- Point Prevalence Estimates of Activity-Limiting Long-Term Symptoms among U.S. Adults ≥1 Month After
   Reported SARS-CoV-2 Infection, November 1, 2021
- 3
- 4 **Short title:** Prevalence of post-COVID conditions
- 5
- 6 Mark W. Tenforde, MD, PhD<sup>1</sup>; Owen J. Devine, PhD<sup>2</sup>; Heather E. Reese, PhD<sup>1</sup>; Benjamin J. Silk, PhD<sup>1</sup>; A.
- 7 Danielle Iuliano, PhD<sup>1</sup>; Ryan Threlkel, MPH<sup>3</sup>; Quan M. Vu, MD<sup>1</sup>; Ian D. Plumb, MBBS, MSc<sup>1</sup>; Betsy L.
- 8 Cadwell, MSPH<sup>1</sup>; Charles Rose, PhD<sup>1</sup>; Molly K. Steele, PhD<sup>1</sup>; Melissa Briggs-Hagen, MD, MPH<sup>1</sup>; Daniel
- 9 Ayoubkhani, MSc<sup>4</sup>; Piotr Pawelek, MSc<sup>4</sup>; Vahé Nafilyan, PhD<sup>4</sup>; Sharon H. Saydah, PhD, MHS<sup>1</sup>; Jeanne
- 10 Bertolli, PhD, MPH<sup>1</sup>
- 11
- 12 <sup>1</sup> CDC COVID-19 Response Team, Atlanta, GA, USA
- 13 <sup>2</sup> Eagle Global Scientific, LLC, Alpharetta, GA, USA
- <sup>3</sup> General Dynamics Information Technology, Inc., Atlanta, GA, USA
- 15 <sup>4</sup>Office for National Statistics, Newport, UK
- 16
- 17 Corresponding author:
- 18 Mark Tenforde MD, PhD, MPH, DTM&H
- 19 Centers for Disease Control and Prevention
- 20 1600 Clifton Road NE, H24-7
- 21 Atlanta, GA, USA 30329-4027
- 22 E-mail: pij6@cdc.gov
- 23 Phone: 404.861.0404
- 24 Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily
- 25 represent the official position of the Centers for Disease Control and Prevention.

26

Published by Oxford University Press on behalf of Infectious Diseases Society of America 2022. This work is written by (a) US Government employee(s) and is in the public domain in the US.

### 1 Abstract

2 Background: Although most adults infected with SARS-CoV-2 fully recover, a proportion have ongoing

3 symptoms, or post-COVID conditions (PCC), after infection. The objective of this analysis was to estimate

- 4 the number of US adults with activity-limiting PCC on November 1, 2021.
- 5 Methods: We modeled the prevalence of PCC using reported infections occurring from February 1, 2020

6 – September 30, 2021, and population-based, household survey data on new activity-limiting symptoms

7 ≥1 month following SARS-CoV-2 infection. From these data sources, we estimated the number and

8 proportion of US adults with activity-limiting PCC on November 1, 2021, as 95% uncertainty intervals,

9 stratified by sex and age. Sensitivity analyses adjusted for under-ascertainment of infections and

- 10 uncertainty about symptom duration.
- 11 **Results:** On November 1, 2021, at least 3.0–5.0 million US adults were estimated to have activity-

12 limiting PCC of ≥1 month duration, or 1.2%–1.9% of US adults. Population prevalence was higher in

13 females (1.4%–2.2%) than males. The estimated prevalence after adjusting for under-ascertainment of

14 infections was 1.7%–3.8%.

15 **Conclusion:** Millions of US adults were estimated to have activity-limiting PCC. These estimates can

16 support future efforts to address the impact of PCC on the U.S. population.

17 Key words: Post-COVID conditions; long COVID; disability; COVID-19; modeling; prevalence

# 1 Introduction

2	The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome
3	associated coronavirus 2 (SARS-CoV-2), has had a devastating global impact. In the United States, almost
4	1 million COVID-19-related deaths were reported through April 2022 [1]. Although most individuals
5	infected with SARS-CoV-2 survive, a proportion experience post-acute sequelae that may last for weeks
6	or longer [2, 3]. Various post-COVID conditions (PCC), often referred to as long COVID, have been
7	described. Common among them are fatigue and body aches, respiratory symptoms, and neurocognitive
8	dysfunction, although a variety of additional sequelae are observed [4-7].
9	Understanding the prevalence of PCC is important for enumerating the full impact of the COVID-
10	19 pandemic, allocating resources and developing evidence-based prevention and management
11	strategies, and planning for and mobilizing healthcare and social support services. Although several
12	clinical case definitions for PCC have been developed [8, 9], a universally agreed definition does not exist
13	[10-12]. Challenges in defining PCC and evaluating its prevalence include non-specific signs and
14	symptoms that may have other causes; knowledge gaps in pathophysiology [13, 14]; limited duration of
15	follow-up leading to incomplete understanding of its natural history; and heterogeneity in design,
16	outcomes, and populations evaluated across published studies [15].
17	We developed a model-based approach to provide estimates of the point prevalence of activity-
18	limiting PCC among US adults on November 1, 2021. These estimates are intended to provide a
19	foundation for future research focused on estimating the prevalence of PCC over time as the COVID-19
20	pandemic evolves and definitions of and instruments for assessing PCC continue to mature.
21	

