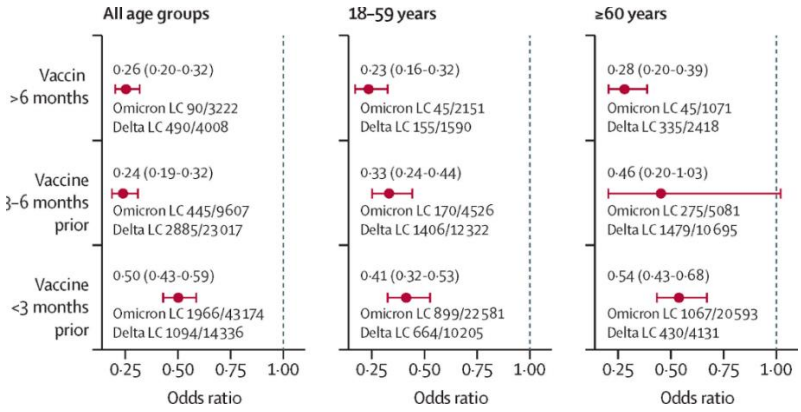
[74] EHR data from March 2020–November 2021, for persons in the United States aged ≥18 years were used to assess the incidence of 26 conditions often attributable to post-COVID among patients who had received

patients than among controls for all 26 incident conditions, with risk ratios (RRs) ranging from 1.2 (substance-related disorder) to 2.2 (acute pulmonary embolism). Whilst among patients aged 18–64 years, the risks were higher among case-patients than among controls for 22 incident conditions, with RRs ranging from 1.1 (anxiety) to 2.1 (acute pulmonary embolism); no significant difference was observed for cerebrovascular disease, or mental health conditions, such as mood disorders, other mental conditions, and substance-related disorders. According to the researchers, these odds translate into one in five COVID-19 survivors aged 18–64 years, and one in four survivors aged ≥65 years experiencing a condition that might be attributable to previous COVID infection.[75]

Omicron and prevalence of long COVID

Researchers from King's College London reported in *The Lancet* on what they characterised as the first peer-reviewed study on the long COVID risks associated with Omicron. This study found that the odds of experiencing long COVID were between 20-50% less during the Omicron period as compared to the Delta period, depending on age and time since vaccination. In sum, 4.5% of Omicron cases (56,003) experienced long COVID as compared to 10.8% of Delta cases (41,361). Overall, researchers reported a reduction in odds of long COVID with Omicron as compared to Delta of 0.24–0.50 depending on age and time since vaccination[76].[77] Omicron cases were less likely to experience long COVID for all vaccine timings, with odds ratios ranging from 0.24 (0.20–0.32) for those with vaccination more than 6 months prior to 0.50 (0.43–0.59) for those who received their vaccine less than 3 months prior (see Figure 2 below for stratification by age group). However, given the anticipated peaks of Omicron, the researchers concluded that future numbers of people with long COVID "will inevitably rise".[78]

Figure 2 Odds ratio of long COVID (LC) adjusted by age and vaccination status



Source: The Lancet[79]

a previous COVID-19 diagnosis (case-patients) compared with the incidence among matched patients without evidence of COVID-19 in the EHR (control patients).

[75] Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021 - PMC (nih.gov), 27 May 2022

[76] The researchers noted that there was insufficient data available to estimate the odds of long COVID in unvaccinated people, nor did they estimate effects in children.

[77] Omicron Half as Likely as Delta to Lead to Long COVID: Study | The Scientist Magazine® (the-scientist.com), 17 June 2022

[78] Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2 - The Lancet (18 June 2022)

[79] ibid

It should be noted that this study was based on self-reported data[80], with no direct testing of infectious variations (instead these were assumed from national data) and no objective measurement of illness duration. Further, the researchers cautioned that these samples were not fully generalisable to the UK population as a whole due to sex and socioeconomic biases. Finally, the researchers highlighted that the period of assessment of Omicron cases was "slightly shorter" than for Delta in order to "enable swift reporting".[81] Further, this study does not take account of new Omicron subvariants (BA.4 and BA.5), which carry their own unique mutations (e.g. changes in the viral spike protein that potentially alter its ability to latch onto cells and evade some immune responses).[82] Commentary in *The BMJ* by Kevin McConway, Emeritus Professor of Applied Statistics at the Open University assessed the study as follows:

> *These are observational data, so there are inevitable questions about cause and effect. The results also come from self reported symptoms in a self selected group of people who submitted data using the Zoe app, who aren't particularly typical of the UK population as a whole."*[83]

Further, he asserted that:

> *The potential lower risk of long covid in people infected during omicron is entirely trumped by the much bigger number of new infections during the omicron wave."*[84]

Vaccination – protective effects against long COVID

Earlier this year, a rapid evidence briefing (based on a small number of studies conducted up to 12 January 2022[85]) from the UK Health Security Agency on the effectiveness of vaccination against long COVID reported that there was evidence that vaccinated people subsequently infected with COVID-19 were less likely to report symptoms of long COVID than unvaccinated people, in the short term (4 weeks after infection), medium term (12 to 20 weeks after infection) and long term (6 months after infection).[86]

However, a recent article in *Nature* reported on a large-scale study that found that vaccines "offer less protection against lingering symptoms than expected", reducing the likelihood of long COVID by approximately 15%. Further, this study found no difference in the type or severity of symptoms (e.g. brain fog and fatigue) between those who had been vaccinated and those who had not. All told, with an overall protection of the vaccine from long COVID of only approximately 15% as found in the *Nature* study referenced above, the implications of this were described as follows:

