

Impact of long COVID on health-related quality-of-life: an OpenSAFELY population cohort study using patient-reported outcome measures (OpenPROMPT)



Oliver Carlile,^{a,*} Andrew Briggs,^a Alasdair D. Henderson,^a Ben F. C. Butler-Cole,^b John Tazare,^a Laurie A. Tomlinson,^a Michael Marks,^{a,e,f} Mark Jit,^a Liang-Yu Lin,^a Chris Bates,^c John Parry,^c Sebastian C. J. Bacon,^b Iain Dillingham,^b William A. Dennison,^d Ruth E. Costello,^a Alex J. Walker,^b William Hulme,^b Ben Goldacre,^b Amir Mehrkar,^b Brian MacKenna,^b The OpenSAFELY Collaborative, Emily Herrett,^{a,g} and Rosalind M. Eggo^{a,g}



^aLondon School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

^bBennett Institute for Applied Data Science, Nuffield Department of Primary Care Health Sciences, University of Oxford, OX2 6GG, UK

^cTPP, TPP House, 129 Low Lane, Horsforth, Leeds, LS18 5PX, UK

^dPatient and Public Involvement Steering Committee, London, UK

^eHospital for Tropical Diseases, University College London Hospital, London, WC1E 6JD, UK

^fDivision of Infection and Immunity, University College London, London, WC1E 6BT, UK

Summary

Background Long COVID is a major problem affecting patient health, the health service, and the workforce. To optimise the design of future interventions against COVID-19, and to better plan and allocate health resources, it is critical to quantify the health and economic burden of this novel condition. We aimed to evaluate and estimate the differences in health impacts of long COVID across sociodemographic categories and quantify this in Quality-Adjusted Life-Years (QALYs), widely used measures across health systems.

Methods With the approval of NHS England, we utilised OpenPROMPT, a UK cohort study measuring the impact of long COVID on health-related quality-of-life (HRQoL). OpenPROMPT invited responses to Patient Reported Outcome Measures (PROMs) using a smartphone application and recruited between November 2022 and October 2023. We used the validated EuroQol EQ-5D questionnaire with the UK Value Set to develop disutility scores (1-utility) for respondents with and without Long COVID using linear mixed models, and we calculated subsequent Quality-Adjusted Life-Months (QALMs) for long COVID.

Findings The total OpenPROMPT cohort consisted of 7575 individuals who consented to data collection, with which we used data from 6070 participants who completed a baseline research questionnaire where 24.6% self-reported long COVID. In multivariable regressions, long COVID had a consistent impact on HRQoL, showing a higher likelihood or odds of reporting loss in quality-of-life (Odds Ratio (OR): 4.7, 95% CI: 3.72–5.93) compared with people who did not report long COVID. Reporting a disability was the largest predictor of losses of HRQoL (OR: 17.7, 95% CI: 10.37–30.33) across survey responses. Self-reported long COVID was associated with an 0.37 QALM loss.

Interpretation We found substantial impacts on quality-of-life due to long COVID, representing a major burden on patients and the health service. We highlight the need for continued support and research for long COVID, as HRQoL scores compared unfavourably to patients with conditions such as multiple sclerosis, heart failure, and renal disease.

Funding This research was supported by the National Institute for Health and Care Research (NIHR) (OpenPROMPT: COV-LT2-0073).

Copyright © 2024 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Long COVID; HRQoL; QALY; PROMs

The Lancet Regional Health - Europe
2024;40: 100908
Published Online xxx
<https://doi.org/10.1016/j.lanepe.2024.100908>

*Corresponding author.

E-mail address: oliver.carlile@lshtm.ac.uk (O. Carlile).

^gMarks equal contribution.

Research in context**Evidence before this study**

We searched for research published between 1st January 2020 and 1st November 2023, published in English, for the Title/Abstract terms (Post COVID-19 syndrome, PCS, long COVID, post-acute-covid-19) AND (quality-adjusted life-years, QALYs) with only 3 results. 1 described a theoretical framework, 1 estimated cost-effectiveness of COVID-19 self-testing, and 1 estimated the morbidity burden attributable to long COVID symptoms compared to death. Long term assessment to patients hospitalised with acute COVID-19 has been reported, but relatively little research has been conducted across the general population. It is also not known how long COVID affects different patient demographics despite evidence socioeconomically deprived individuals are more likely to report long COVID.

Added value of this study

Utilising a combination of patient-reported measures and historically recorded data in medical records highlights disparities that exist in long COVID. 24.6% of respondents

self-reported long COVID, with fewer than 10% having any recorded diagnosis in electronic records. Few studies previously estimated the impact of long COVID on quality-adjusted life-years. By comparing resulting quality-adjusted life-months to participants who do not self-report long COVID emphasises the 0.37 QALM loss of HRQoL due to long COVID. Self-reported long COVID was associated with worse EQ-5D-5L utility scores than patients experiencing heart failure, multiple sclerosis and end-stage renal disease.

Implications of all the available evidence

Highest quality-adjusted life loss being reported in individuals who will participate in the workforce for longer requires further research on the associated economic costs. The limited recovery of participants affected by long COVID over three months highlights where policymakers need to support individuals. Targeted interventions with randomised controlled trials may help to provide a positive outlook specifically for a subset of individuals who have been heavily impacted by long COVID for multiple months and years.

Introduction

Following infection by SARS-CoV-2, the majority of patients will recover within 4 weeks but 10–15% do not, and may face significant impacts on their health-related quality-of-life (HRQoL).¹ The National Institute for Health and Care Excellence (NICE) in the UK developed three clinical definitions for the effects following infection: ‘acute COVID-19’ for signs and symptoms of COVID-19 between 0 and 4 weeks, ‘ongoing symptomatic COVID-19’ for symptoms between 4 and 12 weeks, and ‘post COVID-19 syndrome’ with symptoms persisting 12 weeks or longer not explained by an alternative diagnosis.² The latter two definitions refer to long COVID.

Persistent symptoms reported to occur after infection are wide-ranging, with the most common being fatigue, shortness of breath, muscular, joint and chest pains, headaches, persistent cough, and altered senses of smell and taste.³ As of 2nd January 2023, the Office for National Statistics figures for the prevalence of self-reported long COVID estimated 2 million people in the UK were experiencing symptoms persisting longer than four weeks, not explained by other diagnoses. An estimated 1.5 million people (77%) with self-reported long COVID reported symptoms adversely affected day-to-day activities, and 380,000 (19%) reported ability to undertake day-to-day activities had been ‘limited a lot’.⁴ With an estimated 22.2 million UK cases of COVID-19 as of May 2022, the burden of long COVID may be wide ranging for the NHS.⁵ With the extensive symptoms of long COVID, the impact on HRQoL can be significant, with Walker et al.⁶ estimating EQ-5D scores

among patients referred to post-COVID clinics in England and Wales were worse than those among patients with metastatic cancers.

Few studies have assessed Quality-Adjusted Life Years (QALYs) attributable to long COVID as most focused on the effect of acute COVID-19 on HRQoL. Sigfrid et al.,⁷ examined EQ-5D-5L survey results in the UK at least 90 days after suspected SARS-CoV-2 hospitalisation between 17th January to 5th October 2020. 54% reported they had not fully recovered at time of follow-up, with 93% reporting persistent symptoms. Previous studies of QALYs lost due to COVID were limited to small numbers of respondents, for example in Sandmann et al.⁸ estimating losses for 548 positive cases against a control group of 651 respondents, and have not explored inequalities by patient characteristics.

This study addresses this gap, specifically identifying the impact of long COVID, the contribution of symptom-specific Patient Reported Outcomes Measures (PROMs) to assessment of quality-of-life, and aims to quantify how this results in QALY losses.

Methods**OpenPROMPT**

We conducted a cohort study using *Airmid*, the in-house smartphone application of TPP, which is the software provider for 34% of all primary care providers in England.⁹ Full details of the study protocol and methods have been previously published.¹⁰ All adults in England were eligible to take part in OpenPROMPT, if they could

understand English and had a smartphone. Advertising for participants was done using social media, and through general practices. Therefore it is not possible to give the numbers eligible or invited.¹⁰ Participants were requested to fill questionnaires in 30-day intervals: day 0 (the point of enrolment in the study), then days 30, 60, and 90. Survey responses were categorised as falling in these points of time if completed within 5 days of the 30-day intervals. There was also a questionnaire at recruitment collecting demographic information. Recruitment took place between November 11th 2022 and July 31st 2023.