#### 1 Methods

#### 2 Data sources

3 Our objective was to estimate the number of adults (aged ≥18 years) residing in the US on November 1, 2021 experiencing PCC that adversely affected their daily activities at least 1 month following infection 4 5 with SARS-CoV-2. In developing the estimates, we chose reported activity-limiting symptoms attributed to prior SARS-CoV-2 infection as our primary outcome to capture PCC associated with significant 6 7 functional impairment. Other PCC-related outcomes reported in published studies [15], such as  $\geq 1$ persistent symptom of any severity or new clinical diagnoses, were not evaluated and might lead to 8 9 different estimates of PCC prevalence. The period of at least 1 month post-infection corresponds with Centers for Disease Control and Prevention (CDC) definitions of PCC [16]. 10

11 We developed PCC point prevalence estimates using two primary data sources. First, to estimate the number of adults in the general US population who were at risk of having PCC on 12 November 1,2021, we used the total number of infections reported to CDC through the Nationally 13 Notifiable Disease Surveillance System (NNDSS) between February 1, 2020 and September 30, 2021 [17]. 14 We used data through September 30, 2021, to predate the effects of the Omicron variant and its 15 sublineages (because the probability of PCC after Omicron may be different from the probability of PCC 16 17 after previous variants), and of reinfections with SARS-CoV-2, which have been reported with increasing frequency subsequently [18]. November 1, 2021 was selected for estimating the point prevalence of PCC 18 to allow at least a 1-month interval between time of infection, for those most recently infected, and 19 initiation of PCC. 20

The second primary data source was the household Coronavirus Infection Survey (CIS) conducted by the Office for National Statistics in the United Kingdom (UK) [19]. This data source employs population-based sampling including non-hospitalized adults with primarily mild or asymptomatic acute SARS-CoV-2 infection, to represent most SARS-CoV-2 infections. In the CIS, persons
with PCR-confirmed SARS-CoV-2 infection were asked the following questions, "Would you describe
yourself as having 'long COVID', that is, you are still experiencing symptoms more than 4 weeks after
you first had COVID-19, that are not explained by something else?" If yes: "Does this reduce your ability
to carry-out day-to-day activities compared with the time before you had COVID-19?"

6 Summary CIS data on responses to these questions were available from participants recruited 7 April 2020 through August 2021 within strata defined by days since positive test (range 42 to 168 days), sex, age group (18-49, 50-64, ≥65 years), and severity of acute infection (asymptomatic or symptomatic) 8 9 [20]. All CIS participants are regularly tested for SARS-CoV-2, irrespective of symptoms, so the data 10 include both symptomatic and asymptomatic infections. However, the CIS is a household survey and does not include people in communal establishments such as hospitals or care homes. In order to 11 12 estimate PCC for persons from inpatient settings who were included in NNDSS counts, we assumed their probability of PCC was 1.5 to 3.5 times greater than the PCC probability among those who were 13 14 symptomatic but not hospitalized. These estimates were based on evidence demonstrating that various symptoms and other post-COVID-19 sequelae correlate with the severity of acute SARS-CoV-2 infection 15 16 [4, 21, 22].

CDC receives reports of SARS-CoV-2 infections from US states and other jurisdictions in two 17 18 primary ways (1). For a portion of infections, line listed (LL) data are reported. These reported cases 19 (including asymptomatic infections identified by laboratory testing results) include information on date 20 of testing, age, sex, hospitalization status on date of testing, and acute COVID-19-related symptoms 21 experienced when the SARS-CoV-2 test was administered. CDC also receives aggregate counts of SARS-22 CoV-2 infections in which only the total numbers of cases are reported over time (i.e., no additional 23 information beyond date of report is provided). Given the lack of identifying information in either data 24 source, it is not possible to determine the precise extent of overlap in counts of reported infections in

the LL and aggregate data. More than 26 million non-fatal SARS-Cov-2 infections among persons aged ≥
18 years were reported in LL format between February 2020 and September 2021. However, LL data
underestimates the total number of reported infections. During the same period, approximately 36
million non-fatal SARS-CoV-2 infections were reported among those aged ≥18 years in aggregate form.
To develop a more complete estimate of reported cases, we added the difference between the number
of non-fatal infections reported in aggregate and the number reported in LL format.

