

Occurrence and persistence of symptoms, diagnoses and prescriptions after community-diagnosed COVID-19: a matched cohort study using the OpenSAFELY platform

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ABSTRACT

Background: We aimed to explore the occurrence and persistence of symptoms, diagnoses, and prescribing after COVID-19 among populations from earlier (Wave 2) and later (Wave 4) in the pandemic.

Methods: With the approval of NHS England we analysed data from English primary care using TPP SystemOne through the OpenSAFELY data analytics platform. Individuals with community-diagnosed COVID-19 September 2020-January 2021 (Wave 2) were matched to contemporary (2020-2021) and historical (2017-2018) comparators. Individuals with community COVID-19 December 2021-March 2022 (Wave 4) were matched to contemporary comparators (last follow-up March 31st 2023). Occurrence of each of (1) long-COVID symptoms; (2) primary-care diagnoses; and (3) new prescriptions was analysed at anytime during one year after COVID-19 and at: 4-12 weeks, 12-weeks-6 months and 6 months-12 months after COVID-19 to assess persistence.

Results: 902,885 COVID-19 cases (Wave 2) matched to 4,449,265 contemporary (no-COVID-19) comparators. 1,553,160 COVID-19 cases (Wave 4) matched to 7,624,770 contemporary comparators. Positive Wave 2 associations after COVID-19 were observed for: hair loss (OR 1.57, 95% CI 1.48-1.66), mobility impairment (1.41, 1.35-1.48), fatigue (1.46, 1.42-1.49), cognitive impairment (1.39, 1.34-1.44), and loss of taste or smell (1.38, 1.31-1.46). At 6-12 months reporting persisted for mobility impairment, fatigue and cognitive impairment. There were small increases in new prescriptions for NSAIDs (1.24, 1.23-1.26), drugs to treat infections (1.24, 1.23-1.25) and musculoskeletal problems (1.23, 1.22-1.25). Wave 4 associations were generally weaker than Wave 2.

Conclusions: Long-COVID symptoms and new prescribing generally reduce over time and are potentially less problematic following less-severe illness. Fatigue/cognitive/mobility symptoms persist following COVID-19.

Summary boxes

What is already known on this topic

- Evidence, up to February 2021, indicated that in the UK following COVID-19 there were increased primary care consultations for new symptoms, and specific new diagnoses and prescriptions.
- However, we do not know if increased primary care contacts after COVID-19 continue over time, what has happened to long-COVID primary care contacts after early 2021 (when Omicron became the dominant COVID-19 strain and when vaccine or hybrid immunity became prevalent), or whether individuals are receiving other broader diagnoses or prescriptions following COVID-19.

What this study adds

- Based on analysis up to April 2023, compared to matched (age, sex, NHS-administrative region) comparators, individuals with prior COVID-19 had more primary care records for most symptoms, broad diagnostic categories, and new prescriptions studied; associations were present in both those who consulted their GP frequently and those who consulted their GP infrequently before their COVID-19, with strongest evidence seen for persisting general fatigue/cognitive/mobility symptoms following COVID-19.
- We saw declining associations over time following COVID-19 (from 4 weeks to 12 months) for most symptoms and new prescriptions.

How this study might affect research, practice or policy

- Although there is a reduced burden of impact of long COVID symptoms over successive waves, there is an ongoing burden of complications highlighting the need for adequate resourcing of primary care, particularly relating to persisting ME/CFS type symptoms.

INTRODUCTION

Over 6% of people who have had the novel coronavirus-2019 disease (COVID-19) report multiple persisting symptoms after initial infection.¹ Symptoms persisting after acute COVID-19 infection have been variously termed: long-COVID, post-COVID syndrome, long-haul COVID, chronic COVID-19, and post COVID-19 condition'.²⁻⁵ Although terms have been used interchangeably in the literature, we will refer to these symptoms as long-COVID. Definitions of how long symptoms need to persist to be classified as long-COVID in the literature vary from more than 3 weeks up to more than 3 months.^{4,5} As of April 2024, the UK Office for National Statistics survey estimated that 3.3% of the UK population self-reported long-COVID symptoms,⁶ commonly including: fatigue, cognitive problems, shortness of breath, headaches, chest pain, sleep disorders, and musculoskeletal pain.^{7,8}

Existing research has described the types and frequency of symptoms, diagnoses and prescriptions associated with long-COVID and risk factors for progression to long-COVID.⁹⁻¹³ However, little is known about which symptoms persist the longest in those with long-COVID, what happens to patterns of diagnoses and prescribing over time, or how long-COVID may differ depending on pandemic wave of infection. Characterising long-COVID in relation to duration of symptoms, patterns of diagnoses and prescribing over time and severity related to pandemic wave is vital for supporting health service planning and to guide future research focus and pandemic preparedness.