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[80] This study is based on self-reported data derived from the UK's COVID Symptom Study app. For further information, see: ZOE Health Study (joinzoe.com)

[81] Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2 - The Lancet (18 June 2022)

[82] What Omicron's BA.4 and BA.5 variants mean for the pandemic (nature.com), 23 June 2022

[83] Covid-19: Long covid risk is lower with omicron than delta, researchers find | The BMJ, 17 June 2022

[84] ibid

[85] Fifteen studies were identified that reported on the effectiveness of vaccination against long COVID (search up to 12 January 2022): 7 studies examined whether vaccination before infection reduced the symptoms or incidence of long COVID, 7 studies examined whether vaccination in people with long COVID reduced or cleared the symptoms of long COVID, and 1 study examined both. Further information in respect of this can also be at: UKHSA review shows vaccinated less likely to have long COVID than unvaccinated (www.gov.uk)

[86] UK Health Security Agency The effectiveness of vaccination against long COVID Feb 2022 (icpcovid.com)

> *.. the burden of Long COVID is likely to be substantial even in fully vaccinated populations. Therefore, vaccination alone may not be enough to mitigate the long-term health consequences of SARS-CoV-2 infection.*[87]

These findings contrast with previous, smaller-scale studies[88], which reported "much higher protection rates", as well as a large UK study (published in *The Lancet* in January) that found two doses of a COVID vaccine halved the risk of long COVID. Further, a US study of EHRs found that the protective effects of vaccination against some post-acute sequelae appears to affect primarily those <60 years-old (described as large and robust effects), whilst in the ≥60 year-old group, protective effects were described as smaller and not statistically robust.[89] Of note, in the context of these conflicting/contradictory findings, is that a pre-print (non-peer reviewed) of a systematic review and meta-analysis of the impact of vaccination on long COVID noted the following in respect of the methodological soundness of existing data:

> *Current studies suggest that COVID-19 vaccinations may have protective and therapeutic effects on long COVID. However, more robust comparative observational studies and trials are urgently needed to clearly determine effectiveness of vaccines in prevention and treatment of long COVID.*[90]

Concerning the protective nature of vaccination, commentary in *Nature* highlighted that one methodological limitation in respect of existing research studies centres on the limited/lack of data included from people infected during the Omicron waves.[91]

Recent data from the UK Office of National Statistics provides some insights on the risk of long COVID in the context of vaccination status and variants[92]. Relevant findings from this statistical bulletin are presented in the text box below/overleaf, with relevant figures overleaf.[93]

Triple-vaccinated adults – similar risk for Omicron variants vs. Delta

- Of triple-vaccinated adults, 4.5%, 4.2% and 5.0% self-reported having long COVID 12 to 16 weeks after a first laboratory-confirmed coronavirus (COVID-19) infection compatible with the Omicron BA.1, Omicron BA.2 or Delta variants, respectively, using data to 27 May 2022.
- There was no statistical evidence of differences in the odds of reporting long COVID between infections compatible with the Omicron BA.1, Omicron BA.2 and Delta variants among adults who were triple vaccinated when infected; this was after statistically adjusting for socio-demographic characteristics for all comparisons, and for time since last vaccine dose when comparing Omicron BA.1 and BA.2.

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87 Vaccines only partially protect against Long COVID | Nature Reviews Immunology, 10 June 2022

88 For instance, see Long-COVID symptoms less likely in vaccinated people, Israeli data say (nature.com), 25 January 2022

89 Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections - PMC (nih.gov), 18 April 2022

90 Impact of COVID-19 vaccination on long COVID: a systematic review and meta-analysis | medRxiv, 22 June 2022

91 Long COVID risk falls only slightly after vaccination, huge study shows (nature.com), 25 May 2022

92 Specifically, data from the UK COVID-19 Infection Survey was used to estimate the likelihood of self-reported long COVID after a first COVID infection compatible with Omicron variants versus Delta variant.

93 Self-reported long COVID after infection with the Omicron variant in the UK - Office for National Statistics (ons.gov.uk), 18 July 2022

Double-vaccinated adults – lower risk for Omicron variants vs. Delta

- Of double-vaccinated adults, 4.0% self-reported long COVID 12 to 16 weeks after a first infection compatible with the Omicron BA.1 variant, compared with 9.2% for those compatible with the Delta variant.
- The odds of reporting long COVID were 48.2% lower for first COVID-19 infections compatible with the Omicron BA.1 variant than those compatible with the Delta variant among adults who were double vaccinated when infected; this was after statistically adjusting for socio-demographic characteristics.

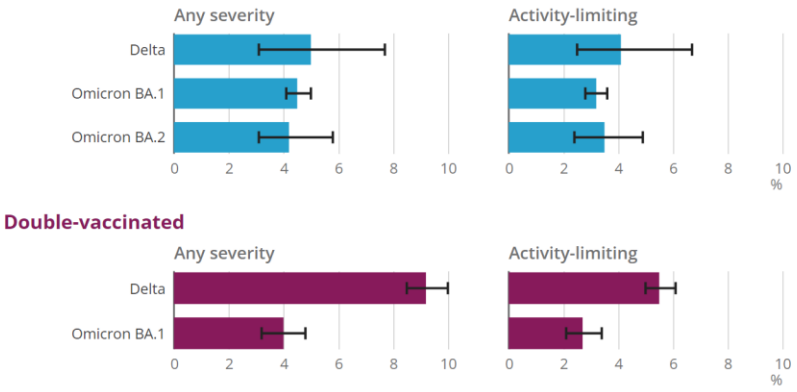
Reproduced from UK Office of National Statistics[94]

