National Institute for Health and Care Excellence

COVID-19 rapid guideline: managing the long-term effects of COVID-19

[H] Evidence review for case definition

NICE guideline NG188

November 2021

Guideline version (Final)

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COVID-19 rapid evidence review: Case definition

November 2021

Literature search

NICE's information services team identified relevant evidence through focused evidence searches up to 19th July 2021. These search records were subsequently assessed for inclusion (see Appendix 3 for further details).

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the protocols (see Appendix 1). One reviewer screened titles and abstracts, with a second reviewer checking 10% of entries.

Having identified the evidence, 1 reviewer assessed the full text references of potentially relevant evidence to determine whether they met the inclusion criteria for this evidence review. All uncertainties were discussed and referred to an adviser if needed. See Appendix 4 Study flow diagram for the study flow chart of included studies and the list of excluded studies, with reasons for exclusion.

Review questions

What is the trajectory of post-COVID-19 syndrome (PCS)? Does this differ based on patient characteristics? For example, age, sex, ethnicity, comorbidities, severity of acute COVID-19

Are fluctuating symptoms and episodes of disability features of post-COVID-19 syndrome? Does this differ based on patient characteristics? For example, age, sex, ethnicity, comorbidities, severity of acute COVID-19

The review protocols are shown in Appendix 1.

Included studies

The literature search identified 4499 articles which were sifted on title and abstract. Of these, 27 articles were considered for assessment at full text. There was a total of 7 studies included in the review and 20 studies excluded. See Table 1.

Table 1 Included studies

Study	Country, study design, dates	Population (n)	Approach	Outcomes
Walker 2021	UK, retrospective cohort study (preprint) Feb 2020 to 25 April 2021	• All people registered with a general practice on the 1st November 2020 • N=23,273 included in analysis • 55% people aged 45-69 years • 65% female • 4% White ethnicity	Describes the use of long COVID codes in electronic health records (EMIS and TTP SystmOne) in English primary care	• Diagnostic codes • Referral codes • Assessment codes
Menges 2021	Switzerland, retrospective cohort study (preprint) 6 October 2020 and 26 January 2021	• Zurich SARS-CoV-2 Cohort study (diagnosed between February 2020 and 05 August 2020) • Patients were enrolled a median of 7.2 months (range 5.9 to 10.3 months) after diagnosis • N=431, median age 47 years. 49.7% female	Baseline questionnaire including questions on: • socio-demographics • medical comorbidities and risk factors • acute SARS-CoV-2 infection • current health status and symptoms, • healthcare contacts since diagnosis, • HRQoL	• Measurements of recovery • New or ongoing symptoms • Healthcare utilisation • Diagnoses • COVID-19 related complications
Vaes 2021	Netherlands, cross-sectional study (Published)	• Members of two Long COVID Facebook groups and a COVID-19 panel (www.coronalongplein.nl)	An online survey with questions regarding: • Demographics • Pre-existing comorbidities	• Work productivity

Study	Country, study design, dates	Population (n)	Approach	Outcomes
		• 239 patients with confirmed diagnosis included in the analysis • Median age 50 years • 82.8% female	• COVID-19 diagnosis • Intensive care unit (ICU) or hospital admission • Current self-reported health status • Received care	• Health, functional status and QoL • Received care
Delbressine 2021 (Secondary publication of Vaes 2021)	Netherlands, cross-sectional study (Published)	• Members of two Long COVID Facebook groups and a COVID-19 panel (www.coronalongplein.nl) • 239 patients with confirmed diagnosis included in the analysis • Median age 50 years • 82.8% female	Participants were asked about the average time they spent walking in the previous seven days and which sports/activities they performed before COVID-19 and at the time of completing the questionnaires (approximately three and six months after symptom onset)	• Self-reported walking time • Activities
Davis 2021	International, cross-sectional study (Published)	• People who have had COVID-19 or suspected COVID-19 who have or had ongoing symptoms on social media or online patient support groups • N=3762, age range 30 to 60 years, 79% female, 85% White ethnicity	• Launched 6 September 2020 • The survey was created by a team of patients with COVID-19 who are members of the Body Politic online COVID-19 support group and formed the Patient-Led Research Collaborative • Consisted of 257 questions • Timepoint 7 months	• Symptom duration • Symptoms over time • Diagnosis • Changes in symptoms • Impact on activities
Lambert 2021	USA, cross-sectional study (Preprint)	• Members of Survivor Corps on Facebook and other online COVID-19 groups • August and November 2020 • N=5163, 55% aged 35-55 years, 86% female	The survey collected: • self-reported demographic information • extensive medical history • experiences with COVID-19	• Duration of symptoms • Impact of symptoms

Study	Country, study design, dates	Population (n)	Approach	Outcomes
Ziauddeen 2021	UK, cross-sectional study (Preprint)	• Members of the Facebook Long COVID Support Group, UK doctors #longcovid Facebook Group, Survivor Corps Facebook Group and the Body Politic Support Group on Slack • N=2550, mean age 46.5 years, 82.8% female, 93.3% White ethnicity	Questions included: • demographic information • baseline health • the pattern of illness • symptoms that remained/appeared over the course of the illness • functional status, impact on health, activity, ability to work including current employment status, and healthcare usage	• Duration of illness • Course of illness • Functional ability • Work • Healthcare utilisation

Key results

Diagnosis of Post-COVID-19 syndrome or alternative conditions

Up until January 2021, Long COVID codes were used in electronic health records in primary care systems in England for 23,273 people (Walker 2021). Some people had multiple codes on their record, accounting for a total of 36,507 codes being used. Of these codes, 23,468/36,507 (64.3%) were the diagnostic code for "Post COVID-19 syndrome" and 2,989/36,507 (8.2%) were the diagnostic code for "Ongoing symptomatic disease cause by severe acute respiratory syndrome coronavirus 2" (Walker 2021).

The Zurich SARS-CoV-2 cohort enrolled 431 adults from the general population with laboratory confirmed SARS-CoV-2 infection (Menges 2021). Of these adults, 77 (18%) were given a diagnosis at 6 months follow-up. Of these 27 (35%) were diagnosed with a medically evaluated COVID-19 complication, 11 (14%) were diagnosed with a self-evaluated COVID-19 related complication and 39 (51%) were diagnosed with a non-COVID-19 related diagnosis or was unclear. The study did not report what these diagnoses were (Menges 2021). Similarly, a survey from the Patient-Led Research Collaborative (Davis 2021) found that around 1633 people (43.4%) were diagnosed with at least one condition after initial acute COVID-19 illness.

Referral and assessment

Referral codes were less frequently used in electronic health records (Walker 2021). 1809/36,507 (2.9%) codes were the referral code for being signposted to YOUR COVID Recovery, 6332/36,507 (17.3%) were the referral code for referral to a post-COVID assessment clinic and 1806/36,507 (4.9%) were the referral code for referral to the YOUR COVID Recovery rehabilitation platform (Walker 2021). Assessment tools accounted for <1% of all the codes used. The assessment tools coded included the Newcastle post-COVID syndrome follow-up screening questionnaire, COVID-19 Yorkshire Rehabilitation screening tool and the Post-COVID-19 Functional Status Scale patient self-report (Walker 2021).

Healthcare utilisation

The Zurich SARS-CoV-2 cohort included 81 people who had previously been hospitalised for COVID-19 (Menges 2021). Of these people 8 (10%) had been re-hospitalised for reasons related to COVID-19 (Menges 2021).

A survey of Long COVID Facebook groups (n=239) found the number of people receiving physiotherapy or rehabilitation between 3 and 6 months of follow-up (31.8% and 11.7% respectively) was significantly higher compared to the period between initial infection and 3 months follow-up (4.2%; $p<0.05$) (Vaes 2021).

Symptom numbers and duration

The Patient-Led Research Collaborative 7-month follow-up survey found that 2454 (65.2%) respondents experienced symptoms for more than 180 days after development of initial symptoms (Davis 2021). They found that for those people that did not recover within 90 days, the average number of symptoms peaked at month 2 from initial illness (mean number of symptoms 17.16 95% CI 17.78 to 16.54). For those people experiencing symptoms for longer than 6 months, the mean number of symptoms was 13.79 (95% CI 12.68 to 14.88) (Davis 2021). Another survey found that at 6 months, 98 (41%) people reported 1 to 5 symptoms, 69 (40%) people reported 6 to 10 symptoms and 32 (13%) reported >10 symptoms (Vaes 2021).

A survey of Facebook Long COVID groups found that symptom duration ranged from 2 weeks to over 100 days (Lambert 2021). Similarly, another survey reported mean duration of illness to be 7.2 (SD 1.8) months (Ziauddeen 2021).

Course of illness

The Patient-Led Research Collaborative suggested that symptoms were clustered in three groups according to their time courses (Davis 2021). Cluster 1 features symptoms that are most likely to occur early in the illness, peaking at 2 to 3 weeks and decreasing over time. These include gastrointestinal and ear, nose and throat (ENT) symptoms. Cluster 2 features symptoms that have a relatively stable probability over time such as chest pain, tachycardia, abdominal pain, neuropsychiatric symptoms and respiratory symptoms. Cluster 3 features that are most likely to increase sharply over the first 2 months. Their probability can remain stable (e,g, constipation), decrease slightly over time (e.g. post-exertional malaise

and fatigue) or increase slightly in later months (e.g. tinnitus, hearing loss, muscle spasms and tremors) (Davis 2021).

Timing of symptom onset varied and was described as occurring in "waves" (Lambert 2021). The first wave of symptoms was described as being heavily dominated by neurological and cardiovascular manifestations with some indicators of an immune response. The second wave of symptoms included microvascular consequences. The third wave of symptoms suggested impact of endocrine function. The time course of these waves was not reported in the study (Lambert 2021).

Changes in symptoms

The Patient-Led Research Collaborative survey (n= 3762) found that 85.9% (84.8% to 87%) of people reported experiencing relapses of symptoms (Davis 2021). Relapses were characterised as occurring in an irregular pattern (52.8%, 95% CI 51.2% to 54.4%) and in response to a specific trigger (52.4%, 95% CI 50.8% to 54%). 164/3762 (4.4%) reported experiencing a temporary break in symptoms (Davis 2021). Similarly, another survey (n=5163) found that 97.8% reported that at least one of their symptoms would temporarily resolve and then later return (Lambert 2021).

The Zurich SARS-CoV-2 cohort found that 106/431 (24.6%) people reported new or ongoing symptoms but did not specifically report fluctuating symptoms (Menges 2021).

Triggers of symptom relapses

The Patient-Led Research Collaborative survey (n= 3762) found that the most commonly reported triggers of relapses or worsening of symptoms were: Physical activity: 70.7%, (95% CI 69.2% to 72.1%); Stress: 58.9%, (95% CI 57.3% to 60.5%); Exercise: 54.39%, (95% CI 52.8% to 56.0%); Mental activity: 46.2%, (95% CI 44.7% to 47.8%); during menstruation: 34.3%, (95% CI 32.0% to 36.5%) and before menstruation: 35.2%, (95% CI 33.0% to 37.3%) (Davis 2021). Similar triggers of relapses were identified in another survey (n=5163): physical activity (77.2%); stress (55.1%); disturbance in sleep patterns (46.9%); cognitive activity (42.2%) and domestic chores (35.0%) (Lambert 2021). The survey also found that 23.2% people

reported symptoms varying by time of day and 15.8% people reported not always being able to identify a trigger (Lambert 2021).