Consequently the primary aims of our study were to: (1) investigate how primary care recording of symptoms, diagnoses and prescriptions vary with time period after initial infection with long-COVID and (2) investigate how symptoms, diagnoses and prescriptions vary between a low population immunity, high strain severity period of the pandemic (Wave 2, Delta strain) and a higher population immunity, lower strain severity of the pandemic (Wave 4, Omicron strain). A secondary aim was to investigate the role of pre-COVID consultation behaviour on all outcomes under study.

METHODS

We conducted matched cohort studies using primary care electronic health records (EHR) comparing symptom recording, broad diagnostic categories, new prescribing, and long-COVID-19 consultation counts in people with and without COVID-19 from 4 weeks to one year after COVID-19, and by separate time periods of 4-12 weeks, 12 weeks to 6 months, and 6 to 12 months after COVID-19. While the WHO long-COVID definition requires symptoms to persist for a minimum of 3 months after acute disease to be considered long COVID,⁴ we wanted to investigate from 4 weeks onwards due classification elsewhere in the literature only requiring 3 or more weeks of symptoms to be considered as long-COVID,⁵ noting that our 12 week – 6 month period covers the WHO definition. In separate analyses we compared outcomes in community-diagnosed cases of COVID-19 from Wave 2 of the UK's COVID-19 pandemic (B.1.1.7 variant, 1st Sep 2020 to 31st January 2021) to two matched (age, sex, NHS administrative region) comparator populations: 1) contemporary (Wave 2); and 2) historical (2017-2018) (**Figure S1**).

We also compared outcomes in community-diagnosed cases of COVID-19 from Wave 4 (Omicron variant, 15th December 2021 to 31st March 2022) with a matched contemporary (Wave 4) comparator group. Evidence suggests that long-COVID may be independent of initial COVID-19 severity and those with mild initial symptoms from infection still experience ongoing symptoms.^{14,15} Therefore, to ensure that only milder (non-hospitalised) cases were included, we: 1) focused on community-diagnosed COVID-19; 2) excluded those with a history of hospitalisation for COVID-19; and 3) censored at date of hospitalisation for COVID-19.

All computer code and morbidity code lists used to define all study variables are available for download (<https://github.com/opensafely/long-covid-symptoms>).

Data source

We used routinely-collected EHR data from NHS English primary care practices managed by the GP software provider The Phoenix Partnership (TPP) through OpenSAFELY, covering approximately 40% of the population in England. OpenSAFELY is a data analytics platform created on behalf of NHS England to address urgent COVID-19 research questions. (**Text S1**).¹⁶ All data were linked, stored and analysed securely using the OpenSAFELY platform, <https://www.opensafely.org/>, as part of the NHS England OpenSAFELY COVID-19 service. Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free text data are included. All code is shared openly for review and re-use under MIT open license at: <https://github.com/opensafely/long-covid-symptoms>. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared.

The dataset analysed within OpenSAFELY is based on 24 million people currently registered with primary care practices using TPP SystmOne software. Primary care data was linked through OpenSAFELY to: 1) NHS Secondary Uses Service (SUS) on hospitalisations; 2) National coronavirus testing records via the Second Generation Surveillance System (SGSS);¹⁷ 3) Office for National Statistics (ONS) death data.

Study population

We included two cohorts of individuals (no age limits) with COVID-19 from Wave 2 and Wave 4, with contemporary comparator groups selected from the same Wave as the people with COVID-19. We analysed two different Waves to assess the impact of differences in immunity and strain severity on long-COVID outcomes. Wave 2 was selected to represent a cohort early in the pandemic with relatively low immunity who would have been infected with a relatively severe strain of COVID-19 (Delta), while Wave 4 was selected to represent a cohort later in the pandemic with higher immunity who would have been infected with a milder strain of COVID-19 (Omicron). We also included a historical (pre-COVID-19) comparator group (for Wave 2 only). We used two Wave 2 comparator groups, as we felt that the true estimate of the relative difference in outcomes (symptoms, diagnoses, new prescriptions) between people with and without COVID-19 would lie between the estimates for the two comparator groups. Additionally, using two comparator groups offered a limited capacity to differentiate between the effects of COVID-19 and the effects of the social isolation of lockdown. Further details are provided in **Table 1 and Text S2**.

Outcomes

Our outcomes were:

- 1) commonly reported symptoms of long COVID recorded using morbidity coding in primary care (**Table S1**);
- 2) broad body-system categories of diagnoses recorded in primary care (**Table S2**); and 3) new primary care prescriptions for drugs in broad categories (**Table S3**) and in specific subcategories for managing commonly reported long-COVID symptoms (**Table S4**).

Further details are provided in **Text S3**.

A new prescription was based on the first ever record of a prescription in a particular category that occurred after start of follow up. Individuals with prescriptions for a body system category at any time in the year prior to start of follow-up were excluded from analyses of that specific category outcome.

To investigate a broad metric of health care use, we presented descriptive counts of the number of primary care consultations for people with COVID and their comparators during follow-up.