7 The prevalence of PCC among the US adult population on November 1, 2021, was estimated through a series of steps with associated uncertainty assumptions (Table 1). The general steps in the 8 9 estimation process were: 1) assignment of both the LL and aggregate counts of adult non-fatal infections 10 to two-month time intervals corresponding to dates of case reports ranging from February-March 2020 through August-September 2021; 2) imputation of data on age group, sex, and severity of SARS-CoV-2 11 12 acute infection when missing in the LL data and for the entire collection of aggregate data; 3) estimation of excess reported infections in the aggregate data, with excess infection counts added to the 13 14 appropriate strata of the LL data; 4) application of stratum-specific PCC probability estimates from the CIS to corresponding strata of US adults at risk for PCC; and 5) summation of estimates across time-15 since-infection intervals. 16

The modeled measures of PCC prevalence are summarized using 95% uncertainty intervals (UI) derived from 10,000 Monte Carlo realizations of the model outputs. Variation across these Monte Carlo samples reflects repeated sampling from the assumed uncertainty distributions for model input parameters (Supplementary Appendix Table A2, Supplementary Appendix equations [1] – [5]). The lower and upper limits of the UIs are defined by the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the of 10,000 Monte Carlo realizations. We expect our estimates of the number of US adults at risk for PCC to be underestimated, because of undiagnosed SARS-CoV-2 infections and under-reporting of diagnosed infections [1, 23]. We used a modified version of our modeling approach to evaluate the potential impact of this likely underestimation on the PCC prevalence estimates. This sensitivity analysis was conducted by inflating the reported number of infections in the combined LL and aggregate data by a multiplier based on the ratio of the estimated seroprevalence of SARS-CoV-2 in the US to the corresponding time-specific reported number of infections [1, 23].

8 Estimates of the probability of having a PCC with time since infection were available from the 9 CIS for time periods ranging from 42 to 168 days after testing, corresponding to intervals of 10 approximately 1 to 6 months after infection. Using the combined LL and aggregate data, however, we were able to estimate the number of persons at risk for PCC ranging from 1–2 months (August-11 12 September 2021) to 19–20 months (February-March 2020) prior to the prevalence estimation target date of November 1, 2021. As a result, it was necessary to assume trends in probability of PCC for time-13 since-infection periods greater than 6 months. Based on trends observed in the CIS, the probability of 14 PCC was assumed to be constant beyond 6 months in the base model. To investigate the impact of 15 16 violations of this assumption, we considered an alternative model in which the probability of having a 17 PCC decreased for times since infection greater than 6 months at a rate similar to that observed among 18 symptomatic CIS participants during the first 6 months post-infection. Details on the modeling steps and 19 assumptions used to conduct both sensitivity assessments are presented in the Supplementary 20 Appendix. Analyses were conducted using R Version 4.0.3 (Vienna, Austria). The project was determined 21 to be a non-research, public health surveillance activity by CDC. We performed secondary data analysis 22 on de-identified cases reports and survey responses; written informed consent was not obtained.

23

#### 1 Results

#### 2 Model Estimates

3 Through September 30, 2021, approximately 36.3 million SARS-CoV-2 infections were reported in US adults (Table 2), including 19.2 million (53%) in females and 23.1 million in adults 18-49-years old (64%) 4 5 [Table 2]. Of these reported infections, we estimated that approximately 24 million (66%) were symptomatic but not hospitalized for acute infection, 10 million (28%) were asymptomatic and not 6 7 hospitalized, and 2 million (6%) were hospitalized for acute infection. The number of reported infections peaked at 10 million in the December 2020 - January 2021 time interval with an upward trajectory in 8 9 cases by September 30, 2021, when the Delta variant predominated in the US (Figure 1). The time between infection and November 1, 2021, was 1–6 months for 22% of persons, 7-12 months for 44%, 10 and >12 months for 34%, with a median period of 10 months. 11

Survey response rate in the CIS survey ranged from 51% during the initial pilot phase in April 12 2020, when eligible households included respondents to prior ONS surveys, to 12% in August 2021 after 13 enrollment was expanded to include households randomly selected from address lists [24]. Among 14 15 those who enrolled, loss to follow-up rates were low. Defining loss to follow-up as formal withdrawal from the study or non-attendance at the three mostly recently scheduled follow-up visits (loss of 16 17 contact), the average monthly attrition rate was <1% through 2021. From the CIS household survey data, among adults who were generally not hospitalized for acute SARS-CoV-2 infection, the estimated 18 probability of having PCC was higher among those with symptomatic compared to asymptomatic acute 19 20 infection and in females compared to males (Figure 2). The estimated percent of persons with confirmed 21 SARS-CoV-2 infection who were not hospitalized due to infection during the acute phase and reported 22 new activity-limiting symptoms 42 days post infection ranged from 22.7% among symptomatic females 23 aged 50-64 years to 3.3% among asymptomatic males aged  $\geq$ 65 years old. At 168 days post infection,

1 the percentage who reported PCC ranged from 16.8 % among symptomatic females aged 50-64 years to

2 3.0% among 18-49-year-old asymptomatic males.