According to Daniel Ayoubkhani, statistician at the UK Office for National Statistics:

> *"Today's findings show that approximately 4% of adults who are triple vaccinated against COVID-19 will report experiencing long COVID 12 weeks after being infected for the first time with the Omicron BA.1 or BA.2 variants. This represents a similar risk to the Delta variant. However, these findings may not apply to people who have previously had COVID-19 and have been reinfected with the Omicron variant, and we cannot say what the implications are for any future variants in terms of long COVID risk."*[95]

Figure 1: Approximately 4% of triple-vaccinated adults reported experiencing long COVID 12 weeks after being infected with the Omicron BA.1 or BA.2 variants

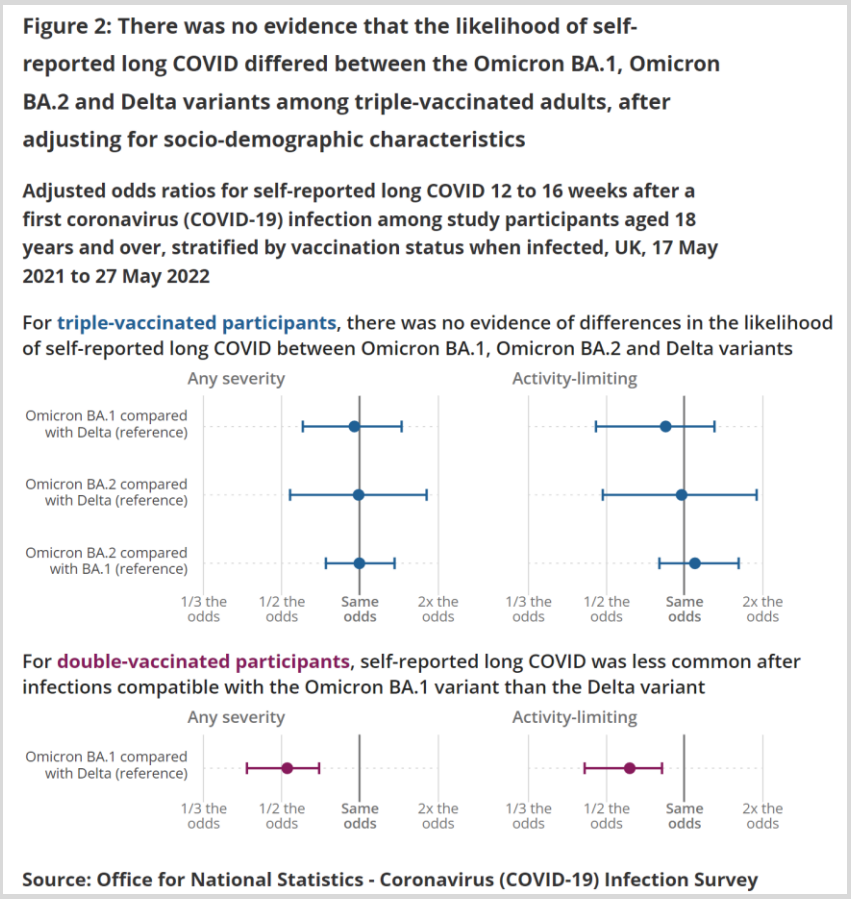
Percentage of study participants aged 18 years and over with self-reported long COVID 12 to 16 weeks after a first coronavirus (COVID-19) infection, stratified by compatible COVID-19 variant and vaccination status when infected, UK, 17 May 2021 to 27 May 2022



Source: Office for National Statistics - Coronavirus (COVID-19) Infection Survey

Reproduced from UK Office of National Statistics[96]

[94] ibid
[95] ibid
[96] ibid



Reproduced from UK Office of National Statistics[97]

Emerging concerns/issues in respect of long COVID

A range of concerns[98] have emerged in respect of long COVID, including those set out below.

More commonly reported in women

A recent major US analytical study[99] found that women were 22% more likely to suffer from long COVID. In addition, sex differences were evident in respect of symptoms, with women more likely to suffer from a range of symptoms (e.g. those affecting the ear, nose and throat, mood, neurological, as well as gastrointestinal and rheumatological disorders and fatigue) whilst men were more likely to experience endocrine disorders (e.g. diabetes and kidney disorders).[100] New data from the US Household Pulse Survey[101] also found that women were more likely than men to

[97] ibid

[98] Three troubling things scientists just learned about Long Covid - NZ Herald, 26 June 2022

[99] Further details of this work, which drew on 35 studies and data from 1.3 million patients, can be found at: Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review (tandfonline.com)

[100] Three troubling things scientists just learned about Long Covid - NZ Herald, 26 June 2022

[101] The U.S. Census Bureau, in collaboration with multiple federal agencies, launched the Household Pulse Survey to produce data on the social and economic impacts of COVID-19 on American households. Further details available at: Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)

report long COVID symptoms at time of data collection (9.6% versus 5.5% of all adults; 21.6% versus 13.3% of adults who ever had COVID). As a proportion of all adults, 17.5% of women reported ever having experienced long COVID as compared with 11.7% of men. Specifically looking at those who ever had COVID, 39.4% of women reported ever having experienced long COVID symptoms as compared to 28.4% of men.[102]