Covariates

Covariates were selected based on being factors that may potentially affect the relationship between COVID-19 and subsequent continuing symptoms and related diagnoses (and related prescribing). We therefore adjusted for age, sex, region, deprivation, ethnicity, rural/urban status, pre-existing ill health, and consultation frequency in the previous year prior to first COVID-19 diagnosis (and equivalent date for matched comparators) (Further details on covariate measurement is provided in **Text S4**). As this was a hypothesis generating study, we adjusted sequentially without a causal framework.

Statistical analysis

We used Python 3.7 for data management, Stata 16.1 for data management and analyses, and R 4.2.2 for data visualisation. To protect patient privacy and prevent the risk of identifying individuals, all reported counts were rounded to the nearest five, and any counts of five or fewer were not disclosed.

We initially described the characteristics of those with community-diagnosed COVID-19 and their respective matched comparator groups. We then described the number and proportion of individuals with community-diagnosed COVID-19, and the matched comparator groups, recorded with: 1) commonly reported COVID-19 symptoms in primary care during follow up; 2) diagnoses recorded in primary care in the broad diagnostic categories; and 3) new prescriptions defined in broad categories.

We used conditional logistic regression to estimate odds ratios (95% confidence intervals), comparing people with and without COVID-19 on whether the following were present at any time during the 12-month period after start of follow-up: 1) any symptom (composite outcome); 2) each individual symptom; 3) diagnosis in each broad diagnostic category; and 4) broad categories of drugs potentially prescribed for relief of long-COVID symptoms. We ran sequential models: 1) Minimally adjusted: stratified on matched set (i.e., implicitly adjusted for matching factors, age, sex, STP region); 2) Additionally adjusting for sociodemographic features (i.e., deprivation, ethnicity, rural/urban location) and pre-existing comorbidities; and 3) Additionally adjusting for primary-care consultations in the year before first COVID-19 infection (or equivalent for matched comparators).

We did not adjust further due to the lack of clarity around the potential causal pathological mechanisms for long-COVID, and because we aimed to assess association, not causation. However, we presented results stratified by previous consultation count in secondary analyses.

Details of follow-up for the 'persistence-of-event reporting' analysis are provided in **Text S5** and **Figure S2**.

As a measure of how much the retention of people in the contemporary comparator cohorts who were subsequently diagnosed with COVID-19 might have impacted our findings (biasing effect estimates towards null), we described counts

of the number of people in the contemporary comparator cohorts (for Waves 2 and 4) who went on to have a diagnosis of COVID-19.

Sensitivity analysis

In our main analyses adjusting for ethnicity, we used a complete-records analysis (only including those with known ethnicity). In a follow-up sensitivity analysis, we used multiple imputation to account for missing ethnicity, comparing long-COVID symptoms in Wave 2 COVID-19 to contemporary comparators.²⁴ Ethnicity data were considered to be missing at random. 10 imputed datasets were created with the multiple imputation model including presence of any symptoms ever, COVID-19 status, deprivation, rural-urban, pre-existing comorbidities, age, number of GP consultations in the previous year and number of prescriptions in the previous year. Estimated odds ratios were combined using Rubin's rules.

Secondary analysis

To generate hypotheses regarding potential differences related to previous health and health-seeking behaviour, we performed an analysis stratified by prior consultation count. We considered primary-care consultation frequency in the year prior to index date in the following categories: 1, 2-5, or 6 or more. In this analysis we excluded those with no consultations in the year prior to index date (see **Text S6**), but conducted a sensitivity analysis where these individuals were included.

Patient and public involvement

Patients and public were not directly involved in developing this study, however OpenSAFELY has involved patients and the public in various ways including development of a public website suitable for a lay audience (<https://opensafely.org>), participation in two citizen juries exploring public trust in OpenSAFELY and co-development of an explainer video (<https://www.opensafely.org/about/>). There is also patient representation on the OpenSAFELY Oversight Board.

RESULTS

The Wave 2 (1st Sep 2020 to 31st January 2021) contemporary comparator cohort included in the 4 week-12 month (anytime) period analyses included 902,885 people with COVID-19 matched to 4,449,265 without COVID-19 (**Figure S3**). After accounting for individuals becoming ineligible in the preceding analysis time period, there were 5 219 455 people included for analysis at the start of the 12-week-6-month period and 5 098 560 at the start of the 6-12-month period (**Text S7** and **Figure S3**) For the Wave 2 historical cohort, the same cohort of 902,885 people with COVID-19 was matched to 4,428 995 people without COVID-19 (**Text S7**).

Individuals with COVID-19 in Wave 2 included more South Asian people than both non-COVID-19 comparator groups (**Table 2**), more people with comorbidities than the contemporary comparators but not the historical comparators, and more frequent primary care consulters than the contemporary non-COVID cohort.

Twenty-six percent (231,570/902,885) of people with COVID-19 in Wave 2 had at least one symptom recorded during follow up, with musculoskeletal pain the most commonly recorded (**Table S6**). Infectious and parasitic diseases were the most commonly recorded diagnosis (**Table S7**), while the most common prescription was for infection-related medications (**Table S8**).