3	Overall, 3.0–5.0 million US adults with documented SARS-CoV-2 infection were estimated to be
4	living with activity-limiting PCC on November 1, 2021, representing approximately 1.2%–1.9% of the US
5	adult population (Table 2). An estimated 0.4–1.3 million cases of activity-limiting PCC were estimated
6	among adults hospitalized during acute infection, corresponding with 13%–25% of all PCC cases. The
7	prevalence was higher in females (1.4%–2.2%) than males (0.9%–1.7%). Adults aged 50-64 years had the
8	highest prevalence of activity-limiting PCC, with an estimated 1.5%–2.5% prevalence, and lower
9	estimates for adults 18-49 and ≥65 years old.
10	Sensitivity analyses
11	In a model incorporating seroprevalence estimates to account for under-ascertainment of infections
12	[23], we estimate that 61.3-90.6 million SARS-CoV-2 infections occurred in US adults through September
13	30, 2021 (Table 3). With adjustment for under-ascertainment of infections, 4.3–9.7 million US adults
14	with any SARS-CoV-2 infection were estimated to be living with activity-limiting PCC, representing 1.7%-
15	3.8% of the US adult population. A second sensitivity analysis, assuming a decrease in the probability of
16	having PCC beyond 6 months and holding other parameters from the primary model constant, resulted
17	in lower PCC prevalence compared to the primary model, with an estimated 2.2–4.2 million US adults
18	living with PCC on November 1, 2021, representing approximately 0.9%–1.6% of the US adult
19	population.

# 20 Discussion

- 21 Using a model-based approach, we estimated that at least 3.0 to 5.0 million US adults were living with
- 22 activity-limiting symptoms of PCC on November 1, 2021. Accounting for underdiagnosis or
- 23 underreporting of SARS-CoV-2 infections, we estimated that 4.3–9.7 million adults were living with

1 activity-limiting PCC at this time. These are pre-Omicron period estimates, which relied on reported 2 infections and used activity-limiting symptoms as criteria for PCC, so they are conservative estimates. 3 Estimates further accounted for uncertainty due to limitations of data sources and an incomplete understanding of the natural history of PCC. The prevalence of PCC is expected to be dynamic and 4 5 influenced by temporal changes in the incidence of infections with circulating SARS-CoV-2 variants and 6 the distribution of time since infection [25, 26]. As the COVID-19 pandemic continues, population-level 7 immunity has increased, with a growing proportion of infections occurring in those with prior infection and those who received COVID-19 vaccinations. This accumulated immunity may further affect the risk 8 9 of PCC [24, 27-30]. Notably, even our conservative estimates suggest a substantial prevalence of activitylimiting symptoms lasting for weeks to months after SARS-CoV-2 infection. This foundational study 10 highlights an urgent need for basic science, epidemiological and clinical research to understand the 11 pathophysiology of and risk factors for PCC, and an evidence base to guide medical management, as well 12 as to assist with planning for and mobilizing healthcare and social support services [31]. 13

A strength of this analysis is the use of data from national surveillance system of SARS-CoV-2 14 cases and hospitalizations combined with data from a population-based, longitudinal household survey 15 16 of individuals after acute infection, most of whom experience mild infection not requiring hospitalization 17 or asymptomatic infection [32, 33]. In contrast, other PCC studies have generally focused on the severe 18 end of the spectrum of acute illness [15], and have often cross-sectionally measured heterogeneous 19 outcomes that may not correlate with functional impairment. A recent systematic review found that a 20 majority of published studies report at least 1 post-acute sequelae of COVID-19 in more than 50% of 21 survivors, including at follow-up periods of >6 months [15]. Compared to a baseline (reference) period 22 predating infection, the CIS captures new onset of activity-limiting symptoms of 4 weeks or longer with 23 longitudinal evaluations. Although the survey relied on self-reporting and did not include a SARS-CoV-2-24 negative comparator population, new onset of impairment evaluated in the survey is likely to reflect

1 ongoing illness correlating with need for clinical or other support services. Multipliers were used to 2 estimate the probability of having PCC in adults after hospitalization for acute infection because of the 3 limitations of household survey data. These individuals may experience long-term sequelae of COVID-19 4 from pathophysiological mechanisms and underlying sequelae that follow less severe acute infection, as 5 well as through additional mechanisms associated with severe disease [34]. Uncertainty in the estimates 6 of probability of having PCC in adults after hospitalization for acute infection is unlikely to have a large impact on prevalence estimates, even though the probability of PCC is higher for those who were 7 hospitalized, as a minority of SARS-CoV-2 infections result in hospitalization [35]. 8

9 The estimated prevalence of PCC was higher in females than males, reflective of higher 10 reporting of activity-limiting symptoms among females participating in the household survey. Similar findings have been observed across studies that assessed a variety of PCC-related outcomes [36-38]. 11 12 Although mechanisms are unclear, differences by sex have been observed in other chronic syndromes that have overlapping characteristics with PCC, including myalgic encephalitis/chronic fatigue syndrome 13 14 (ME/CFS) [39]. Estimates stratified by age suggest that PCC prevalence is distributed across age groups, with highest prevalence among adults aged 50-64 years. Notably, the estimated risk was lower both in 15 16 younger (18-49-years of age) and older (≥65-years of age) adults. This finding may reflect a higher risk of 17 death in older adults [40] or higher vaccine coverage (and associated lower PCC risk) in older compared 18 to younger adults sampled in the CIS. Limitations of data sources precluded the application of our model 19 to generate estimates of the prevalence of PCC by race or ethnicity among US adults.