Differences in immune system function have been posited as a potential "important driver" of sex differences in long COVID:

> *Females mount more rapid and robust innate and adaptive immune responses, which can protect them from initial infection and severity. However, this same difference can render females more vulnerable to prolonged autoimmune-related diseases.*[103]

However, these study authors highlighted limitations in existing work on SARS-CoV-2, with most studies not evaluating or reporting granular data by sex[104], thereby liming "sex-specific clinical insights" in respect of treatment.[105] Further, they commented that:

> *The size of female cohorts and sex-disaggregated data analysis and reporting are insufficient in medical research. The lack of studies reporting sex-disaggregated outcomes for COVID-19 speaks to the need for further, large-scale research that includes sex as an analytical variable and that reports data by sex.*[106]

Reinfection is potentially a long COVID risk

Some very early work is pointing to reinfection potentially being a long COVID risk. For instance, a large scale US study[107] – released ahead of peer review (currently under review at *Nature Portfolio*) – found that reinfection (i.e. repeat SARS-CoV-2 infections) poses a risk:

> *Compared to non-infected controls, assessment of the cumulative risks of repeated infection showed that the risk and burden increased in a graded fashion according to the number of infections. The constellation of findings show that reinfection adds non-trivial risks of all-cause mortality, hospitalization, and adverse health outcomes in the acute and post-acute phase of the reinfection.*[108]

Risk was found to be lowest in people with 1 reinfection, increasing in people with 2 infections and highest in those with 3+ infections. Further, risks were evident in subgroups including those who had received 1 vaccine dose, or 2+ vaccines doses prior to the second infection.[109] The study

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[102] Nearly One in Five American Adults Who Have Had COVID-19 Still Have "Long COVID" (cdc.gov); Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)

[103] Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review (tandfonline.com)

[104] This research only identified 23 studies of COVID-19 sequelae and 12 studies on long COVID which reported sex-disaggregated data.

[105] Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review (tandfonline.com)

[106] ibid

[107] The study used the national health care databases of the US Department of Veterans Affairs to build a cohort of people with first infection (n = 257,427), reinfection (2 or more infections, n = 38,926), and a non-infected control group (n = 5,396,855) to estimate risks and 6-month burdens of all-cause mortality, hospitalisation, and a set of pre-specified incident outcomes.

[108] Outcomes of SARS-CoV-2 Reinfection (researchsquare.com), 17 June 2022

[109] ibid

authors noted that the mechanisms underpinning increased risk of adverse health outcomes in reinfection are "not completely clear" and concluded that:

> *Altogether, the findings show that reinfection adds non-trivial risks of all-cause mortality and adverse health outcomes in the acute and post-acute phase of the reinfection … The evidence suggests that for people who already had a first infection, prevention of a second infection may protect from additional health risks. Prevention of infection and reinfection with SARS-CoV-2 should continue to be the goal of public health policy.*[110]

Commenting on this study, Professor John D. Potter (Centre for Public Health Research, Massey University, Wellington; Formerly Chief Science Advisor, New Zealand Ministry of Health):

> *These findings are based on very large numbers and show a dose-response relationship between number of reinfections and the risk of deleterious outcomes, patterns that are essentially independent of vaccination status.*[111]

However, it should be noted that this research has been released as a pre-print and, as such, has not yet been subject to peer review (though commentary[112] is available). It is included in this briefing paper as it points to an emerging area of concern as opposed to any clear conclusion/consensus concerning potential correlation between reinfection and long COVID. Nonetheless, it was recently reported that Dr. David Nabarro, Special Envoy on COVID-19 for the World Health Organization, highlighted the risks of repeat infection and long COVID:

> *"The more times you get it, the more likely you are to be unlucky and end up with long Covid — which is the thing that none of us want because it can be so serious."*[113]

Increased focus of neurological features

As highlighted by Professor Lambert and referenced earlier in this paper, initial conceptualisations of long COVID as centring on pulmonary and respiratory symptoms have altered with the emergence of increased data on the neurological impacts of long COVID. For instance, a study in the *Annals of Clinical and Translational Neurology* reported that non-hospitalised COVID-19 "long haulers" continued to experience neurologic symptoms, fatigue, and compromised quality of life 14.8 months after initial infection.[114] Another study in the same journal sought to assess the initial features and evolution of neurologic sequelae of SARS-CoV-2 infection. It found that fatigue and headache were the most commonly reported early neurological long COVID symptoms, whereas memory impairment and decreased concentration were most prominent at 6 months. However, whilst persistent symptoms trended towards improvement at follow-up, only one-third of participants had completed resolution of neurological long COVID symptoms at 6 months.[115] Research from the COVID and Cognition Study (a longitudinal study aiming to understand

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[110] ibid

[111] Long COVID: Century-old Lessons We Still Have Not Learned – Public Health Expert, University of Otago, New Zealand, 30 June 2022

[112] For instance, see: Each COVID-19 Reinfection Increases Health Risks (webmd.com), 7 July 2022

[113] Covid warning as more times people get reinfected 'more likely it is they get unlucky' and develop long Covid | The Independent, 28 June 2022

[114] Evolution of neurologic symptoms in non-hospitalized COVID-19 "long haulers" - Annals of Clinical and Translational Neurology - Wiley Online Library, 24 May 2022