For the Wave 4 (15th December 2021 to 31st March 2022) analysis, 1,553,160 people with COVID-19 were matched to 7,624,770 people without (**Figure S4, Table S9, Text S8, Tables S10-S12**).

Details of overall consultation counts during follow-up are provided in **Text S9, Table S13**.

All OR in the subsequent sections refer to fully adjusted models unless specified.

Symptoms after COVID-19

One year – Wave 2, contemporary comparator group

People with COVID-19 in Wave 2 had a 20% increased odds of reporting at least one symptom at any time compared to contemporary comparators (95% CI 19% to 21% increase) (**Figure 1 Panel A, Table S6**). The largest increased odds after COVID-19 were for: hair loss (OR 1.57, 1.48-1.66), mobility impairment (OR 1.41, 95% CI 1.35-1.48), fatigue (OR 1.46, 95% CI 1.42-1.49), cognitive impairment (OR 1.39, 95% CI 1.34-1.44), and loss of taste or smell (OR 1.38, 95% CI 1.31-1.46).

One year – Wave 2, historical comparator group

Compared to historical comparators, there was no association between prior COVID-19 and having at least one symptom during follow-up (0.98, 95% CI 0.97-0.98) (**Figure 1 Panel A, Table S6**). Increased odds after COVID-19 were observed for loss of taste or smell (11.43, 95% CI 10.46-12.49), mobility impairment (1.74, 95% CI 1.66-1.82), cognitive impairment (1.75, 95% CI 1.68-1.82), and hair loss (1.44, 95% CI 1.36-1.52). Lower odds after COVID-19 were observed for sore throat (0.75, 95% CI 0.74-0.76), nasal congestion (0.75, 95% CI 0.73-0.78), and skin rashes (0.76, 95% CI 0.74-0.78).

For Wave 2, subsequent reporting of results in this section are for analysis of the contemporary comparator cohort only (results tables for historical comparators are in **Tables S10-S19**).

One year – Wave 4, contemporary comparator group

Individuals with COVID-19 in Wave 4 had similar increased odds for any symptom during one year as Wave 2, but individual symptoms were less strongly associated with prior COVID-19 than in Wave 2 (**Figure 1 Panel A, Table S10**).

By time period

For those symptoms associated with prior COVID-19 in Wave 2, all associations decreased by time period (**Figure 1 Panel B and Table S14**). For example, for hair loss, the 4-to-12-week period long-COVID-19 OR of 3.49 (95% CI 3.10-3.93) was reduced to an OR of 1.00 (95% CI 0.91-1.09) by the 6-12-month period. For mobility impairment, cognitive impairment and fatigue, despite a reduction in recording over time, substantial associations remained in the 6-12-month period (mobility impairment OR 1.47, 95% CI 1.39-1.56; cognitive impairment 1.69, 95% CI 1.54-1.84; fatigue 1.32, 95% CI 1.28-

1.37). For Wave 4, we saw a similar pattern of a reduction in ORs by time across symptoms, with mobility impairment, cognitive impairment and fatigue closer to the null by the 6-12-month period than for Wave 2. (**Figure S5**).

By previous consultations

The increased odds of having at least one symptom during follow-up (comparing people with COVID-19 in Wave 2 to contemporary comparators) was apparent across all categories of prior consultation frequency for Wave 2 (e.g. OR 1.22, 95% CI 1.19-1.25 in people who only consulted once in the year prior to start of follow-up; OR 1.18, 95% CI 1.16-1.19 in people who consulted between 2-5 times) (**Figure 1 Panel C, Table S15**). Increased odds across all categories of prior consultation frequency for Wave 2 were also observed for mobility impairment, cognitive impairment, and fatigue (**Figure 1 Panel C, Table S15**). Similar patterns were observed for Wave 4.

Diagnoses after COVID-19

One year

We observed small positive associations between prior COVID-19 and every recorded diagnostic category for Wave 2, except for the negative control diagnoses of congenital disease and of perinatal disease (**Figure 2 Panel A, Table S7**). The majority of associations were consistent with less than a 15% increased odds. For Wave 4, direction and magnitude of associations were similar to Wave 2 (**Figure 2 Panel A, Table S11**).

By time period

There was minimal change by time period for the majority of diagnoses studied during Wave 2 (**Figure 2 Panel B, Table S16**), although of note was a 12% increase in neoplasms at the 4-12-wk period (95% CI 7%-17%) which reduced to 5% (95% CI 2%-7%) by the 6 months to 1 year period, and for respiratory system disease, a higher OR after 6 months (OR 1.22, 95% CI 1.20 – 1.23) than during the 4–12-week (**Figure 2 Panel B, Table S16**). Changes by time period were also minimal for the Wave 4 cohort (**Figure S6**).

By previous consultations

The small increases in odds were generally seen across all categories of previous consultation frequency for Wave 2 (**Figure 2 Panel C, Table S17**) and for Wave 4 (**Figure S6**).