The questionnaires consisted of existing validated PROMS which covered a range of themes, with the EuroQol EQ-5D-5L the primary outcome measure for this study. To assess the impact of long COVID on other aspects of HRQoL, symptom specific questionnaires were used including the Medical Research Council (MRC) Dyspnoea breathlessness Scale¹¹ and Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F Fatigue) Scale.¹² Patient-reported responses to OpenPROMPT questionnaires were automatically linked to primary care records managed by TPP SystemOne if the patient was registered at a practice using TPP software, and were stored in the patient health record. We accessed these data via the OpenSAFELY research platform, where all data were linked, stored and analysed securely (<https://opensafely.org/>). All data, including coded diagnoses, medications and physiological parameters, are pseudonymised. No free text data were included.

Due to the difficulties in assessing history of long COVID from medical records, the experience of COVID-19 required a specific questionnaire.¹³ Patients were defined as self-reporting long COVID if they responded both “No I still have symptoms” to the question “Thinking of your last episode of COVID-19, have you now recovered to normal?” and secondly that symptoms lasted either 4–12 weeks, or more than 12 weeks to the question “How long have you had/did you have COVID-19 symptoms overall?”. Participants missing responses to both these questions were defined as not stated.

This study had patient and public involvement from an advisory panel of three individuals with different experiences of long COVID which we met with every 6 months. To obtain feedback on the study, separate PPI events were held in January and September 2023. LSHTM developed a website with information about OpenPROMPT, how to take part and how to contact us regarding the project.¹⁴ OpenSAFELY have developed a publicly available website (<https://opensafely.org/>) through which we invite any patient or member of the public to contact us regarding this study or the broader OpenSAFELY project.

Participant demographics and comorbidities

Participant characteristics were collected through the recruitment questionnaire and linked clinical records.

OpenSAFELY contains electronic health records (EHRs) drawn from primary, secondary care (inpatient, outpatient, emergency) and all prescriptions, allowing in-depth assessment of patient comorbidities. The presence of pre-existing comorbidities at baseline survey response was based upon previous research within OpenSAFELY on fifteen chronic comorbidities¹⁵ (Supplementary Table S1). To estimate socioeconomic status, we used the 2019 Index of Multiple Deprivation (IMD) for participants based on their postcode address. The IMD is a measure using weightings across domains of income, employment, health, education, crime, housing and services, and the living environment to measure deprivation at Lower Super Output Area, neighbourhoods of roughly 1000–3000 people.¹⁶ Specific assessments on the impact of COVID-19 were collected from EHRs, including diagnosis or referral codes for long COVID. The recruitment questionnaire collected ethnicity, education level, and annual household incomes. Age, in bands of 18–29, 30–39, 40–49, 50–59, 60–69, and 70+, sex and NHS region were extracted from the patients EHRs.

Outcomes

The EQ-5D-5L is a standardised measure widely used to collect information on HRQoL across interventions and conditions.¹⁷ It asks respondents to describe their health on that day, covering five dimensions of quality-of-life: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has five possible responses: level 1: no problems, level 2: slight problems, level 3: moderate problems, level 4: severe problems, and level 5: extreme problems/unable to. Responses return a five-digit descriptive code for health state (e.g., 14,523).

Secondary symptom specific PROMS were collected on Fatigue using the FACIT-F scale. Participants responded to 13 statements related to daily functioning and activities with a 7 day recall period. There are five possible responses to each statement: not at all: a value of 0, a little bit: value 1, somewhat: value 2, quite a bit: value 3, and very much: a value of 4. These are summed across the 13 statements, with a highest possible score of 52 indicating severe fatigue.

We assessed breathlessness using the MRC Dyspnoea Scale, which records the degree of breathlessness relating to daily activities with no recall period. The scale defines grade 1 as mild, grades 2–3 as moderate, and grades 4–5 as severe breathlessness, producing a descriptive score between 1 and 5.

EuroQol EQ-5D score

To estimate EQ-5D score, we used the EuroQol mapping function defined within Hernández Alava et al.,¹⁸ to obtain utility values from the three level (3 L) UK value set by mapping to the five level (5 L) format collected in OpenPROMPT using a development of the van Hout¹⁹

crosswalk function. The value set for the UK is derived from population-based studies of valuation for health states using time-trade-off, resulting in a preference based score for each health state. Perfect health with no problems in any dimensions of quality-of-life (i.e., 11,111) returns a score of 1, with death anchored at zero and states deemed worse than death returning negative scores, with a minimum possible score of -0.594 . We used the utility score to generate disutility (1- EQ5D utility) as the lost quality-of-life from a perfect health state. Only data which was linked to TPP medical records were used, as the mapping function requires age to derive utility scores. We excluded participants from analysis who self-defined as non-binary gender because the function accounts for only male/female responses. Scores were compared to the population norms estimated in McNamara et al.,²⁰ for the English population.

Statistical analysis

HRQoL EQ-5D disutility score

We used multivariable regression models for the impact of long COVID on loss of utility from perfect health, referred to as disutility and measured as 1 minus the EQ-5D-5L utility value. To handle individuals with no alteration to HRQoL, we used a two-part model, first modelling the probability of any impact on quality-of-life and secondly the effect on quality-of-life. The first part of the model was a mixed effect logistic regression on the probability of returning disutility greater than zero, indicating loss of HRQoL, with adjustment for within-participant correlation of EQ-5D-5L responses across surveys. The second part of the model employed mixed effects linear models on absolute disutility scores. Missing data were assumed to be missing at random, dependent on the covariates included in the regressions. Models were adjusted for demographic indicators including age, sex, ethnicity and IMD quintiles, and used to assess the impact of variables such as household income, education and previous COVID hospitalisations on the outcome by inclusion in the mixed models. We compared adjusted models including baseline scores as part of the covariate vector, but due to the large proportion of the cohort completing only a baseline set of questionnaires, reported models have baseline scores as part of the outcome vector. With the large proportion of missing questionnaire responses over time, we used multiple imputation by chained equations on the study variables for participants who had completed at least one set of questionnaire.²¹ EQ-5D-5L responses were imputed at the domain level.

Subsequent models included the secondary PROMs (MRC-Dyspnoea Scale and FACIT-F scores) to explore their contribution to long COVID related losses in HRQoL. To match the relationship with disutility, we reversed the FACIT-F scores. With a maximum possible score of 52, higher values now indicate greater fatigue. We sequentially added the PROMs in a stepwise

approach and assessed if overall model fit was improved based on the Akaike Information Criterion (AIC). This assessed the extent with which PROMs on symptom-specific issues influenced the overall HRQoL measured by EQ-5D-5L.

Quality-adjusted life-years (QALYs)

Using results from the longitudinal EQ-5D-5L survey responses, we extrapolated the responses to estimate the QALYs lost due to long COVID. QALYs were calculated using the area under the curve method at individual level using disutility scores.²² The relationship between utility scores over time assumes linearity given the short duration between EQ-5D-5L measurements. Because respondents reported HRQoL for less than 12 months, we did not apply discounting to the total QALYs. The results are shown in quality-adjusted life-months (QALMs) which do not reshape the time aspect of QALYs in terms of years.

QALM losses using a complete case analysis for completion of all surveys were compared to available case analysis. We also separated by a long COVID diagnosis in the participant's EHRs, with consistent evidence that individuals heavily impacted are more likely to respond in data collection.²³ We conducted linear regression models to assess associations between total QALMs lost, adjusting for age, sex, disability, the number of comorbidities and baseline utility.

Data management was performed using Python 3 in OpenSAFELY, with analysis conducted using Stata version 16.1. Code for data management and analysis, as well as codelists are online ([opensafely/openprompt-hrqol \(github.com\)](https://opensafely.github.com/hrqol)).

Ethics

This research is part of the OpenPROMPT study "Quality-of-life in patients with long COVID: harnessing the scale of big data to quantify the health and economic costs" which has ethical approval from HRA and Health and Care Research Wales (HCRW) (IRAS project ID 304354). The Study Coordination Centre has obtained approval from the LSHTM Research Ethics Committee (ref 28,030), as well as a favourable opinion from the South Central-Berkshire B Research Ethics Committee (ref 22/SC/0198). Full ethical approval details are available online ([Supplementary Methods](#)).