[115] Longitudinal evaluation of neurologic-post acute sequelae SARS-CoV-2 infection symptoms - Annals of Clinical and Translational Neurology - Wiley Online Library, 15 June 2022

cognitive problems in long COVID) published in *Frontiers in Aging Neuroscience*[116] found a consistent pattern of memory deficits in those that had experienced COVID infection (original or alpha variant of SARS-CoV-2 only), with deficits increasing with the severity of self-reported ongoing symptoms. Fatigue/mixed symptoms during the initial illness and ongoing neurological symptoms were predictive of cognitive performance.[117] Of note, however, is that a recent study in *Cell* found that neurological symptoms are common even after 'mild' COVID. Using a mouse model of SARS-CoV-2 infection limited to the respiratory tract, this study found that a range of neurological symptoms were present even after the virus had been cleared. Moreover, this study noted that whilst Influenza A virus infection also resulted in neuroinflammation, it did not result in the same prolonged effects on subcortical white matter.[118]

Research from the US National Institutes of Health suggests that the immune response triggered by the SARS-CoV-2 infection damages the brain's blood vessels, potentially leading to short- and long-term neurological symptoms. This small-scale study, published in *Brain* by researchers from the US National Institute of Neurological Disorders and Stroke (NINDS) examined brain changes in 9 people who died after contracting the virus. They found evidence that antibodies (i.e. proteins produced by the immune system in response to viruses and other pathogens) are involved in an attack on the cells lining the brain's blood vessels, leading to inflammation and damage.[119] The potential mechanism associated with this is described as follows:

> *.. antibodies produced in response to COVID-19 may mistakenly target cells crucial to the blood-brain barrier. Tightly packed endothelial cells help form the blood-brain barrier, which keeps harmful substances from reaching the brain while allowing necessary substances to pass through. Damage to endothelial cells in blood vessels in the brain can lead to leakage of proteins from the blood. This causes bleeds and clots in some COVID-19 patients and can increase the risk of stroke.*
>
> *For the first time, researchers observed deposits of immune complexes—molecules formed when antibodies bind antigens (foreign substances)—on the surface of endothelial cells in the brains of COVID-19 patients. Such immune complexes can damage tissue by triggering inflammation.*[120]

In terms of the implications of this for understanding neurological long COVID symptoms, Dr. Avindra Nath, Clinical director at NINDS noted that:

> *"It is quite possible that this same immune response persists in Long COVID patients resulting in neuronal injury … There could be a small, indolent immune response that is continuing, which means that immune-modulating therapies might help these patients. So these findings have very important therapeutic implications."*[121]

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[116] For further details, see: Long COVID associated with cognitive defects that need to be addressed, study urges - Medical News Bulletin

[117] Frontiers | COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study (frontiersin.org), 17 March 2022

[118] When 'mild' COVID-19 is not so mild | Nature Reviews Immunology, 29 June 2022

[119] Small NIH study reveals how immune response triggered by COVID-19 may damage the brain | National Institute of Neurological Disorders and Stroke, 5 July 2022

[120] ibid

[121] ibid

A caveat in respect of the status of the research in this field is that a systematic review of cognitive assessment in patients with long COVID[122] concluded that:

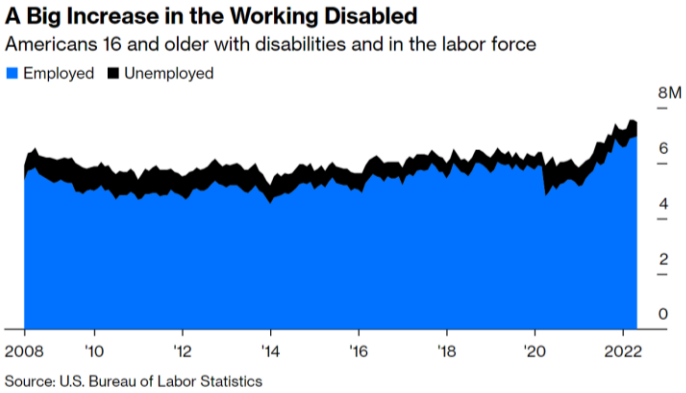
> *Cognitive sequelae in patients with post-infective SARS-CoV-2 can be detected with NPs [neuropsychological] testing. Depending on the psychometric test features, the likelihood of observing cognitive deficits can vary. Further studies on larger sample sizes are needed to investigate the clinical usefulness of second-level tools.*[123]

Impacts of long COVID on the labour force

The impact of long COVID on employment and the labour force, at both a societal and individual level, has been a feature of international work on long COVID[124]. For instance, a UK research article published in *Applied Economics Letters* earlier this month outlined the first estimates of the impact of Long COVID on employment in the UK. It noted that cumulatively 2.9 million people of working age (7% of the total) in the UK have had, or still have, long COVID since the start of the pandemic, with increasing numbers due to high infection rates associated with Omicron. In respect of impacts on the employment sector, this article reported that economic inactivity due to long-term sickness has risen by 120,900 among the working-age population since the beginning of the pandemic, with an estimated 80,000 people having left employment due to long COVID.[125]

Data from the US (see Figure 3 below) also points to an impact of long COVID on the labour force, with more than a million additional Americans, representing a 19% increase from before the pandemic, reporting a disability while continuing to work. Further, this increase in disability among those in the labour force was characterised as representing a "much sharper" increase in percentage terms than for those not in the labour market.[126]

Figure 3 US data in respect of the labour force and disability (reproduced from *Bloomberg*)[127]



[122] Specifically, the study reviewed published studies to "provide a critical narrative of neuropsychological (NPs) deficits commonly observed after SARS-CoV-2 infection and the tests most suited for detecting such cognitive sequelae depending on illness severity".

