National Institute for Health and Care Excellence

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

[G] Evidence reviews for risk factors (update)

NICE guideline NG188

November 2021

Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Literature search

The guideline on managing the long-term effects of COVID-19 is a living guideline. This means that weekly searches of newly published literature are undertaken for continuous evidence surveillance and stored in a database. Published studies, including pre-print and final published versions were screened using the inclusion and exclusion criteria in the relevant review protocols (see Appendix 2). Additional criteria were used for the evidence review of risk factors, as described in the methods and processes. 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 for the study flow chart of included studies and Appendix 8 for the list of excluded studies, with reasons for exclusion.

Review question 3

What risk factors are associated with developing post-COVID-19 syndrome?

The review protocol is shown in Appendix 2.

Included studies

There was 1 meta-analysis identified from the weekly surveillance searches that reported on risk factors for persisting symptoms following acute COVID-19 illness. In addition to this review, there were 3 large cohort studies included in the review. Details of the systematic review are described in Table 1 and the cohort studies in Table 2.

Table 1 Included meta-analysis for review question 3

Study details	Population	Time since acute COVID-19 illness	Findings	Analysis presented

Thompson 2021 Meta-analysis Pre-print	Adults self-reporting COVID-19 infection. COVID-19 cases were defined by self-report, including testing confirmation and health care professional diagnosis Few participants hospitalised (0.8-5.2%).	4 weeks or more	Risk factors associated with a higher risk of long covid were: older age, being female, poor pre-existing mental or general health, asthma, overweight, ethnicity	Meta-analysis of 10 cohort studies Comparison with electronic health record data

Table 2: Included cohort studies for review question 3

Study details	Population	Approach	Outcomes
Taquet 2021 Retrospective cohort Published	236,379 patients with a confirmed diagnosis of COVID-19 and two matched cohorts: patients diagnosed with influenza and patients diagnosed with any respiratory tract infection including influenza.	Data obtained from the TriNetX electronic health records network. Estimated the incidence of 14 neurological and psychiatric outcomes in the 6 months after a confirmed diagnosis of COVID-19	Risks for neurological or psychiatric diagnosis were greatest in, but not limited to, patients who had severe COVID-19.
Whitaker 2021 (REACT 2) Retrospective cohort Pre-print	Random population of 508,707 people in the community in England of which 19.2% reported a history of COVID-19 illness.	Rounds 3-5 of the REACT-2 study where people were asked about prior history of COVID-19 and the presence and duration of 29 different symptoms. Estimated the prevalence of symptom persistence at 12 weeks and attempted to cluster individuals by symptoms experienced.	Risk factors for the persistence of one or more symptoms: Higher in women OR 1.51 95% CI 1.46 to 1.55 and increased with age. Self-reported overweight OR 1.16 95% CI 1.12 to 1.21 Obesity OR 1.53 95% CI 1.47 to 1.59 Smoking OR 1.35 95% CI 1.28 to 1.41 Vaping OR 1.26 95% CI 1.18 to 1.34

			Hospitalisation with COVID-19 OR 3.46 95% CI 2.93 to 4.09 Lower risk with Asian ethnicity OR 0.80 95% CI 0.74 to 0.88
Ayoubkhani 2021 Retrospective cohort study Published	N= 47780 (mean age 65, 55% men) in hospital with COVID-19 and discharged alive by 31 August 2020,	Individuals admitted to hospital with COVID-1, identified using HES admitted patient care records Matched to controls from a pool of about 50 million people in England for personal and clinical characteristics from 10 years of electronic health records	After admission to hospital for COVID-19, 29% were readmitted and 12% died within a mean follow-up of 140 days. Rates of multiorgan dysfunction after discharge were raised in individuals with COVID-19 compared with those in the matched control group. The absolute risk of death, readmission, and multiorgan dysfunction after discharge was greater for individuals aged 70 or more and for individuals of white ethnic background.

Key results

The meta-analysis (Thompson 2021) identified 7 risk factors and protective factors that were associated with a higher risk of persisting symptoms at least 4 weeks from acute COVID-19 illness. This data came from 10 longitudinal studies and was further supported with data from electronic health records. Results of this meta-analysis are shown in Table 3.