Prescriptions after COVID-19

One year

We saw a positive association between prior Wave 2 COVID-19 and new prescriptions for all BNF prescription categories except acute diarrhoea and anti-arrhythmic drugs (**Figure 3 Panel A, Table S8**). The largest associations were for BNF categories for NSAIDs, infections, and musculoskeletal and joint diseases. No associations were larger than a 25% increase in odds and the majority were consistent with a less than 20% increase. For the negative control outcome of malignant disease and immunosuppression, there was a small negative association. Associations were in a similar direction (although reduced in magnitude) for Wave 4 (**Figure 3 Panel A, Table S12**).

By time period

Although for a number of BNF categories the association between prior COVID-19 and new prescribing generally decreased over time for the Wave 2 cohort, for BNF categories with the largest anytime association (e.g., NSAIDs, and musculoskeletal and joint diseases), the strength of association persisted by time period (**Figure 3 Panel B, Table S18**). The association with prescribing for infections suggested a slight increase over time. For Wave 4, associations by time period were similar to those observed for Wave 2 (**Figure S7**).

By previous consultations

For those BNF categories in which positive associations were found between prior Wave 2 COVID-19 and prescribing, increases in odds were observed across all categories of previous consultations (**Figure 3 Panel C, Table S19**). A similar pattern of results was observed for Wave 4 (**Figure S7**).

Sensitivity analyses

Results of sensitivity analyses are discussed in **Text S10**.

DISCUSSION

We found associations between prior community-diagnosed COVID-19 in the UK's pandemic Wave 2 and most symptoms, broad diagnostic categories, and new prescriptions studied. Reassuringly, we saw declining associations over time following COVID-19 (from 4 weeks to 12 months). Relatively strong associations persisted up to 12 months after COVID-19 for fatigue, cognitive impairment and mobility impairment. Observed associations were not just limited to those who frequently consulted their GP prior to COVID-19. Associations in Wave 4 of the pandemic were weaker for all outcomes than those in Wave 2.

Results in context/clinical interpretation

Our results showing increased primary care symptom recording are consistent with other UK-based studies.^{18,19} Our study generates new results relating to individuals from both Waves 2 and 4, symptom reporting over time, and the role of pre-COVID consultation rates on observed associations. Increases in loss of taste and smell, and hair loss following COVID-19 are consistent with previous time-to-event analysis of UK data.¹⁹ However, our 'persistence-of-event-reporting' approach indicated that these symptoms do not persist. Our findings on symptoms are consistent with international studies,^{15,20,21} including those with test-negative designs,^{20,22} and our findings demonstrating a reduction in long-COVID EHR-recorded symptoms over time are broadly consistent with previous studies.^{18,23}

Our findings of increased diagnoses following COVID-19 are generally consistent with findings from studies looking at specific diagnoses,^{13,24,25} and with results for respiratory and mental health conditions.²² We noted an increase in the diagnoses of neoplasms in the 4-12 weeks after COVID-19 that is very unlikely to be due to COVID-19 itself (the timeframe is implausible for the complex pathological mechanisms involved in the development of cancer), but more likely to be explained by higher ascertainment in those with recent contact with the health services. Our results for increased NSAID and bronchodilator prescribing conflict with another UK study (which found no increase in NSAIDs and a decrease in bronchodilators),¹³ likely due to differences in comparator groups (**Text S11**).

The increase in symptoms, diagnoses and prescriptions following COVID-19 suggests either a common systemic pathological mechanism, and/or pre-existing poor health in individuals with COVID-19. A previous study suggested COVID-19 may be responsible for only 13% of an individual's ongoing COVID-19 symptoms.²⁶ However, we adjusted for pre-existing comorbidity and found increased risks across all categories of pre-COVID consultation frequency.

Weaker associations for most-outcomes in the less-severe Omicron-dominant Wave 4 suggests a true reduction in long-COVID symptoms or increasing numbers of people who had COVID-19 in our comparator group.

No evidence of association between prior COVID-19 and our two negative control outcome diagnoses of perinatal or congenital disease provides confidence in our results. The small increase in injury and poisoning diagnoses in individuals following COVID-19 compared to those without is discussed in **Text S13**.

Strengths and limitations

This is the first large-scale UK study to look at how symptoms, diagnoses, and new prescribing changes over time following COVID-19 Waves 2 and 4. In contrast to existing studies,^{13,19,24} we applied a 'persistence-of-event-reporting' design, as consulting your GP for fatigue symptoms at six months post COVID-19 may indicate a more severe ongoing post-viral syndrome than reporting fatigue at four weeks only.

We were only able to capture symptoms that individuals consulted for, and that GPs recorded using morbidity codes. Absence of a record does not mean that someone does not have the symptom. However, our approach selected people whose symptoms were sufficiently severe for a GP consultation, and that their GP felt were sufficiently prominent to record. Inclusion of negative control outcomes increased confidence in our findings for the outcomes under study.

It is possible that some symptoms may be more likely to be recorded more than once due to recording templates in GP software, meaning results for some symptoms may reflect how data is captured in primary care software.