[123] Cognitive Assessment in SARS-CoV-2 Patients: A Systematic Review (frontiersin.org), 1 July 2022

[124] At national level, an article in the *Irish Examiner* earlier this month reported that, out of the 478,485 people who received enhanced illness benefit (EIB) for up to 10 weeks, 3,783 people have received illness benefit for long COVID.

[125] The impact of Long COVID on the UK workforce (tandfonline.com), 6 July 2022

[126] Long Covid Is Showing Up in the Employment Data - Bloomberg, 15 June 2022

[127] The author highlighted that the dip in disability in Spring 2020 was "likely not for real" as the decrease in survey response rates in the early months of the pandemic – with lower-income households seeing the biggest drop – likely skewed the results. Figure reproduced from here.

EU-OSHA, the European Agency for Safety and Health at Work, recently published a discussion paper on the impact of long COVID on workers and workplaces. Noting that most of research on Long COVID has been focused on improving understanding of the disease, EU-OSHA asserted that more research is required on the effects of long COVID on working-age people. In respect of occupational health specifically, the agency identified a range of areas for further research with a view to enhancing knowledge on workplace issues including:

- the occupational needs of these workers;
- the impact of long COVID on the workplace and for employers;
- the relevance for safety-critical work; and
- how to reduce the social inequalities associated with the disease the most effective workplace-based interventions that maximise the work ability of affected individuals.[128]

Estimating the 'burden of disease' associated with long COVID

The Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle, which is a research centre that has categorised the global health burden of various diseases since the 1990s, has undertaken similar work in respect of estimating the health burden associated with COVID (and long COVID)[129]. Whilst this work has not yet been published, *Nature* reported that estimates of the burden of long COVID have been presented to US authorities. These findings suggest that an estimated 4.6 million people in the US in 2020 and 2021 had symptoms that persisted for at least 3 months, with symptoms categorised around 3 clusters of symptoms, centring on fatigue, cognitive problems and ongoing respiratory issues. Of note is that 85% of these cases resulted from a COVID infection that did not require hospitalisation. All told, modelling from the IHME suggests that 5% of women and 2% who had a mild case of COVID still had symptoms 6 months on from the acute phase of the illness. For those who had been hospitalised, this increased to 26% of women and 15% men, with further increases for those who had spent time in ICU (to 42% and 27% respectively).The INHM team reported that people with long COVID had an average disability weight of 0.21 – which was classed as equivalent to complete hearing loss or severe traumatic brain injury.[130]

Work is ongoing in respect of strengthening the evidence-base on long COVID[131], including through standardisation of estimates of the burden associated with disease (see textbox for details). For instance,

> Burden of Disease (BoD) frameworks facilitate estimation of the health impact of diseases to be translated into a single measure, such as the Disability-Adjusted-Life-Year (DALY). DALYs achieve this through standardising the effects of morbidity and mortality on population health loss as a function of time. The DALY is a health gap metric which measures the healthy life years lost due to diseases, injuries, or risk factors.
>
> *Reproduced from Moran et al. (2022)*

[128] Impact of Long Covid on workers and workplaces and the role of OSH | Safety and health at work EU-OSHA (europa.eu), 20 May 2022

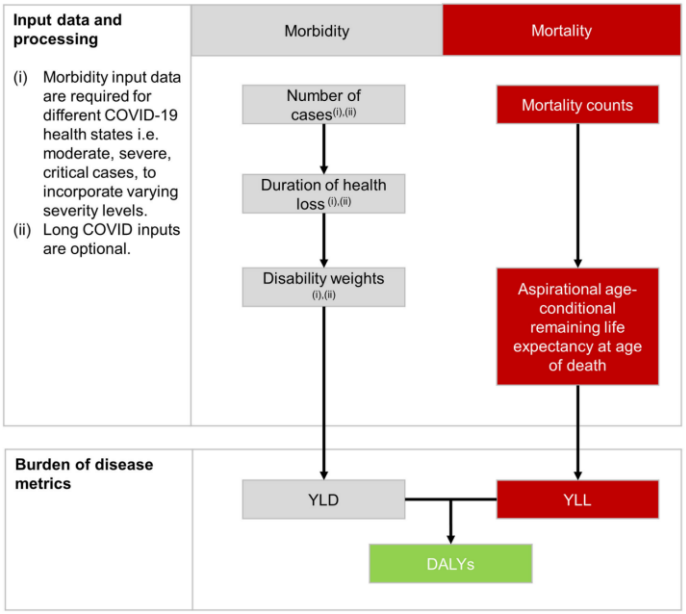
[129] For its estimates of the burden of long COVID, the IHME sought out ongoing cohort studies logging symptoms and, in some instances, assessments of general health before COVID-19 developed. Its model pulls together data from 10 cohorts worldwide and includes more than 5,000 people treated in the community or hospital, as well as data from medical records and published studies.

[130] The pandemic's true health cost: how much of our lives has COVID stolen? (nature.com), 18 May 2022

[131] For instance, see The pandemic's true health cost: how much of our lives has COVID stolen? (nature.com), 18 May 2022

the European Burden of Disease Network has prepared a protocol to provide guidance for anyone planning to assess the burden of disease of COVID-19 at national level using disability-adjusted life years (DALYs), which aims to foster harmonisation of methodologies for estimating the burden of disease of COVID across a range of countries[132].[133] The processes associated with the calculation DALYs of COVID at national level as part of the consensus methodology developed by the European Burden of Disease Network are set out in the Figure 4 below.