These estimates are subject to several limitations. Multipliers were used to scale the probability of having PCC in adults hospitalized for acute SARS-CoV-2 infections due to the absence of direct sampling in the UK household surveys. We did not account for differential PCC risk in those experiencing reinfection or with prior COVID-19 vaccination due to limitations of survey data. Because the majority of SARS-CoV-2-positive CIS participants were unvaccinated at the time of infection over the study period

[30], sample size was insufficient to include activity-limiting PCC by vaccination status cross-stratified by
age, sex, and severity of acute illness. This analysis predated circulation of the Omicron variant and its
sublineages, which is associated with less severe COVID-19 compared to previously circulating SARSCoV-2 variants, and potentially differential risk of PCC [25, 27]. Several key parameters had a large
degree of uncertainty. To account for these uncertainties, sensitivity analyses were performed to
provide a broader range of prevalence estimates.

7 UK household survey data were used to estimate the probability of having PCC over time in a US population. Models did not account for differences between populations, such as differences in certain 8 9 sociodemographic characteristics, vaccine coverage and products, underlying health conditions, and 10 access and availability of health services that may influence the probability of experiencing PCC and reporting activity-limiting PCC. COVID-19 vaccination before, as well as after, incident SARS-CoV-2 11 12 infection may modify the risk of PCC and risk of continuing to experience persistent symptoms in those who already have symptoms when vaccinated [24, 30]. Differences in COVID-19 vaccination coverage 13 14 over time between the UK and US may therefore contribute to differences in the risk of activity-limiting PCC between settings, although infections among individuals fully vaccinated against COVID-19 were 15 16 relatively uncommon during the study period. A recent systematic review and meta-analysis also found 17 differences in PCC risk across geographic regions, but some of these differences may be attributable to 18 differences in sociodemographic characteristics, follow-up time, and COVID-19 study populations including severity of infections, among other factors [41]. Our analysis included longitudinal follow-up 19 20 and results were stratified into meaningful groups, including age, sex, and severity of acute illness, likely 21 to correlate with risk of activity-limiting PCC across different settings. Modeling methods, including use 22 of US case data, may address some of the differences in the underlying SARS-CoV-2-infected population 23 between the US and UK.

Finally, in the absence of a universally accepted definition of PCC, we used a primary outcome measure intended to capture self-reported PCC that interfered with daily activities. Self-reported outcomes may be subject to bias and other definitions of PCC likely would have resulted in different estimates. Respondents may also define activity-limiting symptoms differently and the survey does not capture the severity of activity-limiting symptoms. Use of existing functional scales that grade severity might provide more granularity on degree of disability associated with PCC.

7 Our findings conservatively suggest that millions of US adults were living with activity-limiting symptoms of PCC on November 1, 2021. The modeling framework used for this analysis is intended to 8 9 serve as a foundation for future research estimating and monitoring the prevalence of PCC. Further 10 analyses will need to consider growing population immunity through natural infection and vaccination, differences in risks of PCC with Omicron or other emerging variants, and changing probabilities of having 11 12 PCC with longer times since infection. Ideally, estimates should be stratified by race and ethnicity, age 13 groups that include children, and other sociodemographic characteristics. These estimates provide an 14 initial framework to understand the prevalence of PCC in the adult US population and highlight the 15 importance of continued prevention efforts to reduce the incidence of SARS-CoV-2 infections and mitigate not only acute COVID-19 but also the subsequent impact of long-term, activity-limiting 16 17 symptoms among adults.

18

## 19 ACKNOWLEDGEMENTS

20 Funding sources: Primary funding was provided by CDC

Funding statement: This project was funded by CDC, and CDC co-authors took part in the project design,
conduct, analysis, and manuscript preparation. The findings and conclusions in this report are those of
the authors and do not necessarily represent the official position of the CDC or UK's Officer for National
Statistics.

Potential Conflicts of Interest Disclosures: All authors have completed and submitted the International
 Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential
 conflicts of interest were disclosed.

### 1 References

- 2 1. Centers for Disease Control and Prevention. CDC COVID Data Tracker. Available at:
- 3 <u>https://covid.cdc.gov/covid-data-tracker/#cases\_casesper100klast7days</u>. Accessed on: 4 May 2022.
- 4 2. Carfi A, Bernabei R, Landi F, Group GAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19.
- 5 JAMA **2020**; 324:603-5.
- 6 3. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to
- 7 Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network United
- 8 States, March-June 2020. MMWR Morb Mortal Wkly Rep 2020; 69:993-8.
- 9 4. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature
- 10 **2021**; 594:259-64.
- 15. Havervall S, Rosell A, Phillipson M, et al. Symptoms and Functional Impairment Assessed 8 Months
- 12 After Mild COVID-19 Among Health Care Workers. JAMA **2021**; 325:2015-6.
- 13 6. Morin L, Savale L, Pham T, et al. Four-Month Clinical Status of a Cohort of Patients After
- 14 Hospitalization for COVID-19. JAMA **2021**; 325:1525-34.
- 15 7. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from
- 16 hospital: a cohort study. Lancet **2021**; 397:220-32.
- 17 8. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term
- 18 effects of COVID-19. Available at: <u>https://www.nice.org.uk/guidance/NG188</u>. Accessed on: 18 Apr 2022.
- 19 9. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi
- 20 consensus, 6 October 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-
- 21 <u>Post\_COVID-19\_condition-Clinical\_case\_definition-2021.1</u>. Accessed on: 18 Apr 2022.
- 22 10. Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to
- 23 SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. JAMA 2020;
- 24 324:2251-2.