Role of the funding source

This work is independent research funded by the National Institute for Health and Care Research (NIHR) [OpenPROMPT: COV-LT2-0073]. The OpenSAFELY Platform is supported by grants from the Wellcome Trust (222097/Z/20/Z) and MRC (MR/V015737/1, MC_PC_20059, MR/W016729/1). In addition, development of OpenSAFELY has been funded by the Longitudinal Health and Wellbeing strand of the National Core Studies programme (MC_PC_20030:

MC_PC_20059), the NIHR funded CONVALESCENCE programme (COV-LT-0009), NIHR (NIHR135559, COV-LT2-0073), and the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (grant ref MC_PC_20058) and Health Data Research UK (HDRUK2021.000).

The views expressed in this publication are those of the author(s) and not necessarily those of NIHR or The Department of Health and Social Care. Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Results

Descriptive analysis

Overall, 6070 participants with linked TPP EHRs completed the recruitment questionnaires and were included in the analysis. 61% were female, with a median age of 53 (IQR 43–62) and the majority of participants were White (5765/6045, 95%) (Table 1). 1495/3975 participants (24.6%) self-reported long COVID, but only 6% had a long COVID diagnosis in their EHR (Table 1). As not all questions were mandatory, we treated non-responses to both questions required for defining long COVID as not stated, corresponding to 2095/6070 (34.5%) participants.

705 respondents reported no problems across any dimensions of EQ-5D-5L at baseline survey. The distribution of EQ-5D disutility scores was positively skewed, with a small number (<50) having severe losses on HRQoL (Fig. 1a). The distribution of participant responses to each dimension of EQ-5D-5L shows greater impact of long COVID for anxiety and depression and pain and discomfort, with little impact on mobility and self-care (Fig. 1f).

Health-related quality-of-life

Participants self-reporting long COVID were highly likely to report loss of HRQoL compared to participants who did not report long COVID (OR 4.7 (3.72; 5.93) for returning a loss of HRQoL and 0.056 (0.04, 0.07) unit lower quality of life) (Fig. 2). The largest odds ratio for reporting a loss of HRQoL was for disability, but there were also associations with presence of comorbidities and gender. Coefficients for HRQoL loss were higher in those with comorbidities and with lower incomes (Fig. 2). Odds ratios for reporting any disutility and coefficients for disutility are given in Supplementary Table S2. Similar results were found when we compared the imputed models with a complete case analysis for individuals with no missing data (Supplementary Tables S4 and S5).

We found associations between the breathlessness and fatigue PROMs and HRQoL (Fig. 3). A unit increase

in FACIT-F, i.e., reporting higher levels of fatigue, is estimated to have an odds ratio of 1.19 (95% CI: 1.17; 1.22) for reporting loss in HRQoL. Severe grades of breathlessness (grades 4–5) were not significant in predicting loss of quality-of-life, compared to reporting no effect but caused substantial unit loss of HRQoL for participants who had reported loss of HRQoL, at 0.14 (0.1; 0.17) and 0.24 (0.19; 0.3) units respectively. After adjusting for breathlessness and fatigue, the remaining estimated reduction in HRQoL due to reported long COVID was lower. The OR fell from 4.7 (3.72; 5.93) to 1.46 (0.89; 2.38), with no effect on the unit loss of HRQoL.

Individual QALM losses

People who self-reported long COVID had lower utility scores for every month after recruitment (Fig. 4a). Comparing utility scores for participants across survey responses showed little variation with time for both long COVID and non-long COVID respondents.

We estimated QALMs using a linear regression model accounting for age, comorbidities, disability, baseline utility and sex, to show predicted QALMs by age group (Fig. 4b). As QALMs were generated using disutility scores, they follow the same relationship whereby higher QALMs indicates the respondent had worse HRQoL across timepoints. Lower ages represented the higher QALMs for both long COVID and recovered participants. Using the complete case approach, total QALMs for long COVID amounted to 0.81 compared to 0.44 for individuals who did not report long COVID. For available case data, QALMs amounted to 0.22 and 0.12 QALMs for long COVID and recovered participants respectively. At month 1, QALMs for long COVID respondents were between 0.25 and 0.26 and between months 2 and 3 this was between 0.17 and 0.28 (Table 2).

Discussion

We have shown the impact of self-reported long COVID on HRQoL using a novel cohort study, which linked PROMs directly to the patient's EHR. The mean EQ-5D score for those who self-reported long COVID was 0.49 compared to 0.71 among those without long COVID. The difference exceeds the 0.063 minimally important difference expected for EQ-5D-5L populations.²⁴ Reported disabilities and number of diagnosed comorbidities were also associated with lower quality-of-life. The burden of long COVID was greatest in the working-age population, with higher QALMs for respondents who will participate in the labour market for longer.^{18–40} Comparing the utility of the whole cohort to the population norms estimated in McNamara et al.,²⁰ quality-of-life scores were slightly lower for non-long COVID individuals in OpenPROMPT than the population norm score of between 0.798 for females and 0.836 for males for participants at the same age.

Variable	Study population N (%)	EQ-5D-5L completed N (%)	Long COVID N (%)
	N = 6070	N = 4630	N = 1495
Age^a			
18–29	475 (7.8)	375 (8.1)	130 (8.7)
30–39	915 (15.1)	725 (15.7)	295 (19.7)
40–49	1365 (22.5)	1065 (23)	440 (29.3)
50–59	1625 (26.8)	1230 (26.5)	400 (26.9)
60–69	1200 (19.8)	890 (19.3)	185 (12.5)
70+	490 (8.1)	345 (7.5)	45 (2.9)
Ethnicity^b			
White	5785 (95.4)	4430 (95.7)	1430 (95.5)
Mixed	85 (1.4)	65 (1.4)	25 (1.8)
Asian/Asian British	115 (1.9)	70 (1.5)	20 (1.5)
Black/African/Caribbean/Black British	30 (0.5)	25 (0.5)	0
Other/not stated	50 (0.8)	40 (0.9)	15 (0.9)
Sex^b			
Male	2055 (33.8)	1510 (32.6)	375 (24.9)
Female	3690 (60.8)	2880 (62.2)	1045 (70)
Intersex/non-binary/other/refused	325 (5.3)	240 (5.2)	75 (5.1)
Region^a			
East	1425 (23.5)	1110 (24)	340 (22.8)
East Midlands	1230 (20.3)	965 (20.8)	305 (20.3)
London	135 (2.2)	95 (2)	20 (1.5)
North East	260 (4.3)	210 (4.5)	75 (5.1)
North West	515 (8.5)	375 (8.1)	125 (8.4)
South East	395 (6.5)	310 (6.7)	105 (7)
South West	1000 (16.5)	755 (16.3)	240 (16.2)
West Midlands	185 (3)	130 (2.8)	45 (3.1)
Yorkshire and The Humber	920 (15.1)	685 (14.8)	235 (15.7)
Highest education^b			
Primary School/Less	30 (0.5)	20 (0.5)	0
Secondary/high school	1435 (23.6)	1075 (23.2)	335 (22.4)
College/University	3195 (52.7)	2475 (53.5)	835 (55.7)
Postgraduate qualification	1350 (22.3)	1015 (22)	305 (20.5)
Not stated	55 (0.9)	40 (0.9)	15 (0.9)
Household Income^b			
£6000–12,999	555 (9.2)	430 (9.3)	135 (9.2)
£13,000–18,999	515 (8.5)	410 (8.9)	160 (10.7)
£19,000–25,999	710 (11.7)	550 (11.9)	190 (12.8)
£26,000–31,999	625 (10.3)	470 (10.2)	160 (10.6)
£32,000–47,999	1060 (17.5)	780 (16.8)	230 (15.3)
£48,000–63,999	790 (13)	600 (13)	200 (13.4)
£64,000–95,999	645 (10.6)	490 (10.5)	135 (9)
£96,000 +	390 (6.4)	295 (6.3)	70 (4.5)
Not stated	780 (12.8)	605 (13)	215 (14.4)
IMD (quintiles)^a			
1st (most deprived)	920 (15.1)	705 (15.3)	280 (18.8)
2nd	1050 (17.3)	800 (17.3)	185 (19)
3rd	1215 (20.1)	940 (20.3)	290 (19.5)
4th	1215 (20)	930 (20)	275 (18.3)
5th (least deprived)	1375 (22.6)	1030 (22.2)	285 (19.2)
Missing	295 (4.8)	220 (4.8)	80 (5.2)
Disability^b			
No	3650 (60.1)	2765 (59.8)	690 (46.3)
Yes	2290 (37.7)	1770 (38.2)	765 (51)

(Table 1 continues on next page)