A proportion (up to 19%) of our overall study population had missing ethnicity data. However, our sensitivity analyses using multiple imputation to account for missing ethnicity were consistent with our main analyses.

As this is a hypothesis-generating descriptive study we are not able to rule out residual confounding. Our modelling strategy may be limited due to the current lack of clarity around the potential causal pathological mechanisms linking initial COVID-19 to ongoing symptoms, which meant that we focused on the study of association, rather than causation. However, our effect estimates offer insights into the burden of specific long-COVID symptoms and diagnoses, providing vital information for follow-up studies investigating underlying mechanisms. Additional strengths and limitations are provided in **Text S12**.

Implications for policy and research

Our findings related to fatigue, cognitive problems and mobility impairment warrant further research applying a causal approach and investigating potential effect modifiers. Future work should also address whether the decline in symptom reporting continues beyond 12 months, how the increased ORs across all categories of previous consultation frequency relate to absolute changes in outcomes post-COVID, and whether vaccination might reduce ongoing symptoms (**Text S14**). Given the substantial proportion of the population who have had COVID-19 and will continue to be infected, our results highlight the potential high resource need of people with ongoing symptoms. Cognitive/mobility impairment and fatigue affect the ability to work, so there is potential for far reaching economic implications.

Conclusions

Our results suggest long-COVID symptom reporting reduces over time and that symptoms are potentially less problematic following less severe strains of COVID-19. In line with time-to-event analyses, loss of taste and smell and hair loss were initially strongly associated, but by 6 months after COVID-19, using a 'persistence-of-event-reporting' design we saw no evidence of association. In contrast, for symptoms commonly seen in ME/CFS (fatigue, cognitive problems, mobility impairment), associations persisted up to 12 months after COVID-19. Prescribing for drugs to manage symptoms increased following COVID-19, with similar reductions over time. Increases in symptoms and prescribing were not just limited to frequent consultors. We saw persisting reporting of general fatigue/cognitive/mobility symptoms following COVID-19, and health services need to be planned accordingly. Future pandemic planning should consider that both people with pre-existing health conditions and more healthy people who previously had limited contact with health services can be affected by functional somatic symptoms that impact daily life, and that while there is a reduced burden of impact over successive waves, there is an ongoing burden of complications highlighting the need for adequate resourcing of primary care.

DECLARATIONS AND ACKNOWLEDGEMENTS

Contributions

KEM, LAT, KW, SJWE, and IJD were involved in the development of the study. KEM, CM, VM, and LAT contributed to the development of the code lists that defined the variables used in the study. KW was responsible for data management and statistical analyses. TC, VM, RC, and LY contributed to output checking. KEM and KW wrote the first draft. All authors contributed to and approved the final manuscript.

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Ethical approval

The study was approved by the Health Research Authority (REC reference 20/LO/0651) and by the London School of Hygiene and Tropical Medicine (LSHTM) ethics board (Reference 21863).

Data sharing

All code is shared without investigator support. Our study protocol and analysis plan are available as additional online-only supplementary material.

Software and Reproducibility

Data management was performed using Python with analysis carried out using STATA and R. Code for data management and analysis are archived online at <https://github.com/opensafely/long-covid-symptoms/tree/master/analysis>, as well as codlists at <https://github.com/opensafely/long-covid-symptoms/tree/master/codlists>.

Data access and verification

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 are available at: <https://github.com/opensafely/long-covid-symptoms/tree/master>, and a record of all the jobs executed on the OpenSAFELY server for this project can be found at: <https://jobs.opensafely.org/long-covid-symptoms/long-covid-symptoms/logs/>.

The data management and analysis code for this paper was led by KW.

Transparency statement

The lead author (the manuscript's guarantor) KW, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf).

VM holds a Doctoral Research FW grant from the NIHR. PI and AW received support from the NIHR-UKRI Convalescence long COVID Study, a grant awarded to UCL with the University of Oxford as collaborators. AM 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. AM is a former employee and interim Chief Medical Officer of NHS Digital. AM has consulted for health care vendors, the last time in 2022; the companies consulted in the last 3 years have no relationship to OpenSAFELY. BG has received research funding from the Bennett Foundation, the Laura and John Arnold Foundation, the NHS National Institute for Health Research (NIHR), the NIHR School of Primary Care Research, NHS England, the NIHR Oxford Biomedical Research Centre, the Mohn-Westlake Foundation, NIHR Applied Research Collaboration Oxford and Thames Valley, the Wellcome Trust, the Good Thinking Foundation, Health Data Research UK, the Health Foundation, the World Health Organisation, UKRI MRC, Asthma UK, the British Lung Foundation, and the Longitudinal Health and Wellbeing strand of the National Core Studies programme; he has previously been a Non-Executive Director at NHS Digital. BG receives personal income from speaking and writing for lay audiences on the misuse of science. SE is on the CEPI funded SPEAC meta-DSMB for all CEPI funded vaccines, but it is not related to this paper. ID's research group has received grants from GlaxoSmithKline and AstraZeneca and holds shares in GSK. RW's institution receives grants from NIHR and UKRI. LT is an unpaid member of three trial steering committees (NIHR funded trials). UKRI has provided grant support to KM's institution.