Impact on activities

At the time of completing the survey (n=2550), participants reported that being ill affected their ability to carry out activities such as domestic chores (84.3%), leisure (84.8%) and social (77.1%) activities, work (74.9 %), self-care (50.0%), childcare (35.8%), and caring for other adults (26.1%), as well as affecting their mental health (63.7%) (Ziauddeen 2021). At 6 weeks from the start of symptoms 32.3% reported that they were unable to live alone without any assistance, and 34.5% reported moderate functional limitations. 89.5% of participants said they avoided certain activities/duties at 6 weeks from onset of illness (Ziauddeen 2021).

Another survey found that problems with mobility, self-care, and daily activities, who had pain or discomfort, or felt anxious or depressed improved at 6 months follow-up compared to 3 months (Vaes 2021). However, 62% still reported moderate to extreme problems with daily activities at 6 months (Vaes 2021). There was improvement of functional status in 26.8% of 239 respondents but deterioration in 15.5% of respondents (Vaes 2021). The survey also found that people were significantly less dependent of a partner or family for personal care at 6 months follow up but the proportion of people still needing help was still significantly higher compared to before COVID-19 illness (Vaes 2021).

The same 239 participants reported improvement in walking at 6 months compared to 3 months but was still significantly lower than before COVID-19 illness. In contrast, the proportion of participants that reported walking and cycling indoors at 6 months was significantly higher compared to before COVID-19 illness (Delbressine 2021).

The surveys reported that symptoms had an impact on the ability to work. One survey reported symptoms that had the most impact were fatigue, personality change, a sensation of “brain pressure”, inability to sleep, inability to exercise, difficulty concentrating, memory problems, confusion, shortness of breath, and the fluctuating nature of symptoms (Lambert 2021). The Patient-Led Research Collaborative (n=3762) found that at 7 months 27.3% (95% CI 25.3% to 29.4%) of unrecovered participants were working the same hours as they were before COVID-

19 illness compared to 49.3% (40.8% to 57.9%) of recovered participants (Davis 2021). 45.6% (95% CI 43.2% to 48%) of unrecovered respondents were working reduced hours at 7 months and 22.3% (95% CI 20.5% to 24.3%) were not working due to their health condition (Davis 2021). Similarly, another survey found that at 7.7 months since acute COVID-19 illness, 9.7% of 2550 participants reported working reduced hours, 19.1% reported being unable to work and 1.9% reported being made redundant or having to take early retirement (Ziauddeen 2021).

Another survey (n=239) found that the mean work time missed in the previous week due to ill health and impairment while working reduced from 73% to 52% and from 66% to 60%, respectively (both $p<0.001$) (Vaes 2021).

Subgroups

One study found that a higher percentage of females and individuals who had previously been hospitalised reported not having fully recovered compared to males and non-hospitalised people respectively (Menges 2021). The study found that a higher percentage of females reported new or ongoing symptoms compared to males (Menges 2021).

Strengths and limitations

All included studies were assessed to be of high risk of bias. This was mainly due to the retrospective nature of the study designs and most data being self-reported which increases the risk of recall bias. There was also an increased risk of selection bias as participants in the cross-sectional studies were recruited through platforms targeting those with persistent symptoms. The respondents to the surveys were predominantly white, female and of higher socioeconomic status. Some of the surveys targeted the same social media groups so there may be a potential for duplication of the evidence base due to the similar nature of the questions. However, there were themes emerging from the evidence that were consistent across all studies, such as the variance and fluctuation of symptoms.

A modified GRADE approach was carried out to assess the certainty of the body of evidence. As all the of data from the studies were descriptive, a narrative approach to GRADE was undertaken. All outcomes were rated as very low certainty. This is due to the high risk of bias of all the studies but also the inability to measure

imprecision. Some outcomes were additionally downgraded for inconsistency due to different study designs.

GRADE profiles are reported in Appendix 7.

Expert panel discussion

This section describes how the expert panel considered the evidence in relation to the recommendations within the guidance.

Benefits and harms

The panel recognised the importance of having a case definition for describing the long-term effects of COVID-19 and the need to review it as more information on the condition becomes available. Having a case definition allows clinicians to effectively diagnose, treat and manage a condition and distinguish it from other conditions. The panel considered that the updated evidence review continued to support the current case definition and therefore no changes were made.

The panel acknowledged that this case definition may be interpreted as a diagnosis of exclusion. However, they discussed that ongoing symptomatic COVID-19 and post-COVID-19 syndrome have many features in common with other conditions, some of which could be considered life threatening. Therefore, ongoing symptomatic COVID-19 and post-COVID-19 syndrome should not be the first conditions to be excluded for reasons of patient safety.

Certainty of the evidence

There is a lack of certainty in the evidence base. Most studies included in the review were cross-sectional surveys and were judged to be of high risk of bias due the retrospective nature of the studies. All the data in the studies were self-reported and therefore prone to recall bias. The surveys were disseminated to online social media groups which will have included participants who were self-selected and therefore may not be representative of the general population. Most participants were female and of white ethnicity. Some of the same social media groups were targeted for more than one survey so there is a possibility of duplication and double counting due to the similar nature of the questions. However, there were themes emerging from the

evidence that were consistent across all studies, such as the variance and fluctuation of symptoms.

Preferences and values

The panel understood from the qualitative evidence that the fluctuating nature of symptoms and the trajectory of the disease led to increased fear and uncertainty and a sense of limited information and knowledge. The panel acknowledged the importance of having a case definition to reduce the uncertainty around the trajectory of illness.

Resource and other considerations

Not applicable.

Other considerations

Whilst there are concerns that a case definition may inadvertently exclude people who do not present in a typical way, including children and older adults, the panel discussed that the case definition was broad enough to capture people who need help and support for the long-term effects of COVID-19.

The panel expect that having a case definition for the long-term effects of COVID-19 would be acceptable to patients. This is due to there being limited knowledge of the condition and patients reporting experiences of not being taken seriously. The key features of the case definition reflect patient experiences of illness trajectory seen in the evidence, including the fluctuating nature of symptoms.

The panel discussed the new WHO definition A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021 (who.int) They agreed that it was very similar to the NICE definition of Post-COVID-19 syndrome in that it usually occurs 3 months from the onset of COVD-19 and cannot be explained by alternative diagnosis. There is also agreement that symptoms may fluctuate over time. However, the expert panel agreed it was important to recognise the ongoing symptomatic COVID-19 population with symptoms between 4 - 12 weeks from onset of COVID-19 and therefore favoured to keep the NICE definition in place at this time.

Appendix 1 Methods used to develop the guidance

Please see the methods chapter for details on how this guideline was developed.

Appendix 2 Review protocols

Review question 1

What is trajectory of post-COVID-19 syndrome (PCS)? Does this differ based on patient characteristics? For example, age, sex, ethnicity, comorbidities, severity of acute COVID-19

Criteria	**Notes**
Population	Adults and children experiencing ongoing symptoms beyond the duration of acute COVID-19 illness (>4 weeks)
Exposure	• History of SARS-CoV-2 infection which has been laboratory-confirmed or • History of symptoms suggestive of acute COVID-19 illness
Comparators	Any or no comparator
Outcomes	Time of referral to PCS services Signs and symptoms experienced at time of follow up (These include physical, cognitive, psychological and psychiatric symptoms) Patient reported outcomes such as: • Self-reported recovery • Changes in symptoms • Changes in functioning and disability using WHO ICF framework Proportion of people with alternative diagnoses Number of people diagnosed with PCS (SNOMED and READ codes) Time to diagnosis with PCS (including time to coding with SNOMED and READ codes)

	End organ damage effects
Settings	Any

Subgroups	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes
	• Severity of initial COVID 19 illness (using definition in MAC guideline)
	• Underlying or pre-existing conditions
	• Characteristics such as age, sex ethnicity, disabilities included in the EIA
	• Vaccination status

Study types	The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. Preferred: • Systematic reviews of cohort studies • Cohort studies (prospective or retrospective) • Cross-sectional studies • Qualitative studies • Mixed methods studies
Countries	Any
Timepoints	At least 4 weeks from initial acute COVID-19 illness onset

Review question 2

Are fluctuating symptoms and episodes of disability features of post-COVID-19 syndrome? Does this differ based on patient characteristics? For example, age, sex, ethnicity, comorbidities, severity of acute COVID-19

Criteria	Notes
Population	Adults and children experiencing ongoing symptoms beyond the duration of acute COVID-19 illness (>4 weeks)
Exposure	• History of SARS-CoV-2 infection which has been laboratory-confirmed or • History of symptoms suggestive of acute COVID-19 illness
Comparators	Any or no comparator
Outcomes	Signs and symptoms experienced at the time of follow-up (These include physical, cognitive, psychological and psychiatric symptoms) Time to recovery from any ongoing COVID-19 symptoms. Time to recurrence of any symptoms Number of recurrences of any symptoms Triggers for recurrence of symptoms Worsening of symptoms at the time of follow-up Onset of new symptoms at the time of follow-up Referral for investigations based on symptoms People with alternative diagnoses Number of people diagnosed with PCS (SNOMED and READ codes) Number of recurrences Readmission to hospital or attendance at other acute care facilities Impact on quality of life, activities of daily living and return to work

Settings	Any

Subgroups	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes
	• Severity of initial COVID 19 illness (using definition in MAC guideline)
	• Underlying or pre-existing conditions
	• Characteristics such as age, sex ethnicity, disabilities included in the EIA
	• Vaccination status

Study types	The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. Preferred: • Systematic reviews of cohort studies • Cohort studies (prospective or retrospective) • Cross-sectional studies • Qualitative studies • Mixed methods studies
Countries	Any
Timepoints	At least 4 weeks from initial acute COVID-19 illness onset
Other exclusions	None

Appendix 3 Literature search strategy

Table 3 Review question 1 and 2 search strategy

Database	Platform	Date searched	Segment searched
NICE COVID-19 Surveillance repository	EPPI-R for Surveillance then the codeset for Long term effects	16/07/2021	Last updated 8 July 2021
NICE Evidence Search Medicines Current Awareness	https://www.evidence.nhs.uk - Apply the Medicines Current Awareness filter	16/07/2021	Searched on 16 July 2021
NICE Evidence Search	https://www.evidence.nhs.uk	19/07/2021	Searched on 19 July 2021
CINAHL	EBSCOhost	16/07/2021	Available on 16 July 2021
MEDLINE ALL	Ovid	16/07/2021	Ovid MEDLINE(R) ALL 1946 to July 15, 2021
Embase	Ovid	16/07/2021	Embase 1974 to 2021 July 15
PsycInfo	Ovid	16/07/2021	APA PsycInfo 1806 to July Week 1 2021
Preprints from medRxiv and bioRxiv	Via EPPI	19/07/2021	2021-07-19
Cochrane COVID-19 Study Register	https://covid-19.cochrane.org/	19/07/2021	Searched on 19 July 2021
Citationchaser	https://estech.shinyapps.io/citationchaser/	16/07/2021	Searched on 19 July 2021