Variable	Study population N (%) N = 6070	EQ-5D-5L completed N (%) N = 4630	Long COVID N (%) N = 1495
(Continued from previous page)			
Not stated	130 (2.1)	95 (2)	40 (2.7)
Number of comorbidities^a			
0	3440 (56.7)	2615 (56.5)	775 (51.8)
1	2035 (33.5)	1575 (34)	580 (38.7)
2	470 (7.8)	355 (7.7)	115 (7.7)
3 +	125 (2)	85 (1.9)	25 (1.7)
Have you had COVID-19^b			
Yes (positive test)	3480 (57.3)	3480 (75.1)	1325 (88.5)
Yes (medical advice)	185 (3.1)	185 (4)	60 (3.9)
Unsure	105 (1.7)	105 (2.3)	15 (1)
No	725 (12)	725 (15.7)	0
Missing	1575 (25.9)	135 (2.9)	100 (6.6)
Number of COVID-19 episodes^b			
0	680 (11.2)	680 (14.7)	0
1	2120 (34.9)	2120 (45.8)	615 (41.1)
2	1295 (21.3)	1295 (28)	560 (37.4)
3 +	535 (8.8)	535 (11.6)	325 (21.5)
Missing	1440 (23.7)	0	0
COVID-19 Hospitalisation^a			
No	5890 (97.1)	4510 (97.4)	1425 (95)
Yes	180 (2.9)	120 (2.6)	75 (5)
Have you had a COVID-19 vaccine^b			
Yes	4510 (74.3)	4510 (97.4)	1450 (97)
No	120 (2)	120 (2.6)	45 (3)
Missing	1440 (23.8)	0	0
Number of long COVID records^a			
0	5710 (94.1)	4325 (93.4)	1235 (82.5)
1	180 (3)	160 (3.4)	130 (8.75)
2+	180 (2.9)	150 (3.2)	130 (8.75)

^aIndicates the use of EHRs. ^bIndicates questionnaire responses.

Table 1: Demographic characteristics reported in recruitment surveys and EHRs.

Sociodemographic groups of similar characteristics to our cohort appear more likely to respond to research related to long COVID.^{15,25} We found that when controlling for long COVID, participants at higher levels of socioeconomic status reported a substantially lower impact on HRQoL. Research on non-pandemic health-related conditions has found consistent inequalities across socioeconomic status, incurring higher associated medical costs, lower life expectancy and higher mortality in people of lower socioeconomic status.²⁶ To prevent similar relationships developing for long COVID, public health interventions should attempt to address the inequalities in order to prevent the gap widening following a global pandemic.

Together, breathlessness and fatigue appear to be major contributors for the decreased HRQoL attributable to long COVID, evidenced by the substantial reduction in odds ratios when FACIT-F and MRC Dyspnoea scales are included. This significant change indicates that EQ-5D may be unable to capture the

impact within the stated dimensions of quality-of-life in a population heavily impacted by both symptoms, especially where fatigue has been previously highlighted as the most persistent symptom impacting HRQoL.^{3,27} As suggested within Sandler et al.,²⁸ further assessment is needed in the interpretation of fatigue in post-COVID-19 syndrome when using EQ-5D measurements. Our results compare similarly to previous use of FACIT-F in a population of post-COVID-19 syndrome (PCS) patients, with a mean non-reversed F-score of 20.67 (SD: 12.12) slightly better than 19.6 in Walker et al.,⁶ both significantly lower than the population norm value of 43.5.²⁹

The EQ-5D quality-of-life index scores at baseline for self-reported long COVID participants in OpenPROMPT (0.49, SD: 0.31) were lower compared to some previous long COVID research. This is consistent across studies who have followed up patients referred to post-COVID syndrome clinics in the UK (mean 0.54, SD 0.26),⁶ online surveys completed in Belgium by self-

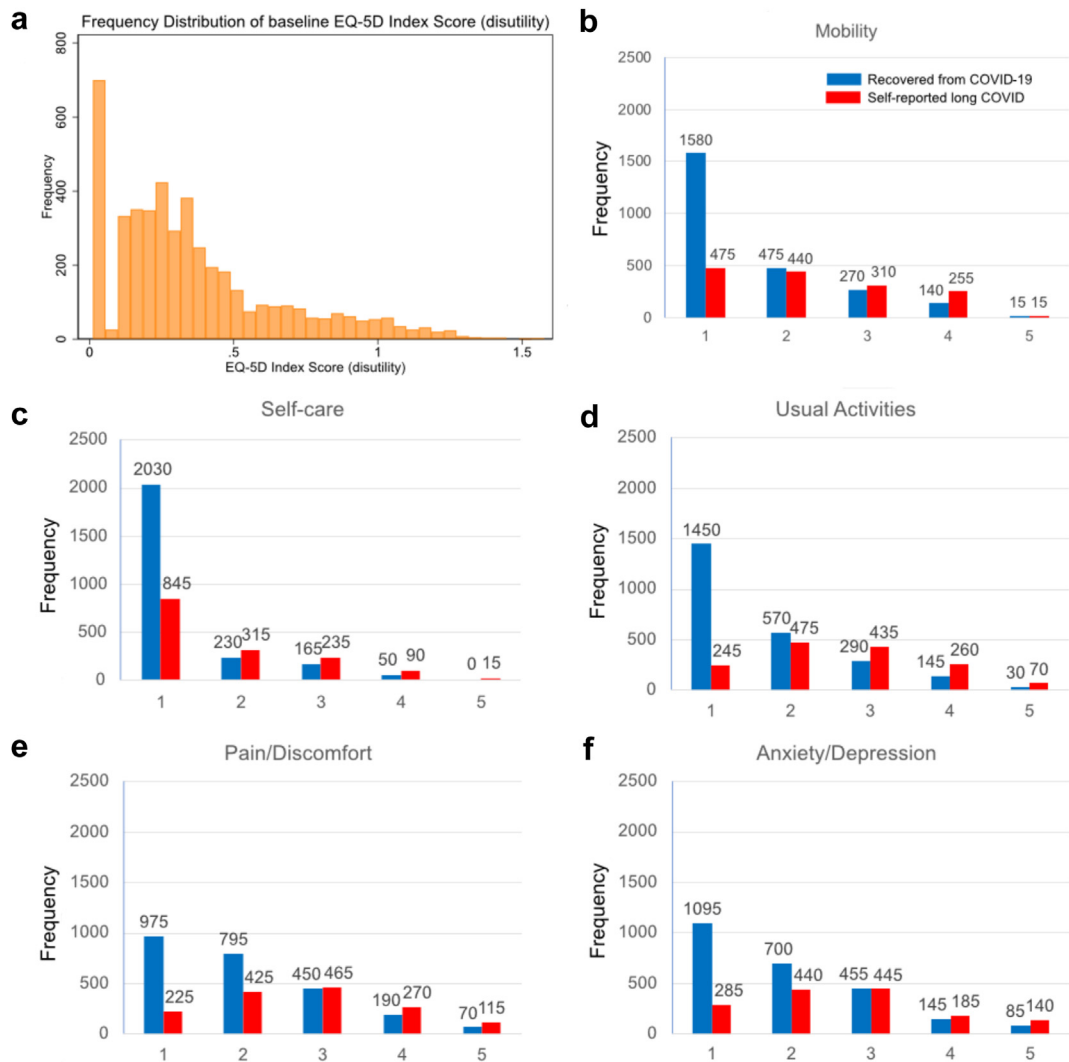
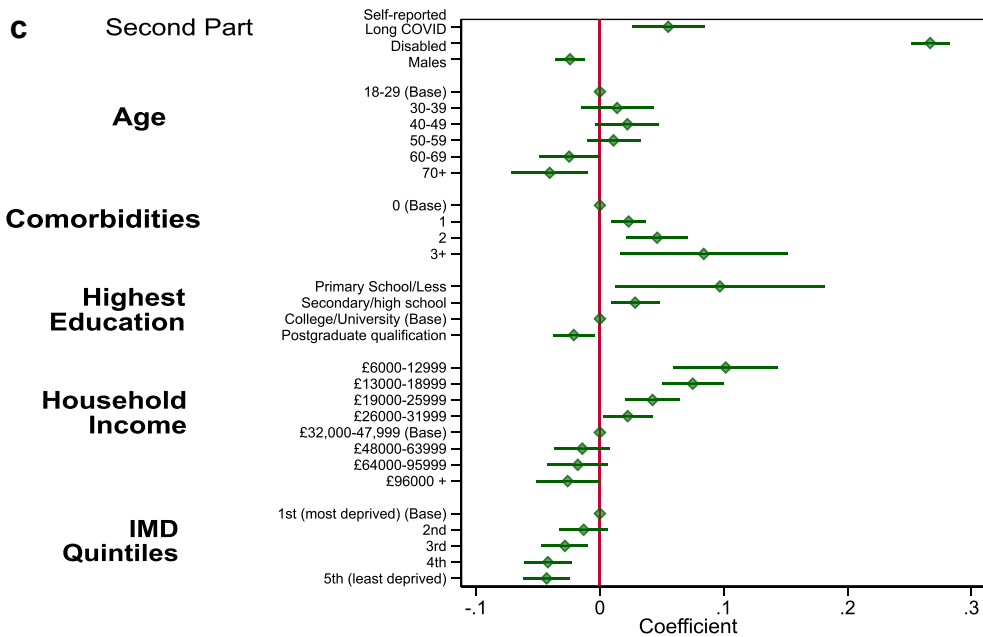
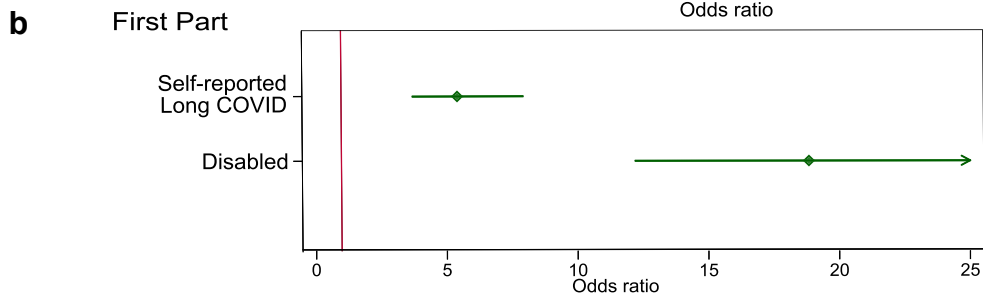
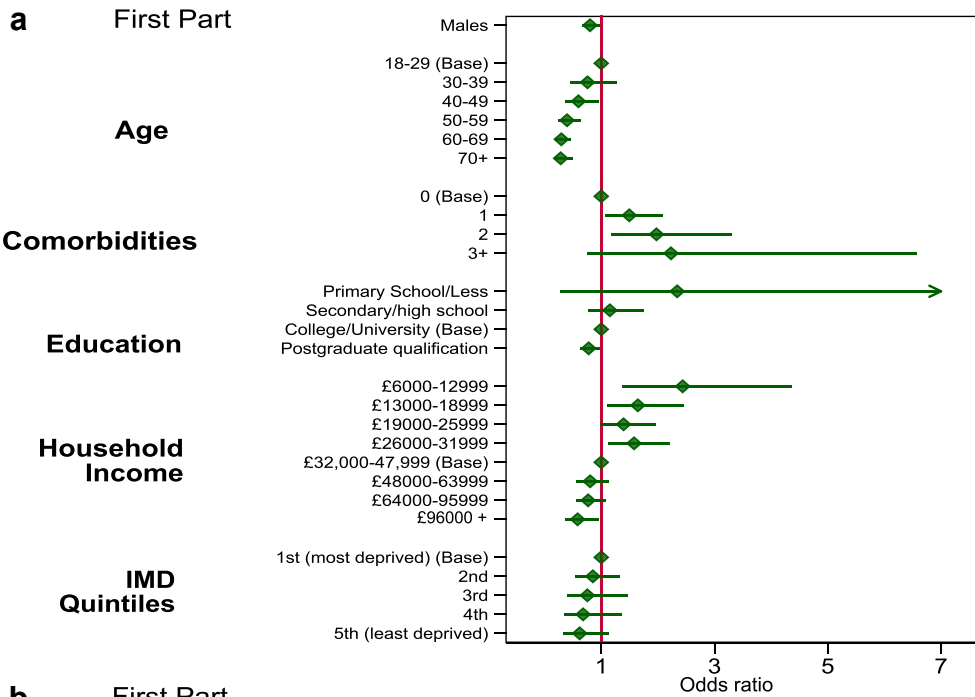