Role of the funding source

The study funder played 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. All researchers were independent from funders and all authors had full access to results of the analyses, however all individual-level data remained in the electronic-health-record vendor's highly secure data centre, avoiding the need for potentially disclosive pseudonymized data to be transferred off-site. This secure software interface, in addition to other technical and organisational controls, minimises re-identification risk.

All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Rights retention

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TABLES

Table 1. Study populations

RECORDED WITH COVID-19	COMPARATORS
<p>Wave 2 cohort</p>	
<p>Individuals with community COVID-19 were selected between 1st September 2020 and 31st January 2021 (i.e., when COVID-19 test and trace was more active, and we were more confident of capturing COVID-19 cases).²⁷</p>	
<p><i>Selection of people with COVID-19 (Wave 2)</i> We selected individuals with COVID-19 based on recording of: 1) primary-care morbidity-coded COVID-19 diagnosis; or 2) SGSS lab record for a positive COVID-19 test between 1st September 2020 and 31st January 2021. We excluded individuals if they had a record for a COVID-19 hospitalisation (ICD-10 codes U07.1 “COVID-19 - virus identified” or U07.2 “COVID-19 - virus not identified” recorded in any diagnostic position) at any time prior to their first community record (i.e., primary-care or SGSS test) for COVID-19 (Figure S2, Text S2).</p>	<p><i>Selection of matched comparators (Wave 2)</i> We individually matched people with community COVID-19 from the Wave 2 cohort, without replacement, on age (within 1 year), sex, and Sustainability and Transformation Plans region (STP, a geographical area used in NHS administration, 31 regions are available in our data) to two cohorts of comparators: 1) <u>Contemporary</u>: individuals registered with practices contributing to OpenSAFELY during the same period (1st September 2020 to 31st January 2021) as those with COVID-19; and 2) <u>Historical</u>: individuals registered with practices contributing to OpenSAFELY between 1st September 2017 and 31st January 2018. We matched each individual with COVID-19 in Wave 2 with up to five contemporary, and up to five historical, comparators.</p>
<p><i>Follow-up of people with COVID-19 (Wave 2)</i> Individuals with COVID-19 in Wave 2 were followed up from four weeks after their initial infection record until the earliest of: death, no longer registered with primary-care practice, first hospitalisation for COVID-19 (code in any diagnostic position), or study end (31st January 2022).</p>	<p><i>Follow-up of matched comparators (Wave 2)</i> Contemporary Wave 2 comparators were followed from the same calendar date as their matched individual with COVID-19 until the earliest of: death, no longer registered with primary-care practice, first hospitalisation for COVID-19, or study end (31st January 2022). Historical comparators were followed from the same calendar date but three years prior to that of their matched individual with COVID-19 until the earliest of: death, no longer registered with primary care practice, first hospitalisation for COVID-19, or study end (31st January 2020).</p>

RECORDED WITH COVID-19	COMPARATORS
Wave 4 cohort	
<p>Individuals with community COVID-19 were selected between 15th December 2021 and 31st March 2022 (Wave 4 end was 29th April 2022, but freely available test and trace ended in the UK on 1st April 2022). Wave 4 was selected as we wanted to investigate the Omicron variant, which was more transmissible but with less severe acute symptoms than the Wave 2 variant (B.1.1.7).¹⁹</p>	
<p><i>Selection of people with COVID-19 (Wave 4)</i> People with COVID-19 in Wave 4 were selected in the same way as described above for Wave 2 but during the Wave 4 time period of 15th December 2021 to 31st March 2022.</p>	<p><i>Selection of matched comparators (Wave 4)</i> Individuals from the Wave 4 cohort were matched using the same approach as described above for the Wave 2 cohort but only to a contemporary cohort of Wave 4 comparators (selected from between 15th December 2021 and 31st March 2022).</p>
<p><i>Follow-up of people with COVID-19 (Wave 4)</i> Individuals with COVID-19 in Wave 4 were followed-up from four weeks after their initial infection record until the earliest of: death, no longer registered with primary-care practice, first hospitalisation for COVID-19 (code in any diagnostic position), or study end (31st March 2023).</p>	<p><i>Follow-up of matched comparators (Wave 4)</i> Contemporary Wave 4 comparators were followed from the same calendar date as their matched individual with COVID-19 until the earliest of: death, no longer registered with primary-care practice, first hospitalisation for COVID-19 (code in any diagnostic position), or study end (31st March 2023).</p>

Table 2. Baseline characteristics of people included in the long-COVID-19 symptoms, diagnoses and prescriptions study by exposure to COVID-19, including exposed to COVID-19 during Wave 2 (1st September to 31st January 2021) and two unexposed-to-COVID-19 comparator groups