Source	No. of results	Total results	Total after deduplication
NICE COVID-19 Surveillance	290	6907	4499
NICE Evidence Search Medicines Current Awareness	118		
NICE Evidence Search	15		
CINAHL	640		

Embase	2485		
MEDLINE	2406		
PsycInfo	143		
Preprints from medRxiv and bioRxiv	58		
Cochrane COVID-19 Study Register	72		
Citationchaser	680		

NICE resources

NICE COVID-19 Surveillance

Name	NICE COVID-19 Surveillance
How the results were selected	This monitoring process re-uses the search results completed for the NICE Evidence Summaries (which have now been superseded) and Surveillance of NICE Rapid Guidelines on COVID-19. The Surveillance process uses a combination of weekly and monthly searches to provide updates from journals, pre-prints, guidelines, policies and other documents on COVID-19 and SARs-CoV-2. The Surveillance process began on 30 March 2020 and it contains items published since 16 March 2020. The monitoring of the COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188) started in October 2020. The Surveillance codeset for NG188 was obtained on 7 July 2021 (containing search results from up to and including 2 July 2021). This contained 402 results. An update was done on 16 July 2021 with items from 8 July 2021. Note that the items added on 15 July 2021 had not been screened and were not part of these results. 429 unique items were screened. The results were manually screened by the searcher in EPPI-R. Obviously irrelevant items (vaccines, lockdowns, face masks, treatments, case reports) were excluded. Items were retained for relevance to the questions (PCS) but were not screened in more detail than that (i.e. included if relevant to the symptoms question).
Results	290

NICE Evidence Search – Medicines Current Awareness

Name	NICE Evidence Search Medicines Current Awareness
URL	https://www.evidence.nhs.uk
Search terms	(coronavirus or COVID19 or SARSCoV2) - Apply the Medicines Current Awareness filter

How the results were selected	The Medicines Current Awareness alerts from NICE Evidence search were obtained from the RIS files downloaded for the RAPID C19 programme at NICE. This started on 5 June 2020 and searched back to 22 May 2020. This was done on 7 July 2021 and included MCA content up to 7 July 2021. A new search directly on the database was done on 16 July 2021 for the results from 6-16 July. This means a total of 4137 results were downloaded, with 2432 reviewed after deduplication, covering 22 May 2020 to 16 July 2021. The results were manually screened by the searcher in EPPI-R. Obviously irrelevant items (vaccines, lockdowns, face masks, treatments) were excluded. Items were retained for relevance to the questions (PCS) but were not screened in more detail than that (i.e. included if relevant to the symptoms question).
Results	118

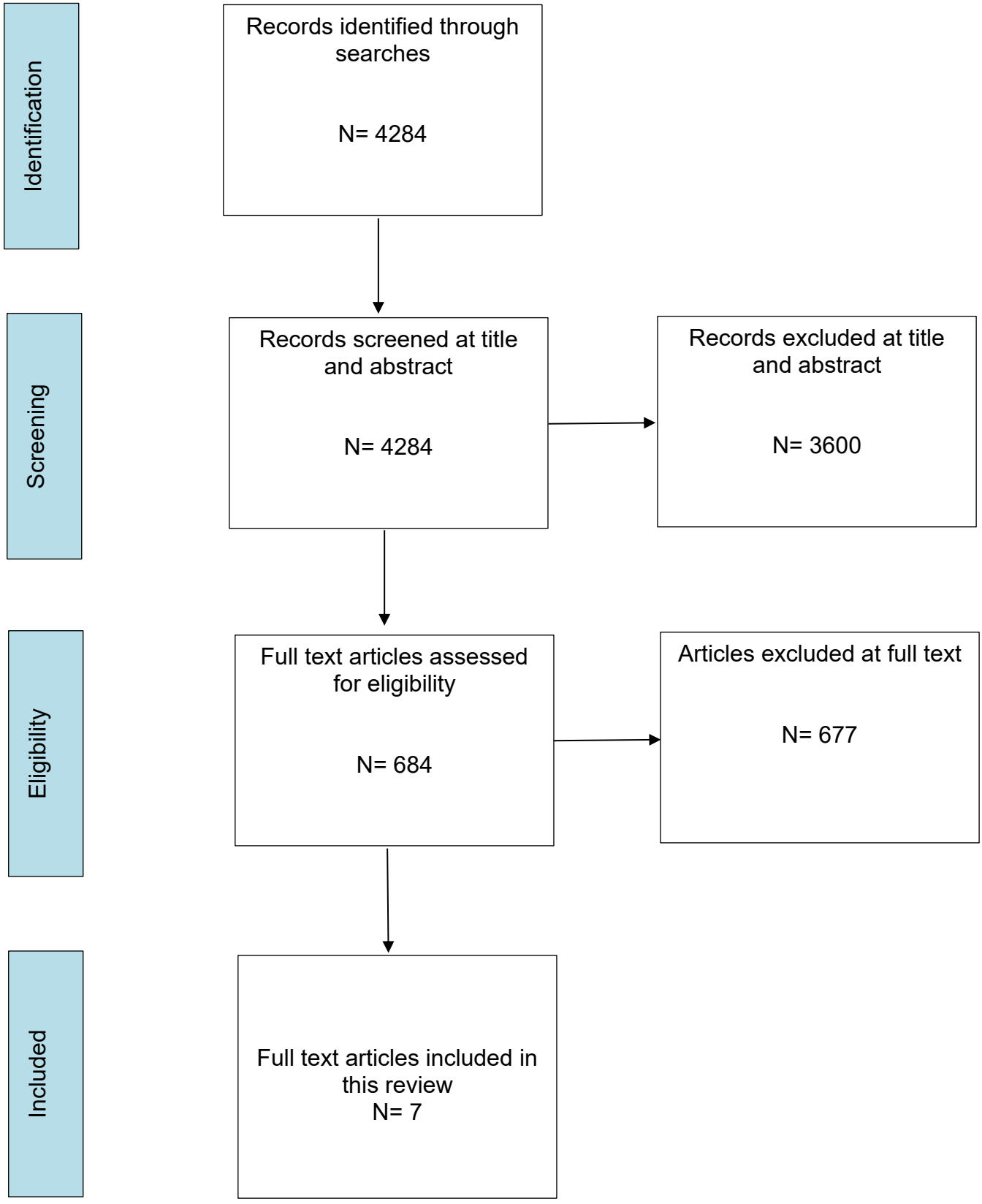
NICE Evidence Search

Name	NICE Evidence Search
URL	https://www.evidence.nhs.uk
Search terms	"long covid*" or "post covid*" or postcovid* or longcovid*
How the results were selected	This involved a search of NICE Evidence but without the source of information filter applied, this time with a search for long covid. The results were manually screened by the searcher in Evidence Search. Obviously irrelevant items (vaccines, lockdowns, face masks, treatments, care reports) were excluded. Items were retained for relevance to the questions (PCS) but were not screened in more detail than that (i.e. included if relevant to the symptoms question).
Admin	506 results screened
Results	15 in 2 files

Database strategies

Full details are available on request.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Study
Collaborative - The, OpenSAFELY, Walker Alex, J, MacKenna, Brian et al. Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY. medrxiv preprint
Davis, Hannah E., Assaf, Gina S., McCorkell, Lisa et al. (2021) Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 0(0)
Delbressine, Jeannet M., Houben-Wilke, Sarah, Vaes, Anouk W. et al. (2021) The impact of post-covid-19 syndrome on self-reported physical activity. International Journal of Environmental Research and Public Health 18(11): 6017
Menges, Dominik, Ballouz, Tala, Anagnostopoulos, Alexia et al. (2021) Estimating the burden of post-COVID-19 syndrome in a population-based cohort study of SARS-CoV-2 infected individuals: Implications for healthcare service planning. na(na): na-na
N, Lambert, S, Corps, Sa, El-Azab et al. (2021) COVID-19 Survivors? Reports of the Timing, Duration, and Health Impacts of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection. na(na): na-na
Vaes, Anouk W., Delbressine, Jeannet M., Houben-Wilke, Sarah et al. (2021) Recovery from COVID-19: A sprint or marathon? 6-month follow-up data from online long COVID-19 support group members. ERJ Open Research 7(2): 00141-2021
Ziauddeen, Nida, Gurdasani, Deepti, Hara Margaret, E et al. Characteristics of Long Covid: findings from a social media surve. medrxiv preprint

Appendix 6 Evidence tables

Davis, 2021

Bibliographic Reference	Davis, Hannah E.; Assaf, Gina S.; McCorkell, Lisa; Wei, Hannah; Low, Ryan J.; Re'em, Yochai; Redfield, Signe; Austin, Jared P.; Akrami, Athena; Characterizing long COVID in an international cohort: 7 months of symptoms and their impact; EClinicalMedicine; 2021; vol. 0 (no. 0)

Study details

Study design	Cross-sectional study
Aim of the study	To investigate the patient's lived experience, emphasizing symptom course and severity over time
Country/ Geographical location	International
Study setting	Online survey
Population description	People with suspected and confirmed COVID-19
Inclusion criteria	• People who have had a COVID-19, or suspected COVID-19 infection and are still suffering or have suffered symptoms for longer than 1 week • 18 years of age or older
Exclusion criteria	None reported
Intervention/test/approach	• The survey was created by a team of patients with COVID-19 who are members of the Body Politic online COVID-19 support group and formed the Patient-Led Research Collaborative • The survey consisted of 257 questions and required a median time of 69.3 min to complete. • To account for Long COVID symptoms that limit sustained focus and attention, respondents were encouraged to take breaks while completing the survey. • Progress was saved for up to 30 days to allow respondents to return to the survey at a later time. • Questions that mentioned technical terms included a description in plain language • The survey was created in English and translated into eight additional languages: Spanish, French, Portuguese, Italian, Dutch, Russian, Bahasa Indonesian, and Arabic.
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	• Links to the survey were disseminated via email, social media, and the online patient support groups

Methods of data analysis	• To investigate disease duration, the survey asked respondents to indicate the number of days their symptoms lasted. • For non-recovered respondents, this number provided only a lower bound on the eventual duration of symptoms • To account for this censoring in the data, they characterised the distribution of durations using the Kaplan-Meier estimator
Attrition/loss to follow-up	Survey response rate was 67.5%
Source of funding	All authors contributed to this work in a voluntary capacity. The cost of survey hosting (on Qualtrics) and publication fee was covered by AA's research grant (Wellcome Trust/Gatsby Charity via Sainsbury Wellcome centre, UCL)
Study limitations (Author)	• The majority of participants did not report having a positive SARS-CoV-2 diagnostic or antibody result but removing this population from the analysis did not change the result. • The retrospective nature of the study exposes the possibility of recall bias, which could impact the reliability of symptom prevalence estimates • Both overreporting and underreporting of symptoms are possible • There could be a sampling bias toward Long COVID patients who joined support groups and were active participants of the groups at the time the survey was published. • The effort to complete the survey may have deterred some respondents who experienced cognitive dysfunction, or were no longer ill and did not have incentives to participate • Most respondents had not been hospitalised (91.6%) • The demographics were strongly skewed towards English speaking (91.9%), white (85.3%), and higher socioeconomic status
Study limitations (Reviewer)	No additional limitations identified.
Summary of findings	**Symptom duration** • The probability of symptoms lasting beyond 35 weeks was 91.8% (95% CI 89.5% to 93.5%) • 2454/3762 (65.2%) respondents experienced symptoms for more than 180 days (6 months) • 233/1308 (17.8%) recovered and 1075/1308 (82.1%) took the survey before reaching 6 months of illness • For those that did not recover in 90 days, the average number of symptoms peaked at month 2 (mean number of symptoms: 17.16 95% CI 17.78 to 16.54) with less decline over time

- Respondents with symptoms for over six months experienced an average of 13.79 symptoms (95% confidence interval 12.68 to 14.88) in month 7

Symptoms over time

- Symptoms were clustered in three groups according to their time courses
- Cluster 1 consists of symptoms that are most likely to occur early in the illness, reaching a high point in the first two or three weeks then decreasing in probability over time.
- Cluster 2 consists of symptoms with a relatively stable probability over time
- Cluster 3 consists of symptoms most likely to increase sharply in the first two months. Their probability may plateau (like constipation), decrease slightly (like post-exertional malaise and fatigue), or increase slightly in the later months (like tinnitus, hearing loss, muscle spasms, and tremors).