Figure 1: Self-reported quality of life measures. Responses are shown for the 3975 non-missing self-reported long COVID respondents for panels b-f. a) Frequency distribution of baseline EQ-5D-5L score (disutility), b) Mobility dimension of EQ-5D, c) Self-care dimension of EQ-5D, d) Usual activities dimension of EQ-5D. e) Pain/discomfort dimension of EQ-5D, f) Anxiety/depression dimension of EQ-5D. Each dimension has five possible responses: level 1: no problems, level 2: slight problems, level 3: moderate problems, level 4: severe problems, and level 5: extreme problems/unable to. Blue marks the participant did not report long COVID, and red that they did.

reported PCS patients (mean 0.57, SD 0.23),³⁰ and in previously hospitalised patients in Iran (mean 0.61, SD 0.006).³¹ EQ-5D index scores are similar to a study of patients defined as very severely impacted in physical and mental impairment by combining responses to symptom questionnaires and physical performance tests approximately 6 months after COVID-19 hospitalisation in the UK (mean 0.43, SD 0.27) which also highlighted the impact of a disability.³² Our results are therefore striking, supporting evidence from PPIE sessions where a subset of participants reported experiencing limited HRQoL over multiple years with little recovery.

To put in perspective the loss of HRQoL from long COVID, our results showed lower EQ-5D scores than from patients experiencing heart failure (mean 0.60),³³ multiple sclerosis (mean 0.59),³⁴ and end-stage renal disease (mean 0.68).³⁵ The significant difference we found compared to utility scores of individuals with chronic obstructive pneumonia disease (COPD) (mean 0.68)³⁶ which presents in similar symptoms to long COVID highlights the importance of continued support for patients reporting long COVID.

A key strength of this study was the linkage of PROMS with the EHR in OpenSAFELY. This allowed more granular research using the EHR with variables



such as income (which is not routinely available in EHRs), reduced the burden on participants of collecting extensive information about their medical history, and has enabled validation of collected data against the EHR, for example the number of COVID infections and hospitalisations. Combining patient responses in a trusted research environment directly into EHRs is a novel research method, with flexible tooling of questionnaires helping provide both additional information and demonstrating the convergence with medical histories. Our previous research demonstrated the difficulty of utilising only EHR data in long COVID research,^{13,37} and the present study shows further limitations of EHR data for this condition: fewer than 10% of the cohort had a recorded diagnosis of long COVID in their EHR, compared to roughly 25% self-reporting long COVID.³⁸ This has implications if patients are severely impacted by long COVID, but feel unable to fully interact with their primary healthcare.

Our cohort of 6070 respondents included in the analysis is larger than previous research on HRQoL in long COVID populations, with a higher proportion of self-reported long COVID respondents.^{6,39} By collecting information on HRQoL using the validated EuroQoL EQ-5D questionnaire, and using validated instruments on breathlessness and fatigue, we were able to determine the contribution of these symptoms to the impact on quality-of-life. However, measurement of other symptoms of long COVID (or their severity) were not included in the study. Patients self-reporting their condition may therefore raise the possibility that symptoms may be unrelated to long COVID. Given the difficulties associated with measuring fatigue in EQ-5D-5L, it is possible that other symptoms are not well suited to measurement across the five dimensions of HRQoL in a population affected by post-COVID-19 syndrome.

Advertising for the study was among the general population and long COVID groups. Importantly, the cohort was self-selected and therefore people with long COVID, or more severe long COVID, may have been more likely to participate. Conversely, those with the most severe long COVID may have been unable to participate due to their symptoms. This study faces a similar weakness to other recruited study cohorts investigating long COVID, whereby individuals of low socioeconomic deprivation are more likely to participate. Compared to the wider OpenSAFELY population, the OpenPROMPT cohort had higher representation of

individuals aged between 40 and 70, white participants, and participants in less deprived areas.^{38,40} Given our and other evidence⁴¹ there is a socioeconomic relationship with the risk of long COVID, the demographics of the cohort do not show this in the sample population. For example, we were unable to find any evidence on the impact of ethnicity on HRQoL due to the low numbers of non-white respondents. These factors may introduce selection bias and impact the generalisability of the findings to all long COVID patients, especially where excess deaths from COVID-19 in ethnic minority groups has been documented.⁴²

The cohort also experienced high loss to follow-up and it is possible that recovery from COVID or long COVID led to loss of interest in completion across the full 90 days. This may mean that any over-representation of long COVID participants in the cohort was exaggerated over time. The lack of a reduction in QALMs lost due to long COVID over time may be attributable to this over-representation, or could have been that the data collection period was too short: for patients suffering long-term symptoms, 3 months is a relatively short period where recovery would be unexpected.⁴³ Conversely, due to the symptoms of long COVID, loss to follow-up may have been due to fatigue, driven by severe long COVID symptoms. Further development of QALYs lost attributable to long COVID should consider the framework set out within Martin et al.,⁴⁴ that separates populations into clearly defined subgroups of long COVID vs. acute COVID-19 when long-term measurements of HRQoL become available. This relies on the level of missingness decreasing as long-term assessments of long COVID become more common.