- 1 11. Nabavi N. Long covid: How to define it and how to manage it. BMJ **2020**; 370:m3489.
- 2 12. Sivan M, Taylor S. NICE guideline on long covid. BMJ **2020**; 371:m4938.
- 3 13. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell
- 4 **2022**; 185:881-95.e20.
- 5 14. Cervia C, Zurbuchen Y, Taeschler P, et al. Immunoglobulin signature predicts risk of post-acute
- 6 COVID-19 syndrome. Nat Commun **2022**; 13:446.
- 7 15. Groff D, Sun A, Ssentongo AE, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-
- 8 CoV-2 Infection: A Systematic Review. JAMA Netw Open 2021; 4:e2128568.
- 9 16. Centers for Disease Control and Prevention. Post-COVID conditions. Available
- 10 at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed on: 4 Apr
- 11 2022.
- 12 17. Reese H, Iuliano AD, Patel NN, et al. Estimated incidence of COVID-19 illness and hospitalization -
- 13 United States, February-September, 2020. Clin Infect Dis **2020**.
- 14 18. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New
- 15 York State. N Engl J Med **2020**; 383:347-58.
- 16 19. Office for National Statistics. Coronavirus (COVID-19) Infection Survey: methods and further
- 17 information. Available
- 18 at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseas
- 19 <u>es/methodologies/covid19infectionsurveypilotmethodsandfurtherinformation</u>. Accessed on: 18 Apr
- 20 2022.
- 20. Office for National Statistics. Estimated percentage of study participants aged 18 years or over with
- 22 activity-limiting self-reported long COVID at various intervals after infection by age group, sex and
- 23 symptomatic status at infection, UK: 26 April 2020 to 1 August 2021. Available
- 24 at: <u>https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseas</u>

- 1 <u>es/adhocs/14286estimatedpercentageofstudyparticipantsaged18yearsoroverwithactivitylimitingselfrep</u>
- 2 ortedlongcovidatvariousintervalsafterinfectionbyagegroupsexandsymptomaticstatusatinfectionuk26apri
- 3 <u>l2020to1august2021</u>. Accessed on: 29 Mar 2022.
- 4 21. Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, Crespo M, Poveda E, Institute CC-otGSHR.
- 5 Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a
- 6 prospective cohort study. Sci Rep **2022**; 12:3369.
- 7 22. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and
- 8 evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-
- 9 19. PLoS Med **2021**; 18:e1003773.
- 10 23. Jones JM, Stone M, Sulaeman H, et al. Estimated US Infection- and Vaccine-Induced SARS-CoV-2
- 11 Seroprevalence Based on Blood Donations, July 2020-May 2021. JAMA **2021**; 326:1400-9.
- 12 24. Ayoubkhani D, Bermingham C, Pouwels KB, et al. Trajectory of long covid symptoms after covid-19
- 13 vaccination: community based cohort study. BMJ **2022**; 377:e069676.
- 14 25. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines
- against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective
- 16 observational study. BMJ **2022**; 376:e069761.
- 17 26. Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2
- 18 omicron variant in South Africa: a data linkage study. Lancet **2022**; 399:437-46.
- 19 27. Madhi SA, Kwatra G, Myers JE, et al. Population Immunity and Covid-19 Severity with Omicron
- 20 Variant in South Africa. N Engl J Med **2022**.
- 21 28. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-
- 22 CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested,
- case-control study. Lancet Infect Dis **2022**; 22:43-55.

- 1 29. Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Beiruti Wiegler K, Abu Jabal K, et al. Association between
- 2 vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional
- 3 study of patients tested between March 2020 and November 2021. medRxiv 2022.01.05.22268800; doi:
- 4 <u>https://doi.org/10.1101/2022.01.05.22268800</u>.
- 5 30. Ayoubkhani D, Bosworth ML, King S, et al. Risk of long Covid in people infected with SARS-CoV-2
- 6 after two doses of a COVID-19 vaccine: community-based, matched cohort study. medRxiv
- 7 2022. 02.23.22271388; doi: https://doi.org/10.1101/2022.02.23.22271388;
- 8 31. The White House. FACT SHEET: The Biden administration accelerates whole-of-government effort to
- 9 prevent, detect, and treat long COVID. Available at: <u>https://www.whitehouse.gov/briefing-</u>
- 10 room/statements-releases/2022/04/05/fact-sheet-the-biden-administration-accelerates-whole-of-
- 11 <u>government-effort-to-prevent-detect-and-treat-long-covid/</u>. Accessed on: 18 Apr 2022.
- 12 32. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic
- 13 Review. Ann Intern Med **2021**; 174:655-62.
- 14 33. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of
- 15 asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis.
- 16 PLoS Med **2020**; 17:e1003346.
- 17 34. Bangash MN, Owen A, Alderman JE, Chotalia M, Patel JM, Parekh D. COVID-19 recovery: potential
- 18 treatments for post-intensive care syndrome. Lancet Respir Med **2020**; 8:1071-3.
- 19 35. Scobie HM, Johnson AG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations,
- and Deaths, by Vaccination Status 13 U.S. Jurisdictions, April 4-July 17, 2021. MMWR Morb Mortal
  Wkly Rep **2021**; 70:1284-90.
- 36. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med **2021**;
- 23 27:626-31.