Diagnosis

- Nearly half of respondents (43.4%) were diagnosed with at least one condition post-acute COVID-19 infection

Changes in symptoms

- A minimum of 85.9% (84.8% to 87.0%) of respondents reported experiencing relapses
- Relapses were characterised as occurring in an irregular pattern (52.8%, 95% CI 51.2% to 54.4%) and in response to a specific trigger (52.4%, 50.8% to 54.0%)
- Most commonly reported triggers of relapses or worsening of symptoms were:
- Physical activity: 70.7%, 69.2% to 72.1%
- Stress: 58.9%, 57.3% to 60.5%
- Exercise: 54.39%, 52.8% to 56.0%
- Mental activity: 46.2%, 44.7% to 47.8%
- During menstruation: 34.3%, 32.0% to 36.5%
- Before menstruation: 35.2%, 33.0% to 37.3%
- 164/3762 (4.4%) experienced a temporary break in symptoms

Impact on activities

- 27.3% (95% confidence interval 25.3% to 29.4%) were working as many hours as they were prior to becoming ill at the time of survey, compared to 49.3% (40.8% to 57.9%) of recovered respondents

	• 45.6%, 43.2% to 48.0% of unrecovered respondents were working reduced hours at the time of the survey • 45.2% (42.9% to 47.2%) of respondents reported requiring a reduced work schedule compared to pre-illness. 22.3% (20.5% to 24.3%) were not working at the time of survey due to their health condition.

Characteristics

Study-level characteristics

Characteristic	Study (N = 3762)
Age (years) Range	30 to 60
Female No of events	n = NR ; % = 78.9
White ethnicity No of events	n = NR ; % = 85

Outcomes

Outcomes

Outcome	Study, N = 3762
Symptom duration Custom value	See summary of findings
Symptoms over time Custom value	See summary of findings
Diagnosis Custom value	See summary of findings
Changes in symptoms Custom value	See summary of findings
Impact on activities Custom value	See summary of findings

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Section	Question	Answer
Overall bias and directness	Risk of bias judgment	High

Section	Question	Answer
Overall bias and directness	Directness	Directly applicable

Delbressine, 2021

Bibliographic Reference	Delbressine, Jeannet M.; Houben-Wilke, Sarah; Vaes, Anouk W.; Machado, Felipe V. C.; Goertz, Yvonne M. J.; Meys, Roy; Franssen, Frits M. E.; Spruit, Martijn A.; Van Herck, Maarten; Burtin, Chris; Spies, Yvonne; Vijlbrief, Herman; van 't Hul, Alex J.; Janssen, Daisy J. A.; The impact of post-covid-19 syndrome on self-reported physical activity; International Journal of Environmental Research and Public Health; 2021; vol. 18 (no. 11); 6017

Study details

Study design	Cross-sectional study
Aim of the study	To assess the impact of COVID-19 on the level of self-reported physical activity (time spent walking per week and leisure-time sports activities) in patients with post-COVID-19 syndrome
Country/ Geographical location	Netherlands and Flanders (Belgium)
Study setting	Online questionnaire
Population description	Not described
Inclusion criteria	Not described
Exclusion criteria	Participants with a presumed COVID-19 diagnosis (n = 766) were excluded from the primary analyses
Intervention/test/approach	The survey contained questions regarding demographics (sex (male/female/other), age (years), body mass index (BMI) (kg/m2), marital status (married or living with partner: yes/no), education level (low/medium/high)), self-reported pre-existing comorbidities, COVID-19 diagnosis (based on reverse transcription polymerase chain reaction (RT-PCR) test and/or computed tomography (CT) scan of the thorax; symptom-based medical diagnosis; no test/medical diagnosis), received care (no care needed/physiotherapy/rehabilitation), symptoms and admission to hospital. Participants were asked about the average time they spent walking in the previous seven days and which sports/activities they performed before COVID-19 (retrospectively) and at the time of completing the two questionnaires (approximately three and six months after symptom onset, respectively
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	The online questionnaire was made available between June 4 and June 11 of 2020 to all members of two long COVID Facebook groups and to an online COVID-19 panel. 1556 participants who agreed to take part in a follow-up of this

	study were asked to complete a second survey between August 31 and September 8 of 2020
Methods of data analysis	Data were presented as mean and standard deviation (SD), median and interquartile range (IQR) or frequency and proportion, as appropriate. Data were tested for normality with a Kolmogorov–Smirnov test. Within-group comparisons were performed using the Friedman test, McNemar's test or standard Cochran's Q test (with Bonferroni corrected post-hoc test). Between-group comparisons were performed using a Mann–Whitney U test or Fisher's exact test. A priori, the level of significance was set at $p < 0.05$.
Attrition/loss to follow-up	1005/1556 participants completed the second questionnaire
Source of funding	Lung Foundation Netherlands grant 4.1.16.085; F.V.C.M. is financially supported by ZonMw (ERACoSysMed #90030355) and R.M. is financially supported by Lung Foundation Netherlands grant 5.1.18.232
Study limitations (Author)	• Since participants were recruited through platforms that targeted patients with persistent symptoms, there is the possibility of selection bias and the external validity of these results might be limited • It is possible that participants that recovered after three months did not feel the need to fill in the questionnaire at six months and therefore are underrepresented • Females are overrepresented in this sample, possibly due to the higher proportion of women that are part of online long COVID support groups • Due to the national regulations that were in place during the first wave of COVID-19 infections, the possibilities for sports and activity were limited • Not everyone would have had the opportunity to have been tested
Summary of findings	**Self-reported walking time** • At 3 months, walking time in the previous week was significantly reduced compared to pre-COVID-19. [3 months 60 (15-120 min) vs pre-COVID-19 120 (60-240 min)] • There was recovery in walking time between 3 months and 6 months from 60 (15–120) min. to 90 (30– 150) min but was still significantly lower than pre-COVID-19 **Activities** • At three months of follow-up, participants reported performing fewer activities compared to pre-COVID-19 and almost 44% of the participants were not able to be physically active or perform sports or activities due to COVID-19. • From three months to six months of follow-up the proportion of participants unable to be physically active

	significantly decreased (from 44% to 12%; $p < 0.05$) and the proportion of participants reporting walking, cycling outdoors/indoors, participating in (physio)fitness/exercise groups and running significantly increased. • The proportion of participants that reported walking and cycling indoors at six months was significantly higher compared to pre-COVID-19

Characteristics

Study-level characteristics

Characteristic	Study (N = 239)
Age Median (IQR)	50 (39 to 56)
Female No of events	n = 198 ; % = 82.8
Hospitalised due to COVID-19 No of events	n = 62 ; % = 25.9

Outcomes

Outcomes

Outcome	Study, , N = 239
Self-reported walking time Custom value	See summary of findings
Activities Custom value	See summary of findings

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Section	Question	Answer
Overall bias and directness	Risk of bias judgment	High
Overall bias and directness	Directness	Directly applicable

Lambert, 2021

Bibliographic Reference	N, Lambert; S, Corps; Sa, El-Azab; Ns, Ramrakhiani; A, Barisano; L, Yu; K, Taylor; A, Esperanca; Ca, Downs; Hl, Abrahim; Rahmani, Amir M.; Borelli, Jessica L.; Chakraborty, Rana; Pinto, N. A.; COVID-19 Survivors? Reports of the Timing, Duration, and Health Impacts of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection; 2021

Study details

Study design	Cross-sectional study
Aim of the study	To evaluate the timing, duration, and health impacts of PASC reported by a large group of primarily non-hospitalized COVID-19 survivors
Country/ Geographical location	USA
Study setting	Online survey
Population description	Not described
Inclusion criteria	• 18 years or older • diagnosed with COVID-19 through a positive SARS-CoV-2 antigen or RT PCR test, physician diagnosis, self-diagnosis, or some other method (e.g., positive antibody test)
Exclusion criteria	While asymptomatic respondents could participate, only data from respondents who reported symptoms were included in the results
Intervention/test/approach	• The survey collected self-reported demographic information, an extensive medical history (including underlying conditions), and experiences with COVID-19 (including hospitalisation) • In addition, the survey listed and asked questions about 101 distinct COVID-19 symptoms and gave respondents the option to report additional symptoms they had experienced that were not listed
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	• In August 2020, a REDCap survey was disseminated to Survivor Corps group members on Facebook and in other online COVID-19 groups. • The survey was sent out again in November 2020 to collect more data. The purpose of the survey was to understand respondents' experiences with the timing and duration of the COVID-19 symptoms and how they were impacted by these symptoms
Methods of data analysis	• For each symptom, the percentage of participants reporting the symptom, average pain or discomfort associated with the symptom, average duration, and average time to symptom onset were calculated • Means were calculated for participants' responses to a 5-point Likert scale from "Not at all" to "Very much" for questions about the pain and discomfort, work impairment, and social relationship impact caused by each symptom • The percentage of participants that reported the symptom as ongoing and the percentage who reported

	the symptom as intermittent was calculated for each symptom • To focus on the experiences of people with PASC, the data analysed were further limited to respondents who had experienced symptoms for longer than 21 days
Attrition/loss to follow-up	Not reported
Source of funding	Not reported
Study limitations (Author)	• The sequelae of acute SARS-CoV-2 infection are just beginning to be understood, and it is clear that PASC affects those who were never hospitalized for severe illness • Further research is needed to determine non-modifiable risk factors associated with increased risk of acquiring PASC, as well as aberrant innate and adaptive immune responses associated with PASC.
Study limitations (Reviewer)	Nothing further to add.
Summary of findings	**Prevalence and duration of symptoms** • Individuals reported an average of 21.4 symptoms with a range of 1 to 93 symptoms occurring • Timing of symptom onset varied and was typically described as occurring in “waves”. • Symptom duration ranged from 2 weeks to over 100 days, with changing symptoms being a prominent, long-lasting feature • The first wave (arrhythmia to burning calves) appeared to be heavily dominated by neurological and cardiovascular manifestations with some indicators of a strong immune response (enlarged and painful lymph nodes), followed by microvascular consequences in the second wave (Covid toes) • The final wave suggested impact on endocrine (thyroid) function • 97.8% reported that at least one of their symptoms was intermittent, meaning it would temporarily resolve and then later return. **Impact of symptoms** • Symptoms perceived to have the most impact on ability to work included fatigue, personality change, a sensation of “brain pressure”, inability to sleep, inability to exercise, difficulty concentrating, memory problems, confusion, shortness of breath, and the relapsing/remitting nature of symptoms.