A further limitation is our definition of long COVID, which was based on questions relating to recovery from long COVID and the most recent COVID episode. In order to piece together HRQoL trajectories of long COVID, it would also have been useful to know the date of the episode of COVID which led to long COVID in order to estimate the time between infection and development of symptoms.

Long COVID has a major impact on HRQoL in our cohort, comparatively worse than in patients experiencing heart failure.³³ The effect was attenuated after adjusting for breathlessness and fatigue, indicating that these symptoms are partly responsible for the impact of long COVID on quality-of-life. This resonates with the input from our PPIE activity.

Fig. 2: Model outputs for disutility. a) Odds ratios for the probability of reporting disutility in the first part of the full model. Note that greater odds ratio relates to a higher odds of reporting a negative change in HRQoL. b) Odds ratios for self-reported long COVID and disability in the first part of the model shown separately to allow visualisation, due to their much higher odds ratios. c) Coefficients for the second part of the model, interpreted as the unit decrease in EQ-5D-5L utility score compared to base level for factor variables for individuals who report loss of HRQoL. Note that negative coefficients relate to lower disutility, i.e., higher quality-of-life.

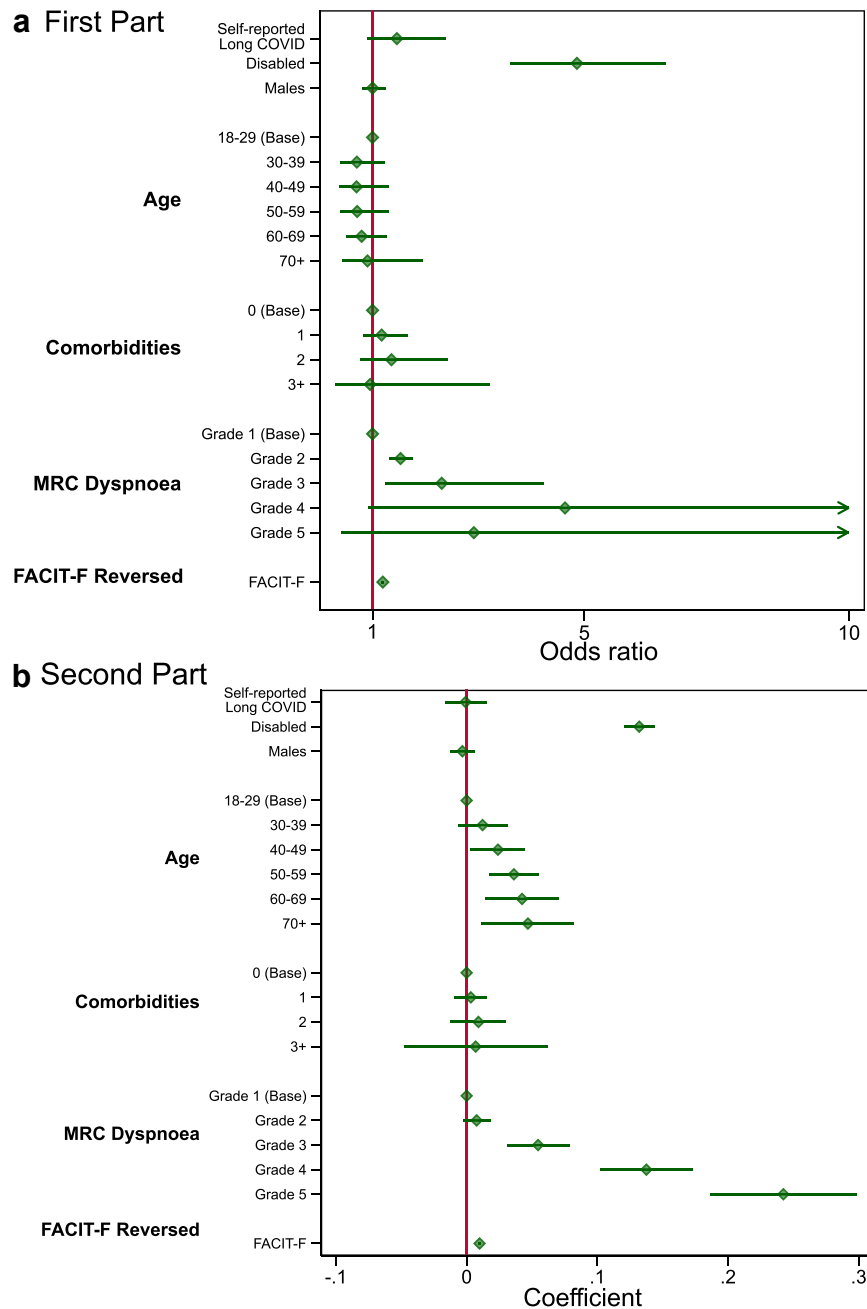


Fig. 3: Model outputs for disutility including additional Patient Reported Outcome Measures (PROMS). a) Odds ratios for the probability of reporting disutility in the first part of the full model including PROMS. Note that greater odds ratio relates to a higher odds of reporting a negative change in disutility. b) Coefficients for the second part of the model include PROMS, interpreted as the unit decrease in EQ-5D-5L utility score compared to base level for factor variables for individuals who report loss of HRQoL. Note that negative coefficients relate to lower disutility, i.e., higher quality-of-life.

Given that the burden of long COVID on HRQoL was heaviest in the working age population, our results indicate important implications for both health services, and the wider economy. A proportion of the UK population seeking higher contact with health services places

greater pressure on stretched public services.⁴⁵ Greater economic costs can be incurred for a substantial part of the UK workforce, with some individuals reducing their labour output, and others leaving the labour market altogether.⁴⁶ With no definitive treatment,

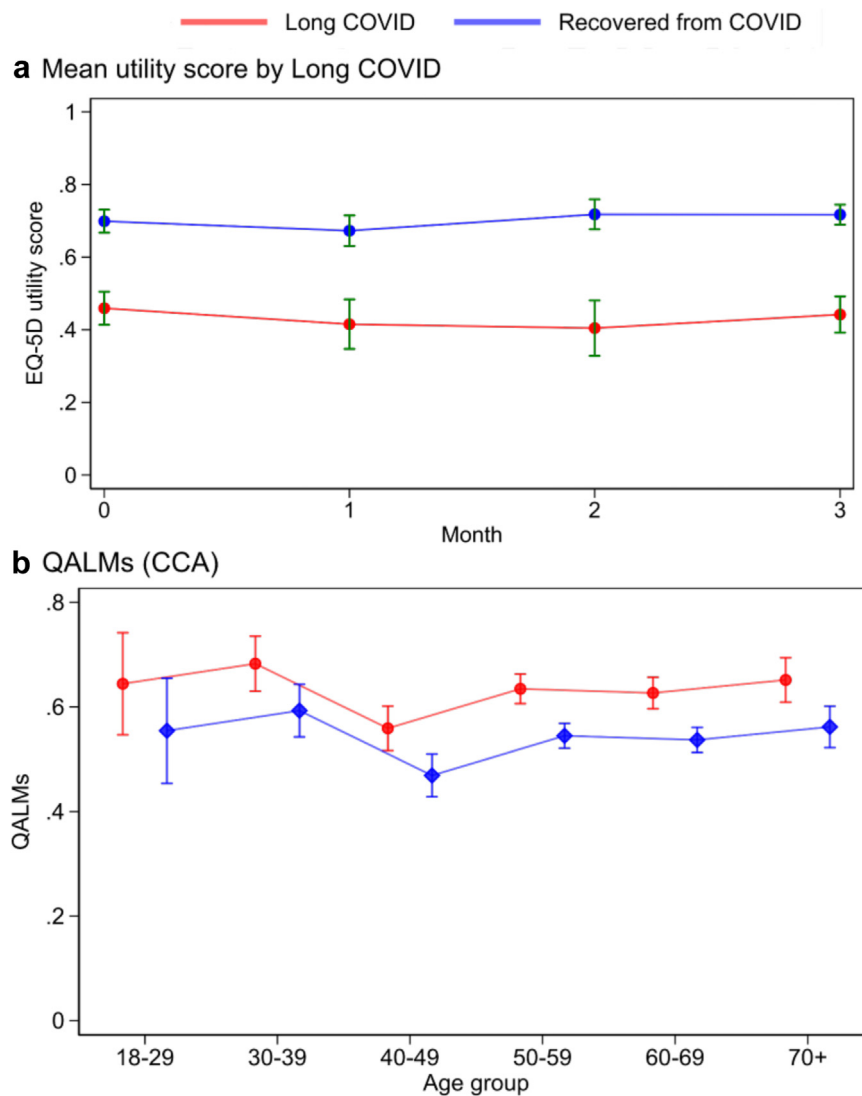


Fig. 4: a) mean utility score in the long COVID vs non-long-COVID groups. Error bars mark 95% confidence intervals. b) Predicted Quality-adjusted Life-Months stratified by long COVID status in the complete case analysis (CCA). The linear regression model also includes a disability, number of comorbidities, and baseline utility.