Table 3: Risk and protective factors associated with higher risk of persisting symptoms (Thompson 2021)

Risk/protective factors	**Data from longitudinal studies** **OR (95% CI)**	**Data from electronic health records** **OR (95% CI)**
Female sex	1.49 (1.24 to 1.79)	1.51 (1.41 to 1.61)
Poor pre-pandemic mental health	1.46 (1.17 to 1.83)	1.57 (1.47 to 1.68)
Poor general health	1.62 (1.25 to 2.09)	1.26 (1.18 to 1.35)
Asthma	1.32 (1.07 to 1.62)	1.56 (1.46 to 1.67)

Overweight or obese	1.25 (1.01 to 1.55)	1.31 (1.21 to 1.42)
Non-white ethnic minority groups	0.8 (95% CI 0.54 to 1.19)	0.75 (0.67 to 0.84) South Asian ethnicity

The results of the meta-analysis were supported by Whitaker 2021 (REACT 2) which also identified that female sex, being overweight or obese were significantly associated with a higher risk of one or more symptoms at 12 weeks since acute COVID-19 illness. They also found Asian ethnicity to be a protective factor. In addition, they identified that smoking (OR 1.35 95% CI 1.28 to 1.41), vaping (OR 1.26 95% CI 1.18 to 1.34) and previous hospitalisation for acute COVID-19 (OR 3.46 95% CI 2.93 to 4.09) were significantly associated with higher risk of having one or more symptoms at 12 weeks.

Taquet 2021 found that risks for neurological or psychiatric diagnosis were greatest in, but not limited to, patients who had severe COVID-19. 'Severe' meant hospitalisation (versus non-hospitalisation), need for ICU (versus non-ICU), or encephalopathy (versus no encephalopathy). Similarly, Ayoubkhani 2021 found that the absolute risk of death, readmission, and multiorgan dysfunction after discharge was greater for individuals aged 70 or more and for individuals of white ethnic background.

Subgroups

No subgroup data was identified.

Strengths and limitations

One of the main limitations of the Thompson 2021 meta-analysis was that the study selection was not carried out using a systematic search but was based on UK longitudinal study databases and UK electronic health records. The authors noted heterogeneity across the studies but did not fully address this within the review.

The evidence included mostly adults and therefore, there was no evidence on the risk factors for long-term effects in children.

The data used in meta-analysis was mostly self-reported which increases the risk of recall bias. Similarly, the cohort studies were also rated as high risk of bias due to issues around participant selection and recall bias. GRADE was used to assess the certainty of the evidence on risk factors. The certainty in the evidence was low to very low. Most outcomes were downgraded due to high risk bias in the studies and imprecision where the 95% CI crossed the line of no effect.

GRADE profiles are reported in MAGICapp.

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 discussed that identifying risk or protective factors associated with developing post-COVID-19 syndrome may help to determine which individuals could be more likely to develop the condition. They can be used to inform the shared decision making process. However, the panel were concerned that using risk factors as part of diagnosis can potentially lead to people who do not have specific risk factors being overlooked. The panel stressed the importance of ongoing monitoring of people who do not have the main risk factors under consideration. These people may be recovering as expected up to 12 weeks but might develop symptoms thereafter.

Certainty of the evidence

The evidence base remains uncertain. All risk and protective factors were assessed in GRADE as being low to very low certainty. Most of the evidence came from a non-systematic meta-analysis of longitudinal studies in the UK although the findings were consistent with data in electronic health records. The panel's main concerns were around the bias that may be introduced due to the self-reporting of symptom persistence, which could mean that the data may not be generalisable to the whole population.

Because of this, the panel were unable to draw firm conclusions from results on specific risk factors and did not change the recommendation.

Preferences and values

Patient experience shows that one of the most important issues around the long-term effects of COVID-19 is the uncertainty around what to expect when recovering from acute COVID-19. This can lead to fear and anxiety for patients. It would be

helpful to discuss risk factors for developing post-COVID-19 syndrome as part of a shared decision-making conversation on expectations around recovery, but the evidence base is currently low quality. The panel did not want to emphasis certain groups and inadvertently miss groups who are not considered ‘at risk’.

Resource and other considerations

The panel noted resource implications of time and expertise needed to assess all the risk factors in a consultation. However, the panel doubted whether the cost could be justified based on such limited evidence, especially since there could be resource savings longer-term by preventing inappropriate service use. The panel wished to avoid directing people along specific pathways inappropriately, for example where asthma is suspected but unconfirmed.

Other considerations

There was no evidence available for risk and protective factors for long-term effects of COVID-19 in children.