Characteristics

Study-level characteristics

Characteristic	Study (N = 5163)
Age: 18-24 years No of events	n = 118 ; % = 2.2
Age 25 -34 years No of events	n = 593 ; % = 11.5
Age 35-44 years No of events	n = 1298 ; % = 25.1
Age 45-54 years No of events	n = 1560 ; % = 30.2
Age 55-64 years No of events	n = 1122 ; % = 21.7
Age 65-74 years No of events	n = 428 ; % = 8.3
Age 75-84 years No of events	n = 40 ; % = 0.8
Age 85+ years No of events	n = 4 ; % = 0.1
Female No of events	n = 4422 ; % = 85.7
Male No of events	n = 714 ; % = 13.8
Non-binary/non-conforming No of events	n = 15 ; % = 0.3
Unknown No of events	n = 10 ; % = 0.2
Transgender No of events	n = 2 ; % = 0
White ethnicity No of events	n = 4198 ; % = 81.3
Hispanic or Latinx ethnicity	n = 330 ; % = 6.4

Characteristic	Study (N = 5163)
No of events	
Multiracial ethnicity No of events	n = 159 ; % = 3.1
Asian/Pacific islander ethnicity No of events	n = 114 ; % = 2.2
Black ethnicity No of events	n = 111 ; % = 2.2
American Indian ethnicity No of events	n = 35 ; % = 0.7
Other ethnicity No of events	n = 22 ; % = 0.4
Middle Eastern ethnicity No of events	n = 19 ; % = 0.4
Never hospitalised for COVID-19 No of events	n = 4918 ; % = 89.3
Provider diagnosis or RT-PCR confirmed SARS-CoV-2 infection No of events	n = NR ; % = 77.1

Outcomes

Outcomes

Outcome	Study, N = 5163
Prevalence and duration of symptoms Custom value	See summary of findings
Impact of symptoms Custom value	See summary of findings

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Section	Question	Answer
Overall bias and directness	Risk of bias judgment	High
Overall bias and directness	Directness	Directly applicable

Menges, 2021

Bibliographic Reference	Menges, Dominik; Ballouz, Tala; Anagnostopoulos, Alexia; Aschmann, Helène E.; Domenghino, Anja; Fehr, Jan; Puhan, Milo A.; Estimating the burden of post-COVID-19 syndrome in a population-based cohort study of SARS-CoV-2 infected individuals: Implications for healthcare service planning; 2021

Study details

Study design	Cohort studies
Trial registration (if reported)	ISRCTN14990068
Aim of the study	To assess the prevalence of impaired health status and physical and mental health symptoms among individuals at least six months after SARS-CoV-2 infection, and to characterise their healthcare utilization
Country/ Geographical location	Zurich, Switzerland
Study setting	Community
Population description	• Data from participants of the Zurich SARS-CoV-2 Cohort study, a prospective, longitudinal cohort of polymerase chain reaction (PCR)-confirmed SARS-CoV-2 96 infected individuals diagnosed between February 2020 and 05 August 2020. • Patients were enrolled between 6 October 2020 and 26 January 2021 at a median of 7.2 months (range 5.9 to 10.3 months) after diagnosis
Inclusion criteria	• Aged 18 years and over • Able to follow study procedures • Sufficient knowledge of German language • Residing in the Canton of Zurich
Exclusion criteria	None reported
Intervention/test/approach	• After enrolment, participants completed an electronic baseline questionnaire including questions on socio-demographics, medical comorbidities and risk factors, details on their acute SARS-CoV-2 infection, current health status and symptoms, healthcare contacts since diagnosis, and health-related quality of life. • All data was collected through the Research Electronic Data Capture (REDCap) survey system. • To capture the longer-term effects of SARS-CoV-2 infection, the authors evaluated whether participants who were symptomatic in the acute phase had fully recovered compared to their normal health status before infection using a four-category scale (i.e., feeling “recovered and symptom free”, “better but not fully recovered”, “neither better nor worse”, or “worse”)

	• They assessed the presence and type of any new or ongoing symptoms since the acute illness using a comprehensive list of symptoms. • They also recorded further new or ongoing symptoms not captured by the preconceived questionnaire
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	Study participants were recruited from within contact tracing at the Department of Health of the Canton of Zurich, Switzerland, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2.
Methods of data analysis	• Descriptive statistics to analyse participants characteristics and outcomes of interest and present results for the entire study population as well as stratified by age groups, sex and hospitalisation status
Attrition/loss to follow-up	Contact information was available for 2209 individuals, among which 1309 were eligible and invited to participate in our study. 442 individuals agreed to participate (participation rate 34%) and 431 were included in this analysis.
Source of funding	The Zurich SARS-CoV-2 Cohort study is part of the Corona Immunitas research program, coordinated by the Swiss School of Public Health (SSPH+) and funded through SSPH+ fundraising, including funding by the Swiss Federal Office of Public Health, the Cantons of Switzerland (Basel, Vaud and Zurich), private funders (ethical guidelines for funding stated by 410 SSPH+ were respected) and institutional funds of the participating universities. Additional funding specific to this study was provided by the Department of Health of the Canton of Zurich and the University of Zurich Foundation.
Study limitations (Author)	• Most participants included in this analysis were diagnosed with COVID-19 during the first pandemic wave in Switzerland and the capacity constraints in testing may have selected for a population with higher risk of experiencing severe disease. • Increased awareness of post-COVID-19 syndrome may have resulted in more frequent reporting of health issues by participants however sensitivity analysis by time periods did not show any relevant difference. • Self-selection bias may have occurred if individuals who are more concerned with their health were more likely to participate. • Participants in the study were younger on average and a lower proportion was hospitalised for COVID-19. • Pre-COVID-19 data for participants was not available. • Interpretation of anxiety and depression is limited due to psychological burden that the pandemic may pose in general.

	• Did not evaluate the use of specialised medical or diagnostic services so the true extent of healthcare service utilisation may be underestimated.
Summary of findings	See outcomes section

Characteristics

Study-level characteristics

Characteristic	**Study (N = 431)**
Age (years) Median (IQR)	47 (33 to 58)
Female No of events	n = 214 ; % = 49.7
Male No of events	n = 217 ; % = 50.3
Initial symptom severity: Asymptomatic No of events	n = 46 ; % = 10.7
Initial symptom severity: Mild to moderate No of events	n = 221 ; % = 51.3
Initial symptom severity: Severe to very severe No of events	n = 164 ; % = 38.1
Non-hospitalised No of events	n = 350 ; % = 81.2
Hospitalised without ICU No of events	n = 71 ; % = 16.5
Hospitalised with ICU No of events	n = 10 ; % = 2.3

Outcomes

Study timepoints

- 6 month (6-8 months after SARS-CoV-2 infection)

Health outcomes

Outcome	**Study, 6 month, N = 431**
Not recovered to normal health No of events	n = 111 ; % = 25.8

Outcome	Study, 6 month, N = 431
Not recovered to normal health Sample size	n = 431
Not recovered to normal health: 18 - 39 years No of events	n = 31 ; % = 18.9
Not recovered to normal health: 18 - 39 years Sample size	n = 164 ; % = NA
Not recovered to normal health: 40-64 years No of events	n = 62 ; % = 31.7
Not recovered to normal health: 40-64 years Sample size	n = 205 ; % = NA
Not recovered to normal health: >65 Years No of events	n = 15 ; % = 24.2
Not recovered to normal health: >65 Years Sample size	n = 62 ; % = NA
Not recovered to normal health: Female No of events	n = 66 ; % = 30.8
Not recovered to normal health: Female Sample size	n = 214 ; % = NA
Not recovered to normal health: Male No of events	n = 45 ; % = 20.7
Not recovered to normal health: Male Sample size	n = 217 ; % = NA
Not recovered to normal health: Non-hospitalised No of events	n = 82 ; % = 23.4
Not recovered to normal health: Non-hospitalised Sample size	n = 350 ; % = NA
Not recovered to normal health: Hospitalised No of events	n = 29 ; % = 35.8
Not recovered to normal health: Hospitalised Sample size	n = 81 ; % = NA

Outcome	Study, 6 month, N = 431
Any new or ongoing symptoms No of events	n = 106 ; % = 24.6
Any new or ongoing symptoms Sample size	n = 431 ; % = NA
Any new or ongoing symptoms: 18 - 39 years No of events	n = 44 ; % = 26.8
Any new or ongoing symptoms: 18 - 39 years Sample size	n = 164 ; % = NA
Any new or ongoing symptoms: 40-64 years No of events	n = 54 ; % = 26.3
Any new or ongoing symptoms: 40-64 years Sample size	n = 205 ; % = NA
Any new or ongoing symptoms: >65 years No of events	n = 8 ; % = 12.9
Any new or ongoing symptoms: >65 years Sample size	n = 62 ; % = NA
Any new or ongoing symptoms: Female No of events	n = 63 ; % = 29.4
Any new or ongoing symptoms: Female Sample size	n = 214 ; % = NA
Any new or ongoing symptoms: Male No of events	n = 43 ; % = 19.8
Any new or ongoing symptoms: Male Sample size	n = 217 ; % = NA
Any new or ongoing symptoms: Non-hospitalised No of events	n = 87 ; % = 24.9
Any new or ongoing symptoms: Non-hospitalised Sample size	n = 350 ; % = NA
Any new or ongoing symptoms: Hospitalised No of events	n = 19 ; % = 23.5

Outcome	Study, 6 month, N = 431
Any new or ongoing symptoms: Hospitalised Sample size	n = 81 ; % = NA
Recovered and symptom free No of events	n = 265 ; % = 61.5
Recovered and symptom free Sample size	n = 431 ; % = NA
Recovered and symptom free: 18-39 years No of events	n = 105 ; % = 64
Recovered and symptom free: 18-39 years Sample size	n = 164 ; % = NA
Recovered and symptom free: 40-64 years No of events	n = 116 ; % = 56.6
Recovered and symptom free: 40-64 years Sample size	n = 205 ; % = NA
Recovered and symptom free: >65 years No of events	n = 44 ; % = 71
Recovered and symptom free: >65 years Sample size	n = 62
Recovered and symptom free: Female No of events	n = 114 ; % = 53.3
Recovered and symptom free: Female Sample size	n = 214 ; % = NA
Recovered and symptom free: Male No of events	n = 151 ; % = 69.6
Recovered and symptom free: Male Sample size	n = 217 ; % = NA
Recovered and symptom free: Non-hospitalised No of events	n = 221 ; % = 63.1
Recovered and symptom free: Non-hospitalised Sample size	n = 350 ; % = NA