- 1 37. Bai F, Tomasoni D, Falcinella C, et al. Female gender is associated with long COVID syndrome: a
- 2 prospective cohort study. Clin Microbiol Infect **2021**.
- 3 38. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19
- 4 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med
- 5 **2021**; 9:1275-87.
- 6 39. Viner R, Hotopf M. Childhood predictors of self reported chronic fatigue syndrome/myalgic
- 7 encephalomyelitis in adults: national birth cohort study. BMJ 2004; 329:941
- 8 40. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-
- 9 19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395:1054-62.
- 10 41. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post
- 11 COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review. J Infect Dis **2022**.

- **Table 1.** Steps and key underlying assumptions used to model estimates of prevalence of activity-
- 2 limiting post-COVID conditions among US adults on November 1, 2021

Step in Estimation Process	Key Assumptions
Use 26,606,924 LL records for survivors of SARS-	Those classified as hospitalized and asymptomatic
CoV-2 infection among those ≥ 18 years of age	were not hospitalized for SARS-CoV-2 infection.
into strata defined by date of infection in 2-	Missing information on hospitalization and symptom
month intervals, sex, age group, and severity of	status can be imputed based on LL data for which
acute infection (i.e., hospitalization/symptom	these data are available.
status).	Persons with LL records missing hospitalization
	status are more likely not to have been hospitalized
	than those with records in which hospitalization
	status is documented.
	Persons with LL records missing symptom status
	(asymptomatic/symptomatic) are more likely to be
	asymptomatic that those with records in which
	symptom status is documented.
	Reinfections comprise a negligible proportion of
	infections reported in the LL data.
Add estimated excess number of survivors <sup>†</sup> of	Excess numbers of survivors of confirmed SARS-CoV-
infection reported to CDC in $\operatorname{aggregate}^{\$}$ form to	2 infections reported to CDC can be estimated as the
LL stratum-specific infection counts to obtain	difference in counts of survivors of infection
total confirmed SARS-CoV-2 infections reported	between the aggregate and LL data in jurisdictions
to CDC from February 2020 through September	where both LL and aggregate data are reported.
2021 in strata of 2-month date of infection	Sex, age group, and hospitalization/symptom status

interval, sex, age group, and severity of acute	for additional survivors of infection reported in
infection (i.e., hospitalized, non-hospitalized	aggregate data can be imputed using the
symptomatic, and non-hospitalized	distribution of infections across these strata
asymptomatic).	observed in the LL data.
	Reinfections comprise a negligible proportion of
	infections reported in the aggregate data.
Apply stratum-specific probabilities of reporting	Responses from UK CIS participants are
PCC that limits daily activities from the UK	representative of responses that would be expected
Coronavirus Infection Survey (CIS) data to the	if the survey was conducted among US residents
appropriate stratum-specific infection counts	with confirmed SARS-CoV-2 infection who were
reported to CDC.	infected between February 2020 and September
	2021.
	Those who were hospitalized for COVID have a
	probability of having PCC that is 1.5 to 3.5 times
	greater [4], regardless of time since infection, than
	the risk for those with an infection that was
	symptomatic but did not require hospitalization.
* Line listed data are comprised of an individual re-	ord for each reported infection. Date of testing age

- 1 \* Line listed data are comprised of an individual record for each reported infection. Date of testing, age
- 2 group, and hospitalization and symptom status are either recorded or reported as missing on each
- 3 record.
- 4 <sup>+</sup> Sum of aggregate reported infections minus reported aggregate deaths within 2-month time of
- 5 infection intervals.
- 6 <sup>§</sup> Reported to CDC as aggregate counts of infections and deaths, by date.

- 1 **Table 2.** Estimated point prevalence of the number of adults in the United States with activity-limiting
- 2 post-COVID conditions (PCC), November 1, 2021

С
3
-

	Cumulative reported	PCC Cases		
	SARS-CoV-2 infections that occurred through			R
	9/30/21	R'		
	N, millions	N, millions (95%	% of infected (95%	% of adult
		UI)	UI)	population
				(95% UI)*
Total	36.3	3.0 - 5.0	8.3 - 13.8	1.2 – 1.9
Sex				
Male	17.1	1.2 – 2.1	6.8 - 12.4	0.9 – 1.7
Female	19.2	1.8 – 2.9	9.5 – 15.3	1.4 – 2.2
Age, years				
18-49	23.1	1.5 – 2.4	6.5 – 10.3	1.1 – 1.7
50-64	8.3	1.0 - 1.6	11.8 - 19.7	1.5 – 2.5
≥65	5.0	0.5 – 1.1	9.6 - 21.7	0.9 – 2.0

4 Abbreviations: UI = uncertainty interval

5 \* https://www.census.gov/data/tables/2020/demo/popest/2020-demographic-analysis-tables.html

- **Table 3.** Estimated number of adults in the United States with activity-limiting post-COVID conditions
- 2 (PCC) under sensitivity analyses, November 1, 2021
- 3