Figure 4 Calculation of DALYs, consensus methodology, European Burden of Disease Network



Reproduced from Pires et al.[134]

At national level, an article published in the *International Journal of Public Health* estimated the direct DALYs associated with COVID in Ireland across the first year of the pandemic, with years lived with disability (YLD)[135] incorporating 5 health states in this study: asymptomatic (which

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[132] BoD COVID studies are being undertaken in The Netherlands, Scotland, Germany, Malta, Ireland, Denmark, France and Belgium.

[133] COVID-19 - European Burden of Disease Network (burden-eu.net)

[134] Frontiers | Burden of Disease of COVID-19: Strengthening the Collaboration for National Studies (frontiersin.org), 3 June 2022)

[135] The authors explain that categorisation of cases by severity is necessary as both duration and disability weight are included in the calculation of YLDs, whereby it would not be expected that a person with moderate COVID-19 would contribute similar YLDs as a person with severe COVID-19. The weighting associated with each of the 5 states are set out below:

Health state	Assumption/description	Disability weight (95% uncertainty interval)	Duration
Asymptomatic	Person was infected with COVID-19 but did not present for a Polymerase Chain Reaction (PCR) confirmation test	Nil	0.00
Moderate	Person had a PCR confirmed COVID-19 diagnoses which was managed in the community and did not require hospitalisation	0.051 (0.032–0.074)	7.79
Severe	Person had a PCR confirmed COVID-19 diagnoses which required hospitalisation but not intensive care	0.133 (0.088–0.190)	10.9
Critical	Person had a PCR confirmed COVID-19 diagnoses which required hospitalisation and admission to intensive care (with or without ventilation)	0.655 (0.579–0.727)	13.1
Post-acute consequences	Person infected with COVID-19 developed chronic sequelae (note persons attributed to the "post-acute consequences" health state did not necessarily have a PCR confirmed COVID-19 diagnoses)	0.219 (0.148–0.308)	28

Burden of disease of COVID-19: Protocol for Country Studies, Brussels, 2020, Burden of Disease Methods: A Guide to Calculate COVID-19 Disability-Adjusted Life Years. Brussels, 2021.

carried no value for YLD estimates), moderate, severe, critical, and post-acute consequences (PAC). However, the authors noted that uncertainties exist in their analysis, particularly in respect of the estimation of the proportion of cases who have transitioned to the health state 'PAC' (i.e. the proportion of patients who go on to experience long COVID), as well as the duration of this health state (i.e. the length of time long COVID symptoms endure). As can be seen from Table 3 below, this study estimated a YLD of 799.8, with the largest contributing health state being post-acute consequences with YLD of 491.8.[136]

Table 3 Years lived with disability estimates (Ireland, 2021)

YLD by health state			
Health State		**YLD**	
Asymptomatic		0	
Moderate		224.1 (140.6, 325.1)	
Severe		51.2 (33.9, 73.1)	
Critical		32.7 (28.9, 36.3)	
Post-Acute Cons		491.8 (332.4, 691.7)	
Total		799.8 (535.7, 1,126.2)	
YLD by sex and health state			
	Health State	**Incidence**	**YLD**
Males	Moderate	96,816	105.3 (66.1, 152.8)
	Severe	6,059	24 (15.9, 34.4)
	Critical	654	15.4 (13.6, 17.1)
	PAC	13,769	231.2 (156.2, 325.1)
Females	Moderate	109,175	118.8 (74.5, 172.3)
	Severe	6,832	27.1 (17.9, 38.7)
	Critical	737	17.3 (15.3, 19.2)
	PAC	15,527	260.7 (176.2, 366.6)
YLD by sex and age-group			
	Age-Group	**Incidence**	**YLD**
Males	0–14	10,557	33.8 (22.7, 47.6)
	15–24	21,114	67.7 (45.3, 95.3)
	25–44	39,881	127.8 (85.6, 180)
	45–64	30,497	97.7 (65.5, 137.6)
	65–79	9,384	30.1 (20.1, 42.3)
	80+	5,865	18.8 (12.6, 26.5)
Females	0–14	11,904	38.1 (25.5, 53.7)
	15–24	23,809	76.3 (51.1, 107.5)
	25–44	44,972	144.1 (96.5, 202.9)
	45–64	34,391	110.2 (73.8, 155.2)
	65–79	10,582	33.9 (22.7, 47.7)
	80+	6,614	21.2 (14.2, 29.8)

Reproduced from Moran et al.[137]

Given the time period associated with this study (first year of pandemic), the largest impact on population health was noted as resulting from premature mortality with Years of Life Lost (YLL) representing 98.5% of the DALYs, with YLD contributing a small percentage of the total DALYs.[138]

Of relevance here is modelling (based on the European Burden of Disease Network protocol guidelines and consensus model) undertaken to estimate the potential acute and post-acute burden of COVID-19 in Australia, taking account of the easing of public health measures. This research found that whilst the mortality impact (YLL) was the largest contributor to the DALY burden (72-74%), this was followed by the morbidity impact of long COVID (19-22%). The authors

[136] Estimating the Direct Disability-Adjusted Life Years Associated With SARS-CoV-2 (COVID-19) in the Republic of Ireland: The First Full Year (ssph-journal.org), 2 June 2022

[137] ibid

[138] ibid

concluded that: *"As vaccination coverage increases, the share of COVID-19 burden driven by longer-term morbidity rises relative to mortality".* [139] Thus, they asserted that:

> *..we have demonstrated that even low rates of incidence of COVID-related permanent illness or disability could still lead to a very significant future burden of disease. Investing now in effective surveillance systems to understand the real incidence and burden of Long COVID and permanent illness or impairment after COVID is therefore essential, in Australia and other jurisdictions.*[140]

Further, the authors of the Irish study referenced above asserted that future research must also focus on estimating the BoD in respect of long COVID:

> *.. future research must also focus on estimating COVID-19 specific DWs [disability weights], an extensive BoD study relating to the indirect effects of the COVID-19 pandemic, and an extensive study relating to the profile and timeline of "Long-COVID."*[141]

Commentary in *Nature* highlights that examining the nature of long COVID in this manner is limited by the timelines associated with the infection itself:

> *Measuring DALYs takes time — often the analyses are done only once a year. That means that some key questions about the burden of COVID-19 — such as how vaccines have affected illness rates and severity — won't be answered for a while. The fact that COVID-19 has been around for only a couple of years means that scientists don't have enough data to make accurate forecasts ..*[142]

Future developments

The US National Institutes of Health (NIH) notes that the complexity of long COVID makes it difficult to identify those with this syndrome. However, it highlights an NIH-supported study published in *Lancet Digital Health*, which they describe as "groundbreaking", that applied machine learning to EHRs to identify those potentially suffering from long COVID. The methodology employed by the researchers was described as follows:

> *They fed that EHR [electronic health records] data into a computer, along with health information from almost 600 patients who'd been seen at a Long COVID clinic. They developed three machine learning models: one to identify potential long COVID patients across the whole dataset and two others that focused separately on people who had or hadn't been hospitalized.*
>
> *All three models proved effective for identifying people with potential Long-COVID. Each of the models had an 85 percent or better discrimination threshold, indicating they are highly accurate.*[143]

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[139] Modelling the potential acute and post-acute burden of COVID-19 under the Australian border re-opening plan | BMC Public Health (biomedcentral.com), 14 April 2022

[140] ibid

[141] Estimating the Direct Disability-Adjusted Life Years Associated With SARS-CoV-2 (COVID-19) in the Republic of Ireland: The First Full Year (ssph-journal.org), 2 June 2022

[142] The pandemic's true health cost: how much of our lives has COVID stolen? (nature.com), 18 May 2022

[143] Using AI to Advance Understanding of Long COVID Syndrome – NIH Director's Blog, 7 June 2022

According to the researchers, this offers the opportunity for efficient recruitment into studies on long COVID[144], which will facilitates increased opportunities to understand long COVID:

> *N3C's longitudinal data[145] for patients with COVID-19 provides a comprehensive foundation for the development of machine learning models to identify patients with potential long COVID. Such models enable efficient study recruitment that, in turn, deepen our understanding of long COVID and offer opportunities for hypothesis generation. Moreover, as more patients are diagnosed with long COVID and more data are available, our models can be refined and retrained to evolve the algorithm as more evidence emerges.*
>
> *For instance, the researchers hypothesised that long COVID might ultimately not have a single definition but rather be understood as a set of related conditions, each with their own symptoms, trajectories and treatments.*[146]

Methodological concerns

The limitations associated with available data, as well as prevailing methodological challenges, have been noted as impacting research on long COVID. For instance, an article in *Nature* noted that large datasets do not necessarily allow scientists to "solve long COVID mysteries" for a variety of reasons. One difficulty relates to the lack of agreement as to how to define and diagnose long COVID, which has been linked to more than 200 symptoms, the severity of which can vary from inconvenient to debilitating.[147]

> *So far, there is no agreement on how to define and diagnose long COVID. The World Health Organization's attempt at a consensus, published in 2021, has not proved popular with patient advocates or researchers, and studies continue to use a range of criteria to define the condition. Estimates of its prevalence can range from 5–50%.*[148]

Beyond definitions, this article notes that whilst large datasets allow researchers to perform complicated statistical analyses to carefully match the demographics of people infected with COVID to an uninfected control group, such research is not without its drawbacks (including that quality and validity does not necessarily equate with quantity). For instance, reliance on EHR was noted as potentially being impacted by behavioural differences (e.g. compared with someone who does not seek medical care for acute COVID, someone who does might be more likely to report long COVID symptoms), as well as variance and lack of consistency associated with the coding of symptoms. Further, it was noted that in countries like the US where health insurance coverage might vary significantly, such methodologies might result in a potential undercount of the number of people with long COVID as some people may not seek medical care for their condition. According to a computational epidemiologist at Harvard Medical School in Boston, Massachusetts:

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[144] For instance, the US National Institutes of Health's RECOVER Initiative seeks to understand long COVID, identify treatments, and accurately identify who has it. For further information, see: RECOVER: Researching COVID to Enhance Recovery.

[145] This refers to the US National COVID Cohort Collaborative (N3C), a national, publicly available data resource sponsored by NIH's National Center for Advancing Translational Sciences. It is part of NIH's Researching COVID to Enhance Recovery (RECOVER) initiative, which aims to improve understanding of Long COVID.

[146] Identifying who has long COVID in the USA: a machine learning approach using N3C data - PMC (nih.gov), July 2022

[147] How common is long COVID? Why studies give different answers (nature.com), 20 June 2022

[148] ibid

> *"The number of data points considered is often so large that we mistakenly assume that these data must be representative … But this isn't necessarily the case".*[149]

[149] ibid

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