Outcome	Study, 6 month, N = 431
Recovered and symptom free: Hospitalised No of events	n = 44 ; % = 54.3
Recovered and symptom free: Hospitalised Sample size	n = 81 ; % = NA

Healthcare utilisation

Outcome	Study, 6 month, N = 81
Rehospitalisations related to COVID-19 No of events	n = 8 ; % = 10
Rehospitalisations related to COVID-19: 18-39 years No of events	n = 1 ; % = 10
Rehospitalisations related to COVID-19: 40-64 years No of events	n = 3 ; % = 7
Rehospitalisations related to COVID-19: >65 years No of events	n = 4 ; % = 14
Rehospitalisations related to COVID-19: Female No of events	n = 4 ; % = 11
Rehospitalisations related to COVID-19: Male No of events	n = 4 ; % = 10

New medical diagnosis

Outcome	Study, 6 month, N = 77
COVID-19 related complication (medically evaluated) No of events	n = 27 ; % = 35
COVID-19 related complication (medically evaluated): 18-39 years No of events	n = 2 ; % = 17
COVID-19 related complication (medically evaluated): 40-64 years No of events	n = 17 ; % = 36
COVID-19 related complication (medically evaluated): >65 years No of events	n = 8 ; % = 44
COVID-19 related complication (medically evaluated): Female	n = 12 ; % = 33

Outcome	Study, 6 month, N = 77
No of events	
COVID-19 related complication (medically evaluated): Male No of events	n = 15 ; % = 37
COVID-19 related complication (medically evaluated): Non-hospitalised No of events	n = 12 ; % = 28
COVID-19 related complication (medically evaluated): Hospitalised No of events	n = 15 ; % = 44
COVID-19 related complication (self-evaluated) No of events	n = 11 ; % = 14
COVID-19 related complication (self-evaluated): 18-39 years No of events	n = 3 ; % = 25
COVID-19 related complication (self-evaluated): 40-64 years No of events	n = 6 ; % = 13
COVID-19 related complication (self-evaluated): >65 years No of events	n = 2 ; % = 11
COVID-19 related complication (self-evaluated): Female No of events	n = 6 ; % = 17
COVID-19 related complication (self-evaluated): Male No of events	n = 5 ; % = 12
COVID-19 related complication (self-evaluated): Non-hospitalised No of events	n = 7 ; % = 16
COVID-19 related complication (self-evaluated): Hospitalised No of events	n = 4 ; % = 12
Non COVID-19 related diagnosis or unclear No of events	n = 39 ; % = 51
Non COVID-19 related diagnosis or unclear: 18-39 years No of events	n = 7 ; % = 58

Outcome	Study, 6 month, N = 77
Non COVID-19 related diagnosis or unclear: 40-64 years No of events	n = 24 ; % = 51
Non COVID-19 related diagnosis or unclear: >65 years No of events	n = 8 ; % = 44
Non COVID-19 related diagnosis or unclear: Female No of events	n = 18 ; % = 50
Non COVID-19 related diagnosis or unclear: Male No of events	n = 21 ; % = 51
Non COVID-19 related diagnosis or unclear: Non- hospitalised No of events	n = 15 ; % = 44

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
Overall bias and directness	Overall risk of bias	High
Overall bias and directness	Directness	Directly applicable

Vaes, 2021

Bibliographic Reference	Vaes, Anouk W.; Delbressine, Jeannet M.; Houben-Wilke, Sarah; Wesseling, Geertjan; Goertz, Yvonne M. J.; Machado, Felipe V. C.; Meys, Roy; Posthuma, Rein; Franssen, Frits M. E.; Hajian, Bita; Simons, Sami O.; Spruit, Martijn A.; van Herck, Maarten; Burtin, Chris; Gaffron, Swetlana; Maier, Dieter; van Loon, Nicole P. H.; Spaetgens, Bart; Pinxt, Claire M. H.; Liu, Limmie Y. L.; van Boven, Job F. M.; Klok, Frederikus A.; Spies, Yvonne; Vijlbrief, Herman; van't Hul, Alex J.; Janssen, Daisy J. A.; Recovery from COVID-19: A sprint or marathon? 6-month follow-up data from online long COVID-19 support group members; ERJ Open Research; 2021; vol. 7 (no. 2); 00141-2021

Study details

Study design	Cross-sectional study
Trial registration (if reported)	trialregister.nl; NL8705
Aim of the study	To evaluate symptoms in members of online long COVID peer support groups up to 6 months after the onset of coronavirus disease 2019 (COVID-19)-related symptoms.
Country/ Geographical location	The Netherlands

Study setting	Online survey
Population description	Members of online long COVID peer support groups
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention/test/approach	The survey contained questions regarding: demographics; pre-existing comorbidities; COVID-19 diagnosis (based on reverse transcriptase(RT)-PCR and/or computed tomography (CT) scan of the thorax, symptom-based medical diagnosis, no test/medical diagnosis); intensive care unit (ICU) or hospital admission; current self-reported health status (good/moderate/poor); and received care (help with personal care/physiotherapy/rehabilitation: yes/no, frequency). In addition, respondents were asked about the presence (yes/no) of a list of symptoms during the acute infection (retrospectively) In addition, participants were asked to complete the following validated questionnaires. 1) The Work Productivity and Activity Impairment questionnaire to assess COVID-19-related absenteeism, presenteeism, overall work impairment (absenteeism and presenteeism combined), and impairment of regular activities during the preceding 7 days
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	Between 4 June and 11 June 2020, 1939 members of two long COVID Facebook groups or an online COVID-19 panel (www.coronalongplein.nl) completed the first survey (T1). 1556 of these respondents consented to be approached for future research, and were invited to complete a second survey between 31 August and 8 September 2020 (T2).
Methods of data analysis	Continuous data are presented as mean±SD or median (interquartile range), as appropriate. Categorical data are presented as absolute and relative frequencies. The proportion of patients selecting “yes” per symptom was calculated, including “other” if selected. Sensitivity analyses were performed to identify potential differences between specific subgroups (hospitalised/non-hospitalised, responders/ non-responders) An exploratory analyses was performed to identify predicting variables of having persistent symptoms about 6 months after the onset of COVID-19 related symptoms, using the following predicting variables in a stepwise logistic regression analysis: age; sex; education level; marital status; body mass index; number of comorbidities; self-reported health status before the onset of COVID-19 related symptoms; and number of symptoms during the infection. Statistics were performed

	using SPSS version 25.0. A priori, the level of significance was set at p<0.05. 239 (24%) patients had a RT-PCR and/or CT scan confirmed diagnosis
Attrition/loss to follow-up	None
Source of funding	Not reported
Study limitations (Author)	• Some questions may have been affected by recall bias • Cannot rule out that the patients who completed the baseline and follow-up questionnaires are the ones who experienced the most symptoms • Long-term follow-up data from COVID-19 patients are lacking, and therefore, little is known about different recovery trajectories in these patients. • Study aimed to evaluate the natural course of symptoms among members of online long COVID peer support groups. Therefore, the findings cannot be generalised to all COVID-19 patients
Summary of findings	**Number of symptoms** • During the COVID-related infection a median of 15 (11–18) symptoms were reported, which was significantly lower about 3 and 6 months later: 6 (4–9) and 6 (3–8), respectively (p<0.001) • After about 6 months, 98 (41.0%) patients reported one to five symptoms, 69 (40%) patients reported six to 10 symptoms, and 32 (13%) patients reported >10 symptoms **Work productivity** • The mean proportion of work time missed in the previous week due to ill health (absenteeism) and impairment while working (presenteeism) reduced from 73% to 52% and from 66% to 60%, respectively (both p<0.001) • Average work productivity loss reduced from 89% to 79%, resulting in an overall working impairment of 71% and 60% after about 3 and 6 months follow-up, respectively (both p<0.001) **Self-reported health, functional status and quality of life** • After 3 months follow-up, only 9.2% of the patients rated their health as “good”, which significantly increased up to 16.7% after about 6 months follow-up (p<0.001) • 83.3% of the patients still reported moderate-to-poor self-reported health after 6 months. • Functional status improved in 26.8% of the patients, and deteriorated in 15.5% of the patients.

	• Proportion of patients who had problems with mobility, self-care, and/or daily activities, who had pain or discomfort, or felt anxious or depressed reduced significantly between 3 and 6 months of follow-up • Still, 62% of the patients had moderate-to-extreme problems with daily activities at 6 months, and 49% of the patients experienced moderate-to-severe pain or discomfort **Received care** • The proportion of patients receiving physiotherapy or rehabilitation between 3 and 6 months of follow-up was significantly higher compared to the period from the infection to 3 months of follow-up (61.9% versus 31.8% and 11.7% versus 4.2%, respectively, p<0.05) • The dependency on partner or family for personal care significantly decreased from 3 to 6 months follow-up (from 46.0% to 21.3% and from 17.2% to 7.1%, respectively, p<0.05) • The proportion of patients needing help from their partner or family was still significantly higher compared to before the infection (21.3% versus 5.0% and 7.1% versus 1.7%, respectively; p<0.05)

Outcomes

Outcomes

Outcome	**Study, N = 239**
Number of symptoms Custom value	See summary of findings
Work productivity Custom value	See summary of findings
Self-reported health, functional status and quality of life Custom value	See summary of findings
Received care Custom value	See summary of findings

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Section	**Question**	**Answer**
Overall bias and directness	Risk of bias judgment	High
Overall bias and directness	Directness	Directly applicable

Ziauddeen, 2021

Bibliographic Reference	Ziauddeen, Nida; Gurdasani, Deepti; Hara Margaret, E; O'Hara; Hastie, Claire; Roderick, Paul; Yao, Guiqing; Alwan, Nisreen; A; Characteristics of Long Covid: findings from a social media survey; medrxiv preprint; 2021

Study details

Study design	Cross-sectional study
Aim of the study	In adults who self-reported suspected or confirmed COVID-19 and were not hospitalised in the first two weeks of their COVID-19 illness, the review aimed to: • Characterise the initial and the ongoing symptoms of Long Covid in terms of their range, nature, pattern, progression and what triggers and relieves them • Describe the impact of Long Covid on daily activities and work
Country/ Geographical location	Worldwide survey
Study setting	Online survey
Population description	Adults aged 18 years or over who thought they had COVID-19 (confirmed or suspected) and who were not hospitalised for the treatment of COVID-19 in the first two weeks of experiencing COVID-19 symptoms.
Inclusion criteria	The survey was restricted to adults aged 18 years or over who thought they had COVID-19 (confirmed or suspected) and who were not hospitalised for the treatment of COVID-19 in the first two weeks of experiencing COVID-19 symptoms. The screening questions for the survey were the following. • Are you aged 18 years or over? • Do you think you have had COVID-19? • Were you admitted to hospital in the first two weeks of experiencing COVID-19 symptoms?
Exclusion criteria	None reported
Intervention/test/approach	• Questions included demographic information, baseline health, symptoms experienced at the start of COVID-19 illness, the pattern of illness over the course, symptoms that remained/appeared over the course of the illness, functional status, impact on health, activity, ability to work including current employment status, and healthcare usage. • Collected data on pre-existing health conditions as a binary (yes/no) variable and used an open text response to collect details on these conditions