	Cumulative reported SARS-CoV-2 infections		PCC Cases	R
	that occurred through			
	9/30/21			
	N, millions	N, millions (95%	% of infected (95%	% of adult
		UI)	(11)	population
				$(95\% \text{ UI})^+$
Sensitivity analysis	1. Adjusting for under-asc	ertainment of infect	tions	
Total	61.3 - 90.6*	4.3 - 9.7	6.4 - 11.5	1.7 – 3.8
Sex				
Male	28.9 - 42.6	1.7 – 4.0	5.2 - 10.1	1.3 - 3.2
Female	32.4- 48.0	2.7 – 5.7	7.4 – 12.7	2.0 - 4.4
Age, years	$\mathbf{O}$			
18-49	38.5 – 57.8	2.2 – 4.9	5.1 – 9.0	1.6 – 3.5
50-64	13.9 – 21.3	1.4 - 3.1	9.1 - 16.3	2.3 – 4.9
≥65	8.3 – 12.6	0.7 – 1.7	7.0 - 16.3	1.3 - 3.2
Sensitivity analysis	2. Assuming decrease in ri	sk of PCC >6 month	s post-infection	
Total	36.3	2.2 - 4.2	6.2 - 11.6	0.9 - 1.6
Sex				
Male	17.1	0.9 - 1.8	5.1 – 10.3	0.7 – 1.4

Female	19.2	1.4 – 2.4	7.1 – 12.8	1.0 1.9
Age, years				
18-49	23.1	1.1 – 2.0	5.0 - 8.7	0.8 - 1.4
50-64	8.3	0.7 – 1.3	8.7 – 16.2	1.1 - 2.1
≥65	5.0	0.4 - 0.9	7.1 – 17.7	0.7 - 1.6

- 1 Abbreviations: UI = uncertainty interval
- 2 \* Uncertainty intervals are presented for the reported SARS-CoV-2 infection counts in sensitivity analysis

3 1 to reflect estimation of these values under assumed under-ascertainment of the true number of

- 4 infections.
- 5 <sup>+</sup> https://www.census.gov/data/tables/2020/demo/popest/2020-demographic-analysis-tables.html

- 1 Figure 1. Number of SARS-CoV-2 infections among adults reported to CDC from February 2020 –
- 2 September 2021\*, by two-month intervals of time of infection<sup>+</sup> and infection severity
- 3 \* 95% uncertainty intervals for number of infections within severity strata reflect imputation performed
- 4 due to missing data.
- 5 <sup>+</sup> The date of SARS-CoV-2 clinical testing was assumed to be equivalent to the date of infection.
- 6 Figure 2. Percent of CIS participants with confirmed SARS-CoV-2 infection reporting long-term COVID-19
- 7 symptoms that limit daily activities; by age, days since infection, and infection severity status\*
- 8

9

Abbreviations: CIS = UK Coronavirus Infection Survey; NH = non-hospitalized

10 \* Estimates do not include the probability of having activity-limiting PCC among adults hospitalized for

11 acute SARS-CoV-2 infection, which was generated using multipliers estimating a 1.5-3.5 relative risk of

- 12 activity-limiting symptoms in hospitalized adults compared to symptomatic adults who were not
- 13 hospitalized.

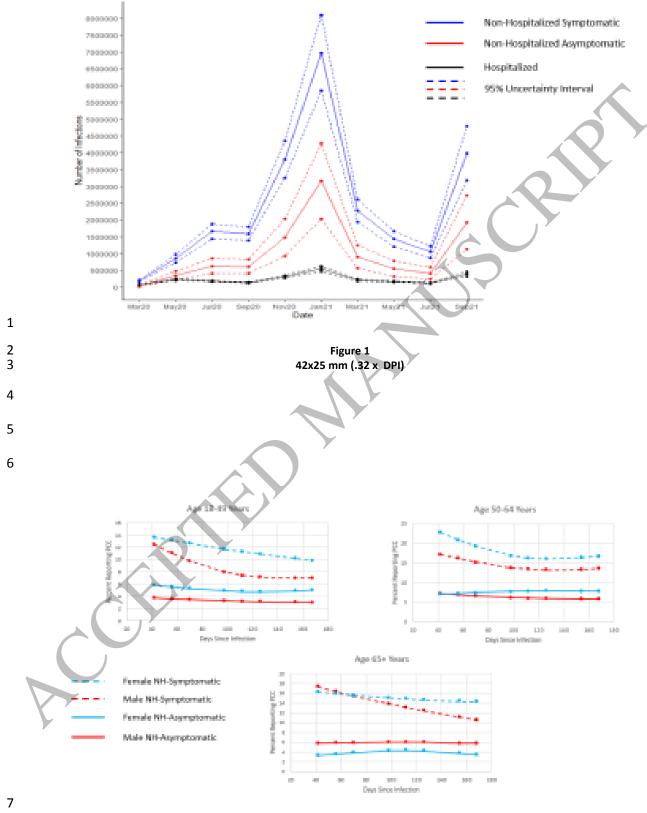




Figure 2 41x23 mm (.32 x DPI)