Characteristic	COVID-19 ¹	No COVID-19 ²	
	Record of COVID-19 in the community during Wave 2 (N=902885 ³)	Wave 2 (2020-2021) comparator group (N=4449265)	Historical (2017-2018) comparator group (N=4428995)
Age (years) ⁴			
0-2	8870 (1.0)	42725 (1.0)	42815 (1.0)
3-5	11105 (1.2)	55885 (1.3)	56070 (1.3)
6-11	37250 (4.1)	186090 (4.2)	185065 (4.2)
12-17	64105 (7.1)	322080 (7.2)	316750 (7.2)
18-39	365930 (40.5)	1782760 (40.1)	1769905 (40.0)
40-49	152825 (16.9)	755605 (17.0)	754545 (17.0)
50-59	146580 (16.2)	726790 (16.3)	727045 (16.4)
60-69	66895 (7.4)	332175 (7.5)	332775 (7.5)
70-79	28445 (3.2)	142245 (3.2)	141585 (3.2)
80+	20880 (2.3)	102900 (2.3)	102440 (2.3)
Mean (SD)	38.4 (18.8)	38.4 (18.8)	38.5 (18.8)
Median (IQR)	37.0 (24.0-52.0)	37.0 (24.0-52.0)	37.0 (24.0-52.0)
Sex ⁴			
Female	493985 (54.7)	2430350 (54.6)	2418380 (54.6)
Male	408900 (45.3)	2018915 (45.4)	2010615 (45.4)
Index of multiple deprivation			
1 (least deprived)	150105 (16.6)	789270 (17.7)	793405 (17.9)
2	167880 (18.6)	849060 (19.1)	851725 (19.2)
3	182440 (20.2)	907620 (20.4)	906370 (20.5)
4	193505 (21.4)	907205 (20.4)	897785 (20.3)
5 (most deprived)	208950 (23.1)	996105 (22.4)	979710 (22.1)
Ethnicity			
White	588570 (65.2)	2974945 (66.9)	3010145 (68.0)
South Asian	95690 (10.6)	327755 (7.4)	314130 (7.1)
Black	22370 (2.5)	116440 (2.6)	107375 (2.4)
Mixed	13185 (1.5)	66035 (1.5)	59195 (1.3)
Other	15075 (1.7)	106185 (2.4)	90360 (2.0)
Missing	167995 (18.6)	857905 (19.3)	847790 (19.1)
Housing density			
Rural	138775 (15.4)	789040 (17.7)	792820 (17.9)
Urban	764105 (84.6)	3660225 (82.3)	3636175 (82.1)
Number of comorbidities diagnosed in the previous year			
0	582350 (64.5)	3155540 (70.9)	2618735 (59.1)
1	136710 (15.1)	587160 (13.2)	682980 (15.4)
2+	183825 (20.4)	706565 (15.9)	1127280 (25.5)
Number of types of distinct BNF groups of drugs prescribed in the previous year			
0	301005 (33.3)	1856835 (41.7)	1560395 (35.2)
1	267860 (29.7)	1215830 (27.3)	1251795 (28.3)
2+	334020 (37.0)	1376600 (30.9)	1616805 (36.5)
Number of GP appointments in the previous year			
0	245810 (27.2)	1579595 (35.5)	1462635 (33.0)
1-5	362585 (40.2)	1645490 (37.0)	1635310 (36.9)
6+	294490 (32.6)	1224180 (27.5)	1331050 (30.1)

Note 1: Record of COVID-19 (test result or primary care diagnosis) during Wave 2. **Note 2:** Wave 2 comparator matched to person with COVID-19 on age, sex, region, calendar date and with no record of any prior COVID-19 on the date of the matched individual's COVID-19 record. Pre-pandemic comparator selected in the same way except date two years prior to the date of the matched individual's COVID-19 record. **Note 3:** All counts in this table rounded to the nearest 5 in order to minimise the risk of secondary disclosure. **Note 4:** Matching variables.

LIST OF FIGURES

Figure 1

Association between having a record of COVID-19 in the community and symptoms being recorded by a GP during the period from four weeks after COVID-19 date (or matched comparator date) until one year after COVID-19: (a) at any time during one year; (b) in three time periods; and (c) by number of GP consultations in the year prior to COVID-19.

Figure 2

Association between a record of COVID-19 in the community & diagnoses being recorded by a GP from four weeks after COVID-19 date (or matched comparator date) until one year after COVID-19: (a) at any time during one year; (b) in three time periods; and (c) by number of GP consultations in the previous year. Wave 2 (1st Sep 2020-31st Jan 2021) and Wave 4 (15th Dec 2021-31st Mar 2022) analyses both used contemporary comparator groups (from the corresponding wave without a record of COVID-19).

Figure 3

Association between a record of COVID-19 in the community & new prescriptions by a GP four weeks after COVID-19 date (or matched comparator date) until one year after COVID-19: (a) at any time during one year; (b) in three time periods; and (c) by number of GP consultations in the previous year. Wave 2 (1st Sep 2020-31st Jan 2021) and Wave 4 (15th Dec 2021-31st Mar 2022) analyses both used contemporary comparator groups (from the corresponding wave without a record of COVID-19).