	• Asked if other members of the household had experienced symptoms of COVID-19 and the duration of their illness. • With the exception of questions on initial symptoms and functional status at six weeks of illness, all questions captured responses at the time of survey completion.
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	This is a cross-sectional online survey using a convenience non-probability sampling method. The survey was posted by the study authors on social media websites (Twitter and Facebook), including on the Facebook Long Covid Support Group (membership at the time of posting was around 30,000, the group was founded in the UK but has international membership too), and the smaller UK doctors #longcovid Facebook Group. Subsequently, it was shared on the Survivor Corps Facebook Group (USA), and the Body Politic Support Group on Slack (international) by members of these groups.
Methods of data analysis	• A minimum duration of illness of four weeks was defined as Long Covid for the purposes of this analysis. • Confirmed infection was defined as reported positive result of nucleic acid amplification test (NAAT) such as PCR, and/or antibody test. • Descriptive percentages and summary statistics were generated for the full sample and stratified separately for those with lab-confirmed and suspected infection. Univariate comparisons between those with and without confirmed COVID-19 infection were carried out using t-test for continuous variables and Chi square test for categorical variables. • Complete case analysis was carried out as missing data was minimal.
Attrition/loss to follow-up	2550/2644 participants were included in the analysis
Source of funding	None
Study limitations (Author)	• Non-representative survey which recruited through online support groups as well as generally through social media. • Sample was not randomly drawn from the population of interest to ensure representativeness, and therefore the findings cannot be generalised to the groups not represented among participants, nor can they be used in any way to calculate the prevalence of Long Covid. • Respondents were predominantly White, female and of higher socioeconomic status. • People living with Long Covid who use social media (and therefore were able to access the survey) could

	have different characteristics to those who do not use such platforms. • Did not ascertain the prevalence/absence of each reported symptom before COVID-19 • Given the variable severity and disability levels among participants at the later stages of the illness, there is also the possibility of recall bias in this survey, as the data about the acute stage was collected retrospectively.
Summary of findings	**Duration of illness** • The mean duration of illness was 7.2 months (SD) 1.8 months • Mean duration of 6.2 months (SD 2.4) in those lab-confirmed compared to 7.6 months (SD 1.3) in those who were not. **Course of illness** • Only 2.3% of participants reported that they felt they had recovered to baseline health before COVID-19 • Common triggers that exacerbated existing symptoms or caused symptoms to return included physical activity (77.2%), stress (55.1%), disturbance in sleep patterns (46.9%), cognitive activity (42.2%), and domestic chores (35.0%). 23.2% reported symptoms varying by time of day. • 15.8% of participants also reported not always being able to identify a trigger and sometimes symptoms returned or worsened without a trigger • Just over half of participants (54.3%) reported sufficient rest in the acute phase of the illness, with 26.0% reporting less rest than they would have liked due to caring or other responsibilities **Functional ability** • At the time of completing the survey, being ill still affected respondents' ability to carry out domestic chores (84.3%), leisure (84.8%) and social (77.1%) activities, work (74.9 %), self-care (50.0%), childcare (35.8%), and caring for other adults (26.1%), as well as affecting their mental health (63.7%). • Using the PCFS Scale to describe how Long Covid affected daily activities at six weeks from the start of symptoms, nearly a third (32.3%) reported that they were unable to live alone without any assistance, and 34.5% reported moderate functional limitations (able to take care of self but not perform usual duties/activities). 89.5% of participants said they

	avoided certain activities/duties at six weeks from onset of illness **Work** • At the time of responding to the survey, 9.7% reported working reduced hours, 19.1% reported being unable to work (out of which 88.3% was reported to be solely due to COVID-19 illness), and 1.9% reported being made redundant or having taken early retirement **Healthcare utilisation** • Most participants reported at least one or more type of healthcare service usage (GP, 111 calls, Accident and Emergency, hospital outpatient appointments) with 12% admitted to hospital after 2 weeks from onset of illness

Characteristics

Study-level characteristics

Characteristic	**Study (N = 2550)**
Age Mean (SD)	46.5 (11)
Male No of events	n = 413 ; % = 16.2
Female No of events	n = 2108 ; % = 82.8
Non-binary No of events	n = 21 ; % = 0.8
Prefer not to say No of events	n = 3 ; % = 0.1
Other No of events	n = 2 ; % = 0.1
White ethnicity No of events	n = 2362 ; % = 93.3
Mixed/Multiple ethnic backgrounds No of events	n = 67 ; % = 2.7

Characteristic	Study (N = 2550)
Asian ethnicity No of events	n = 64 ; % = 2.5
Black/African/Caribbean No of events	n = 23 ; % = 0.9
Other No of events	n = 14 ; % = 0.6
Prefer not to say No of events	n = 3 ; % = 0.1

Outcomes

Outcomes

Outcome	Study, N = 2550
Duration of illness Custom value	See summary of findings
Course of illness Custom value	See summary of findings
Functional ability Custom value	See summary of findings
Work Custom value	See summary of findings
Healthcare utilisation Custom value	See summary of findings

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Section	Question	Answer
Overall bias and directness	Risk of bias judgment	High
Overall bias and directness	Directness	Directly applicable

Walker, 2021

Bibliographic Reference	Collaborative - The, OpenSAFELY; Walker Alex, J; MacKenna, Brian; Inglesby, Peter; Rentsch Christopher, T; Curtis Helen, J; Morton Caroline, E; Morley, Jessica; Mehrkar, Amir; Bacon Sebastian, CJ; Hickman, George; Bates, Christopher; Croker, Richard; Evans, David; Ward, Tom; Cockburn, Jonathan; Davy, Simon; Bhaskaran, Krishnan; Schultze, Anna; Williamson Elizabeth, J; Hulme William, J; McDonald Helen, I; Tomlinson, Laurie; Mathur, Rohini; Eggo Rosalind, M; Wing, Kevin; Wong Angel, YS; Forbes, Harriet; Tazare, John; Parry, John; Hester, Frank; Harper, Sam; Hanlon Shaun, O'Hanlon; Eavis, Alex; Jarvis, Richard; Avramov, Dima; Griffiths, Paul; Fowles, Aaron; Parkes, Nasreen; Douglas Ian, J; Evans Stephen, JW; Smeeth, Liam; Goldacre, Ben; Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY; medrxiv preprint; 2021

Study details

Study design	Cohort studies
Trial registration (if reported)	Not reported
Aim of the study	To describe the use of long COVID codes in English primary care since their introduction, in a cohort of covering approximately 96% of the English population - those covered by the two largest electronic health record providers, EMIS and TPP (SystmOne)
Country/ Geographical location	UK
Study setting	Primary care
Population description	All people registered with a general practice on the 1st November 2020
Inclusion criteria	Not applicable
Exclusion criteria	Not applicable
Intervention/test/approach	Not applicable
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	Primary care records managed by the GP software providers EMIS and TPP were accessed through OpenSAFELY
Methods of data analysis	• Demographic variables were extracted including age (in categories), sex, geographic region, Index of Multiple Deprivation (IMD, divided into quintiles), and ethnicity. • Counts and rates of recorded events were stratified by each demographic variable. Recording of each SNOMED code was assessed individually, in this case counting every recorded code including repeated codes, rather than one per patient

Attrition/loss to follow-up	Calculated proportions of patients with long COVID codes over the whole study period per 100,000 patients, 95% confidence intervals of those proportions, and the distribution of codes by each stratification variable
Source of funding	Jointly funded by UKRI, NIHR and Asthma UK-BLF [COV0076; MR/V015737/] and the Longitudinal Health and Wellbeing strand of the National Core Studies programme
Study limitations (Author)	A key weakness of this data for estimating true prevalence of long COVID in primary care, and factors associated with the condition, is that it relies on clinicians formally entering a diagnostic or referral code into the patient's record: we note that this is a limitation of all electronic health record research for all clinical conditions and activity.

Characteristics

Study-level characteristics

Characteristic	Study (N = 23273)
Age: 0-17 years No of events	n = 342 ; % = 1.5
Age: 18-24 years No of events	n = 861 ; % = 3.7
Age: 25-34 years No of events	n = 2859 ; % = 12.3
Age: 35 -44 years No of events	n = 5110 ; % = 22
Age: 45-54 years No of events	n = 6575 ; % = 28.3
Age: 55-69 years No of events	n = 6230 ; % = 26.8
Age: 70-79 years No of events	n = 954 ; % = 4.1
Age >80 years No of events	n = 342 ; % = 1.5
Female No of events	n = 15120 ; % = 65
male No of events	n = 8153 ; % = 35

Characteristic	Study (N = 23273)
White ethnicity No of events	n = 10743 ; % = 46.2
Mixed ethnicity No of events	n = 286 ; % = 1.2
South Asian ethnicity No of events	n = 1941 ; % = 8.3
Black ethnicity No of events	n = 651 ; % = 2.8
Other ethnicity No of events	n = 256 ; % = 1.1
East of England No of events	n = 1418 ; % = 6.1
East Midlands No of events	n = 1089 ; % = 4.7
London No of events	n = 5286 ; % = 22.7
North East No of events	n = 956 ; % = 4.1
North West No of events	n = 4580 ; % = 19.7
South East No of events	n = 4056 ; % = 17.4
South West No of events	n = 1801 ; % = 7.7
West Midlands No of events	n = 2886 ; % = 12.4
Yorkshire and The Humber No of events	n = 1183 ; % = 5.1
IMD 1 Most deprived No of events	n = 4943 ; % = 21.2

Characteristic	Study (N = 23273)
IMD 2 No of events	n = 5353 ; % = 23
IMD 3 No of events	n = 4535 ; % = 19.5
IMD 4 No of events	n = 4300 ; % = 18.5
IMD 5 Least deprived No of events	n = 3983 ; % = 17.1

Outcomes

Diagnostic codes

Outcome	Study, N = 36507
Post-COVID-19 syndrome No of events	n = 23468 ; % = 64.3
Ongoing symptomatic disease caused by severe acute respiratory syndrome coronavirus 2 No of events	n = 2989 ; % = 8.2

Referral codes

Outcome	Study, N = 36507
Signposting to Your COVID Recovery No of events	n = 1048 ; % = 2.9
Referral to post-COVID assessment clinic No of events	n = 6332 ; % = 17.3
Referral to Your COVID Recovery rehabilitation platform No of events	n = 1806 ; % = 4.9

Assessment codes

Outcome	Study, N = 36507
Newcastle post-COVID syndrome Follow-up Screening Questionnaire No of events	n = 306 ; % = 0.8
Assessment using Newcastle post-COVID syndrome Follow-up Screening Questionnaire No of events	n = 98 ; % = 0.3

Outcome	Study, N = 36507
COVID-19 Yorkshire Rehabilitation Screening tool No of events	n = 149 ; % = 0.4
Assessment using COVID-19 Yorkshire Rehabilitation Screening tool No of events	n = 186 ; % = 0.5
Post-COVID-19 Functional Status Scale patient self-report No of events	n = 25 ; % = 0.1
Assessment using Post-COVID-19 Functional Status Scale patient self-report No of events	n = 25 ; % = 0.1
Post-COVID-19 Functional Status Scale patient self-report final scale grade No of events	n = 13 ; % = 0
Post-COVID-19 Functional Status Scale structured interview final scale grade No of events	n = 0 ; % = 0
Assessment using Post-COVID-19 Functional Status Scale structured interview No of events	n = 51 ; % = 0.1
Post-COVID-19 Functional Status Scale structured interview No of events	n = 11 ; % = 0