	Available case N = 6513		Long COVID Diagnosis N = 6513		Complete case N = 510	
	Long COVID	No long COVID	Long COVID	No long COVID	Long COVID	No long COVID
	Mean (sd)					
1 Month	0.25 (0.15)	0.13 (0.12)	0.26 (0.14)	0.17 (0.15)	0.26 (0.13)	0.16 (0.13)
2 Months	0.2 (0.13)	0.11 (0.11)	0.17 (0.12)	0.13 (0.13)	0.28 (0.14)	0.15 (0.12)
3 Months	0.19 (0.14)	0.10 (0.09)	0.21 (0.12)	0.12 (0.12)	0.27 (0.16)	0.13 (0.12)
Total	0.22 (0.31)	0.12 (0.20)	0.22 (0.3)	0.12 (0.20)	0.81 (0.41)	0.44 (0.36)

Table 2: Mean and standard deviations of quality-adjusted life-months (QALMs) stratified by long COVID for available case analysis, EHR-coded long COVID diagnosis, and complete case analysis (CCA). sd is standard deviation.

targeted research on the holistic approach to community treatment through symptom tracking, or modified pulmonary and cardiac rehabilitation programmes would help define the optimal method and duration of recovery programmes.⁴⁷

Importantly, we know that there is a subset of people with long COVID that experience debilitating symptoms, and our study had participants with long COVID whose HRQoL was in a state ‘worse than death’. Though these represent a minority of people with long COVID, it is vital that support is provided to these people.

In summary, self-reported long COVID had a significant effect on quality-of-life across models accounting for different demographics. Consistent low HRQoL scores being reported across the 3-months by participants with long COVID indicates the need for targeted interventions for a cohort experiencing symptoms upwards of a year. Fatigue and the relationship with EQ-5D requires further specific research on the effectiveness of validated PROMs to capture the severity of a significant symptom in a developing condition with little current clinical treatment.

Contributors

Author contributions were as follows: Conceptualisation (OC, ADH, LAT, MM, MJ, AB, L-YL, EH, RME), data curation (OC, ADH, BFCB-C, CB, JP, SCJB, ID, RME), formal analysis (OC), funding acquisition (BG, EH, RME), methodology (OC, ADH, JT, LAT, MM, MJ, AB, L-YL, WAD, REC, AJW, WH, EH, RME), project administration (BG, AM, BM, EH, RME), software (BFCB-C, CB, JP, SCJB, ID), supervision (EH, RME), visualisation (OC, ADH, EH, RME), writing—original draft (OC). All authors reviewed and approved the final manuscript.

Data sharing statement

Access to the underlying identifiable and potentially re-identifiable pseudonymised electronic health record data is tightly governed by various legislative and regulatory frameworks, and restricted by best practice. The data in the NHS England OpenSAFELY COVID-19 service is drawn from General Practice data across England where TPP is the data processor.

TPP developers initiate an automated process to create pseudonymised records in the core OpenSAFELY database, which are copies of key structured data tables in the identifiable records. These pseudonymised records are linked onto key external data resources that have also been pseudonymised via SHA-512 one-way hashing of NHS numbers using a shared salt. University of Oxford, Bennett Institute for Applied Data Science developers and PIs, who hold contracts with NHS England, have access to the OpenSAFELY pseudonymised data tables to develop the OpenSAFELY tools.

These tools in turn enable researchers with OpenSAFELY data access agreements to write and execute code for data management and data analysis without direct access to the underlying raw pseudonymised patient data, and to review the outputs of this code. All code for the full data management pipeline — from raw data to completed results for this analysis — and for the OpenSAFELY platform as a whole is available for review at github.com/OpenSAFELY.

The data management and analysis code for this paper was led by OC and contributed to by ADH.

Declaration of interests

BG has received funding via the University of Oxford from a wide range of public and charitable funders: the NHS National Institute for Health Research (NIHR), NHS England, the NIHR School of Primary Care Research, the NIHR Oxford Biomedical Research Centre, the Peter Bennett Foundation, the Laura and John Arnold Foundation, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration

Oxford and Thames Valley, UKRI/MRC, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK, the Health Foundation, and the World Health Organisation; he also receives personal income from speaking and writing for lay audiences on the misuse of science. He led the Goldacre Review (“Better, broader, safer: using health data for research and analysis” March 2022) for Secretary Of State for Health and Social Care; I chaired the HealthTech Advisory Board for Sec of State; I was a Non-Executive Director at NHS Digital; I am on the UKHSA Data Science Advisory Board; I have sat on various other local and national committees in the public sector. BMK is also employed by NHS England working on medicines policy and clinical lead for primary care medicines data. AM is a senior clinical researcher at the University of Oxford in the Bennett Institute, which is funded by contracts and grants obtained from the Bennett Foundation, Wellcome Trust, NIHR Oxford Biomedical Research Centre, NIHR Applied Research Collaboration Oxford and Thames Valley, Mohn-Westlake Foundation, and NHS England, and has consulted for health care vendors, the last time in 2022; the companies consulted in the last 3 years have no relationship to OpenSAFELY; he has represented the RCGP in the health informatics group and the Profession Advisory Group that advises on access to GP Data for Pandemic Planning and Research (GDPPR); the latter was a paid role; and he is a former employee and interim Chief Medical Officer of NHS Digital. REC holds shares in AstraZeneca. AB has received consulting fees from AstraZeneca, Roche, Takeda, Daiichi-Sankyo, Eisai, Novartis, Idorsia and Rhythm. LAT has received grants or contracts from MRC, Wellcome, NIHR and GSK for an epidemiological study of kidney disease (no personal payment received) and has consulted for Bayer in relation to an observational study of chronic kidney disease (no personal payment received); she has received support for attending the MHRA Expert advisory group on Women’s health and is an unpaid member of 4 non-industry funded NIHR/MRC trial advisory committees. JP has acted as an expert witness for the GMC with all fees paid to the company, and is an employee of TPP who provide the SystmOne software. MJ received support from NIHR for the funding of this manuscript and has received research grants from BMGF, Gavi, RCUK, WHO, Wellcome Trust, European Commission, InnoHK, TFGH and CDC. All other authors declare no competing interests.

Acknowledgements

We are grateful for support from the TPP Technical Operations team throughout this work, and for generous assistance from the information governance and database teams at NHS England and the NHS England Transformation Directorate.

The OpenSAFELY Collaborative

Alex Walker, Amelia Green, Amir Mehrkar, Andrea Schaffer, Andrew Brown, Ben Goldacre, Ben Butler-Cole, Brian MacKenna, Caroline Morton, Caroline Walters, Catherine Stables, Christine Cunningham, Christopher Wood, Colm Andrews, David Evans, George Hickman, Helen Curtis, Henry Drysdale, Iain Dillingham, Jessica Morley, Jon Massey, Linda Nab, Lisa Hopcroft, Louis Fisher, Lucy Bridges, Milan Wiedemann, Nicholas DeVito, Orla Macdonald, Peter Inglesby, Rebecca Smith, Richard Croker, Robin Park, Rose Higgins, Sebastian Bacon, Simon Davy, Steven Maude, Thomas O’Dwyer, Tom Ward, Victoria Speed, William Hulme, Liam Hart, Pete Stokes, Krishnan Bhaskaran, Ruth Costello, Thomas Cowling, Ian Douglas, Rosalind Eggo, Stephen Evans, Harriet Forbes, Richard Grieve, Daniel Grint, Emily Herrett, Sinead Langan, Viyaasan Mahalingasivam, Kathryn Mansfield, Rohini Mathur, Helen McDonald, Edward Parker, Christopher Rentsch, Anna Schultze, Liam Smeeth, John Tazare, Laurie Tomlinson, Jemma Walker, Elizabeth Williamson, Kevin Wing, Angel Wong, Bang Zheng, Christopher Bates, Jonathan Cockburn, John Parry, Frank Hester, Sam Harper, Shaun O’Hanlon, Alex Eavis, Richard Jarvis, Dima Avramov, Paul Griffiths, Aaron Fowles, Nasreen Parkes, Rafael Perera, David Harrison, Kamlesh Khunti, Jonathan Sterne, Jennifer Quint.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanepe.2024.100908>.