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
Overall bias and directness	Overall risk of bias	High
Overall bias and directness	Directness	Directly applicable

Appendix 7 GRADE profiles

Case definition: Adults and children experiencing ongoing symptoms beyond the duration of acute COVID-19 illness (>4 weeks)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Coding for diagnoses of PCS or alternative conditions after acute illness onset (follow-up: 14 months)							
23704 (2 observational studies)	very serious[a]	serious[b]	not serious	very serious[c]	none	Very low	One study found 23468/36507 (64.3%) of Long COVID codes used on electronic health records were for diagnosis of Post-COVID-19 syndrome and 2989/36507 (8.2%) were for the diagnosis of ongoing symptomatic disease. One study reported 27/77 (35%) people were diagnosed with a medically evaluated COVID-19 complication and 11 (14%) with a self-evaluated COVID-19 complication. 39 (51%) were diagnosed with a non-COVID-19 related diagnosis or was unclear
Coding for referral for ongoing symptoms (follow-up: 14 months)							
23273 (1 observational study)	very serious[d]	not serious	not serious	very serious[c]	none	Very low	One study found that coding was signposted to YOUR COVID Recovery (2.9%), referred to post-COVID assessment clinics (17.3%) and (4.9%) referred to YOUR COVID Recovery rehabilitation platform.
Coding for assessment tools (follow-up: 14 months)							
23273 (1 observational study)	very serious[d]	not serious	not serious	very serious[c]	none	Very low	One study found that assessment tools accounted for <1% of all the codes used. The assessment tools coded included the Newcastle post-COVID syndrome follow-up screening questionnaire, COVID-19 Yorkshire Rehabilitation screening tool and the Post-COVID-19 Functional Status Scale patient self-report
Healthcare utilisation since illness onset (follow-up: 7.2 months)							

Certainty assessment							Summary of findings
320 (2 observational studies)	very serious[e]	serious[f]	not serious	very serious[c]	none	Very low	One study reported that 8/81 (10%) of previously hospitalised patients had been re-hospitalised for reason related to COVID-19. A survey found that the number of people receiving physiotherapy or rehabilitation between 3 and 6 months of follow-up (31.8% and 11.7% respectively) was significantly higher compared to the period between initial infection and 3 months follow-up (4.2%; p<0.05)

Symptom duration (follow-up: 7.2 months)

11475 (3 observational studies)	very serious[e]	serious[f]	not serious	very serious[c]	none	Very low	One survey found that that 2454 (65.2%) respondents experienced symptoms for more than 180 days. Another survey found that symptom duration ranged from 2 weeks to over 100 days and another reported mean duration of illness to be 7.2 (SD 1.8) months

Number of symptoms (follow-up: 7.2 months)

4010 (2 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study found that for those people that did not recover within 90 days, the average number of symptoms peaked at month 2 from initial illness. For those people experiencing symptoms for longer than 6 months, the mean number of symptoms was 13.79 (95% CI 12.68 to 14.88). Another study found that at 6 months, 98 (41%) people reported 1 to 5 symptoms, 69 (40%) people reported 6 to 10 symptoms and 32 (13%) reported >10 symptoms

Course of illness (follow-up: 7 months)

8925 (2 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study suggested that symptoms were clustered in three groups according to their time courses. Cluster 1 symptoms occur early in the illness peaking at 2-3 weeks; Cluster 2 symptoms remain stable over time; Cluster 3 symptoms rise sharply in the first 2 months, can remain stable, decrease over time or increase slightly in later months. Another study was similar in reporting 3 waves of symptoms. The first wave consists of neurological and cardiovascular symptoms, the second wave have microvascular symptoms and the third wave impacts endocrine function.

Changes in symptoms (follow-up: 7 months)

8925 (2 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study (n=3762) found that a minimum of 85.9% (95% CI 84.8% to 87%) people experienced relapses of symptoms which occur in an irregular pattern (52.8%, 95% CI 51.2% to 54.4%) and in response to a specific trigger (52.4%, 95% CI 50.8% to 54%). Another study (n=5163f) found that symptoms would temporarily resolve and then later return.

Triggers of symptom relapses (follow-up: 7 months)

Certainty assessment							Summary of findings
8925 (2 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study (n=3762) found that triggers of relapses were Physical activity: 70.7%, (95% CI 69.2% to 72.1%); Stress: 58.9%, (95% CI 57.3% to 60.5%); Exercise: 54.39%, (95% CI 52.8% to 56.0%); Mental activity: 46.2%, (95% CI 44.7% to 47.8%); during menstruation: 34.3%, (95% CI 32.0% to 36.5%) and before menstruation: 35.2%, (95% CI 33.0% to 37.3%). Another study (n= 5163) identified triggers of relapses to be physical activity (77.2%); stress (55.1%); disturbance in sleep patterns (46.9%); cognitive activity (42.2%) and domestic chores (35.0%).

Impact on activities - Daily activities (follow-up: 6 months)

2789 (2 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study (n=2550) symptoms impacted on the ability to carry out activities such as domestic chores (84.3%), leisure (84.8%) and social (77.1%) activities, work (74.9 %), self-care (50.0%), childcare (35.8%), and caring for other adults (26.1%). At 6 weeks 32.3% were unable to live alone without any assistance, and 34.5% reported moderate functional limitations. Another study (n=239) found that 62% still reported moderate to extreme problems with daily activities at 6 months. People were significantly less dependent of a partner or family for personal care at 6 months follow up but the proportion of people still needing help was still significantly higher compared to before COVID-19 illness

Impact on activities - Work (follow-up: mean 7.7 months)

11714 (4 observational studies)	very serious[e]	not serious	not serious	very serious[c]	none	Very low	One study found that symptoms such as fatigue, personality change, sensation of 'brain pressure', inability to sleep, inability to exercise, difficulty concentrating, memory problems, confusion, shortness of breath, and the fluctuating nature of symptoms impacted on the ability to work. Another study (n=3762) found that 45.6% (95% CI 43.2% to 48%) of unrecovered respondents were working reduced hours at 7 months and 22.3% (95% CI 20.5% to 24.3%) were not working due to their health condition. Another study found that at 7.7 months since COVID-19 illness, 9.7% of 2550 participants reported working reduced hours and 19.1% reported being unable to work. A fourth study (n=239) found that the mean work time missed due to ill health or impairment while working at 3 months compared to 6 months, reduced from 73% to 52% and 66% to 60% respectively.

CI: confidence interval

Explanations

a. Retrospective study design reliant on self-reported or clinician entered data. Coding could be retrospective. High risk of recall bias.
b. Studies enrolled patients in different ways. One study only included SARs-CoV-2 positive patients only.
c. Unable to pool data as descriptive only. Unable to measure imprecision
d. Retrospective study design reliant on clinician entered data. Coding could be retrospective. High risk of recall bias
e. Retrospective study design reliant on self-reported data. High risk of recall bias.
f. Unable to pool due to different study designs

Appendix 8 Excluded studies

Study	Reason for exclusion
Albu, Sergiu, Zozaya, Nicolas Rivas, Murillo, Narda et al. (2021) What's going on following acute covid-19? Clinical characteristics of patients in an out-patient rehabilitation program. NeuroRehabilitation 48(4): 469-480	- Exclude - no outcomes of interest for RQs
Broughan JM, McCombe G, Avramovic G, Crowley D, Downey C, Downey J, Fawsitt R, McHugh T, O'Connor E, Perrotta C, Cotter A, Lambert JS, Cullen W (2021) General practice attendances among patients attending a post-COVID-19 clinic: a pilot study. BJGP open	- Exclude - no outcomes of interest for RQs
Estiri, Hossein, Strasser, Zachary, Brat, Gabriel et al. Evolving Phenotypes of non-hospitalized Patients that Indicate Long Covid. medrxiv preprint	- Exclude - Phenotypes of symptoms
Evans Rachael, Andrea, McAuley, Hamish, Harrison Ewen, M et al. Physical, cognitive and mental health impacts of COVID-19 following hospitalisation: a multi-centre prospective cohort study. medrxiv preprint	- Exclude - Phenotypes of symptoms
Fernandez-de-las-Penas, Cesar, Palacios-Cena, Domingo, Gomez-Mayordomo, Victor et al. (2021) Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. 18(5): 2621-na	- Exclude - non-systematic review
Gavriatopoulou, Maria, Ntanasis-Stathopoulos, Ioannis, Kastritis, Efstathios et al. (2021) Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. Journal of Infection	- Exclude - Signs and symptoms review
Huang, Lu, Zhao, Peijun, Tang, Dazhong et al. (2020) Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC. Cardiovascular imaging 13(11): 2330-2339	- Exclude - no outcomes of interest for RQs
Jason, Leonard A., Islam, Mohammed F., Conroy, Karl et al. (2021) COVID-19 symptoms over time: comparing long-haulers to ME/CFS. Fatigue: Biomedicine, Health and Behavior	- Exclude - no outcomes of interest for RQs
Klein, Hadar, Asseo, Kim, Karni, Noam et al. (2021) Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Exclude - acute COVID-19
Liu, Mengqi, Lv, Fajin, Zheng, Yineng et al. (2021) A prospective cohort study on radiological and physiological outcomes of recovered COVID-19 patients 6 months after discharge. Quantitative Imaging in Medicine and Surgery 11(9): 4181-4192	- Exclude - no outcomes of interest for RQs

Mandal, Swapna, Barnett, Joseph, Brill, Simon E et al. (2021) 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 76(4): 396-398	- Exclude - no outcomes of interest for RQs
Masuda, Reika, Nitschke, Philipp, Yang, Rongchang et al. (2021) Incomplete Systemic Recovery and Metabolic Phenoreversion in Post-Acute-Phase Nonhospitalized COVID-19 Patients: Implications for Assessment of Post-Acute COVID-19 Syndrome. Journal of Proteome Research	- Exclude - no outcomes of interest for RQs
Parry, Arshed Hussain, Wani, Abdul Haseeb, Jehangir, Majid et al. (2021) Medium-term chest computed tomography (CT) follow-up of COVID-19 pneumonia patients after recovery to assess the rate of resolution and determine the potential predictors of persistent lung changes. Egyptian Journal of Radiology and Nuclear Medicine 52(1): 55	- Exclude - no outcomes of interest for RQs
Rando, Halie M., Bennett, Tellen D., Byrd, James Brian et al. (2021) Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. na(na): na-na	- Exclude - Landscaping review
Sarfraz, Zouina, Sarfraz, Azza, Barrios, Alanna et al. (2021) Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care. Journal of primary care & community health 12: 21501327211023726	- Exclude - Signs and symptoms review
Scherlinger, Marc, Felten, Renaud, Gallais, Floriane et al. (2021) Refining "Long-COVID" by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection. Infectious diseases and therapy	- Exclude - no outcomes of interest for RQs
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