References

- Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133–146.
- NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE; 2020. Overview | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE. [cited 2023 Sep 6]. Available from: <https://www.nice.org.uk/guidance/ng188>.
- Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *J R Soc Med*. 2021;114(9):428–442.
- ONS. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics; 2023 [cited 2023 Sep 6]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2february2023>.
- GOV.UK. Cases in the UK | coronavirus in the UK; 2023 [cited 2023 Sep 6]. Available from: <https://coronavirus.data.gov.uk/details/cases>.
- Walker S, Goodfellow H, Pookarnjanamorakot P, et al. Impact of fatigue as the primary determinant of functional limitations among patients with post-COVID-19 syndrome: a cross-sectional observational study. *BMJ Open*. 2023;13(6):e069217.
- Sigfrid L, Drake TM, Pauley E, et al. Long Covid in adults discharged from UK hospitals after Covid-19: a prospective, multi-centre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *Lancet Reg Health Eur*. 2021;8:100186.
- Sandmann FG, Tessier E, Lacy J, et al. Long-term health-related quality of life in non-hospitalized coronavirus disease 2019 (COVID-19) cases with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in England: longitudinal analysis and cross-sectional comparison with controls. *Clin Infect Dis*. 2022;75(1):e962–e973.
- Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open*. 2018;8(2):e020738.
- Herrett E, Tomlin K, Lin LY, et al. Protocol for an OpenSAFELY cohort study collecting patient-reported outcome measures using the TPP Airmid smartphone application and linked big data to quantify the health and economic costs of long COVID (OpenPROMPT). *BMJ Open*. 2023;13(2):e071261.
- UKRI. MRC breathlessness scales: 1952 and 1959; 2016 [cited 2023 Nov 26]. Available from: <https://www.ukri.org/publications/mrc-breathlessness-scales-1952-and-1959/>.
- Tennant KF. Assessment of fatigue in older adults: the FACIT fatigue scale (version 4). Hartford Institute for geriatric nursing 2011 [Try This: Best Practices in Nursing Care to Older Adults].
- Walker AJ, MacKenna B, Inglesby P, et al. Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY. *Br J Gen Pract*. 2021;71(712):e806–e814.
- LSHTM. OpenPROMPT | LSHTM; 2022 [cited 2023 Jul 10]. Available from: <https://www.lshtm.ac.uk/research/centres-projects-groups/openprompt>.
- Thompson EJ, Williams DM, Walker AJ, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun*. 2022;13(1):3528.
- GOV.UK. The English indices of deprivation 2019; 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/loD2019_Statistical_Release.pdf.
- Devlin NJ, Brooks R. EQ-5D and the EuroQol group: past, present and future. *Appl Health Econ Health Policy*. 2017;15(2):127–137.
- Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *Pharmacoeconomics*. 2023;41(2):199–207.
- van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–715.
- McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. *Value Health*. 2023;26(2):163–169.
- Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17(1):162.
- Hunter RM, Baio G, Butt T, Morris S, Round J, Freemantle N. An educational review of the statistical issues in analysing utility data for cost-utility analysis. *Pharmacoeconomics*. 2015;33(4):355–366.
- Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med*. 2021;27(4):626–631.
- McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health*. 2017;20(4):644–650.
- Holt H, Relton C, Talaei M, et al. Cohort Profile: longitudinal population-based study of COVID-19 in UK adults (COVIDENCE UK). *Int J Epidemiol*. 2022:dyac189.
- Maheswaran H, Kupek E, Petrou S. Self-reported health and socio-economic inequalities in England, 1996–2009: repeated national cross-sectional study. *Soc Sci Med*. 2015;136–137:135–146.
- Di Fusco M, Cappelleri JC, Anatale-Tardiff L, et al. Impact of COVID-19 infection on health-related quality of life, work productivity and activity impairment by symptom-based long COVID status and age in the US. *Healthcare*. 2023;11(20):2790.
- Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and post-infective fatigue syndrome: a review. *Open Forum Infect Dis*. 2021;8(10):ofab440.
- Montan I, Löwe B, Cella D, Mehnert A, Hinz A. General population norms for the functional assessment of chronic illness Therapy (FACIT)-Fatigue scale. *Value Health*. 2018;21(11):1313–1321.
- Moens M, Duarte RV, De Smedt A, et al. Health-related quality of life in persons post-COVID-19 infection in comparison to normative controls and chronic pain patients. *Front Public Health*. 2022;10:991572.
- Arab-Zozani M, Hashemi F, Safari H, Yousefi M, Ameri H. Health-related quality of life and its associated factors in COVID-19 patients. *Osong Public Health Res Perspect*. 2020;11(5):296–302.
- Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med*. 2021;9(11):1275–1287.
- Squire I, Glover J, Corp J, Haroun R, Kuzan D, Gielen V. Impact of HF on HRQoL in patients and their caregivers in England: results from the ASSESS study - the British Journal of Cardiology. *BJC*. 2017;34(3):24–30.
- Carney P, O'Boyle D, Larkin A, McGuigan C, O'Rourke K. Societal costs of multiple sclerosis in Ireland. *J Med Econ*. 2018;21(5):425–437.
- Yang F, Lau T, Lee E, Vathsala A, Chia KS, Luo N. Comparison of the preference-based EQ-5D-5L and SF-6D in patients with end-stage renal disease (ESRD). *Eur J Health Econ*. 2015;16(9):1019–1026.
- Nolan CM, Longworth L, Lord J, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax*. 2016;71(6):493–500.
- Henderson AD, Butler-Cole BF, Tazare J, et al. Clinical coding of long COVID in primary care 2020-2023 in a cohort of 19 million adults: an OpenSAFELY analysis. *medRxiv*. 2023. <https://doi.org/10.1101/2023.12.04.23299364>.
- Henderson AD, Carlile O, Dillingham I, et al. Cohort profile: OpenPROMPT. *medRxiv*. 2023 <https://doi.org/10.1101/2023.12.21.23300369>.
- Heightman M, Prashar J, Hillman TE, et al. Post-COVID-19 assessment in a specialist clinical service: a 12-month, single-centre, prospective study in 1325 individuals. *BMJ Open Respir Res*. 2021;8(1):e001041.
- Andrews C, Schultze A, Curtis H, et al. OpenSAFELY: representativeness of electronic health record platform OpenSAFELY-TPP data compared to the population of England. *Wellcome Open Res*. 2022;7:191.
- Shabnam S, Razieh C, Dambha-Miller H, et al. Socioeconomic inequalities of Long COVID: a retrospective population-based cohort study in the United Kingdom. *J R Soc Med*. 2023;116(8):263–273.
- Bosworth ML, Ahmed T, Larsen T, et al. Ethnic differences in COVID-19 mortality in the second and third waves of the pandemic in England during the vaccine rollout: a retrospective, population-based cohort study. *BMC Med*. 2023;21(1):13.

-
- 43 Ballouz T, Menges D, Anagnostopoulos A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ*. 2023;381:e074425.
- 44 Martin C, Luteijn M, Letton W, Robertson J, McDonald S. A model framework for projecting the prevalence and impact of Long-COVID in the UK. *PLoS One*. 2021;16(12):e0260843.
- 45 Lin LY, Henderson AD, Carlile O, et al. Healthcare utilisation in people with long COVID: an OpenSAFELY cohort study. *medRxiv*. 2023. <https://doi.org/10.1101/2023.12.21.23300305>.
- 46 Reuschke D, Houston D. The impact of Long COVID on the UK workforce. *Appl Econ Lett*. 2023;30(18):2510–2514.
- 47 Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long covid—an update for primary care. *BMJ*. 2022;378:e072117.