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

RQ 3: What risk factors are associated with developing post-COVID-19 syndrome?

Criteria	Notes
Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) from the onset of acute COVID-19 illness.
Exposure	Any
Comparators	Not applicable
Outcomes	Risk factors or factors that are associated with post-COVID-19 syndrome (as defined by the study)
Settings	Any

Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes)
	• Health care workers

Study types	Any 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

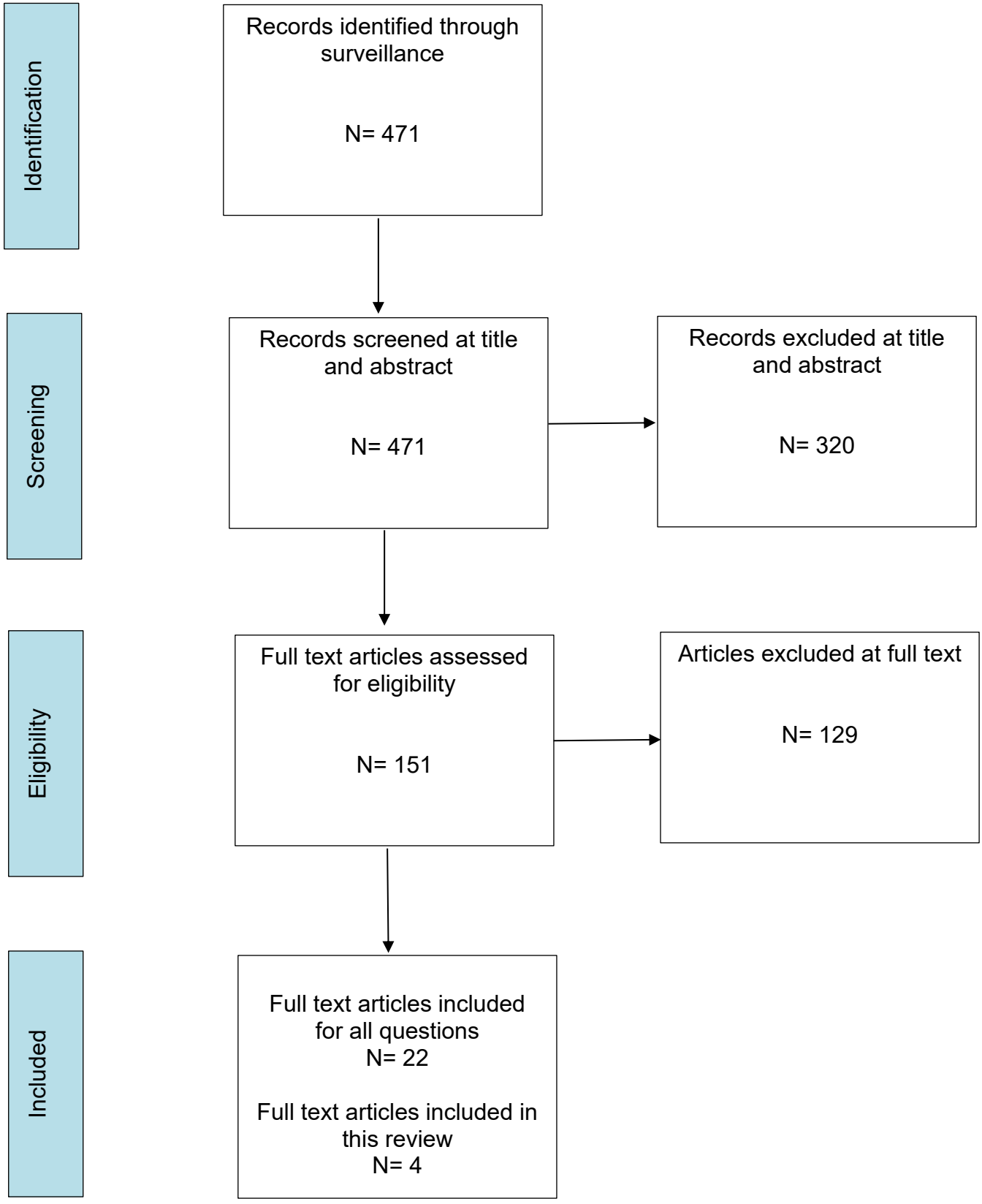
Countries	Any
Timepoints	Not applicable
Other exclusions	None

Appendix 3 Literature search strategy

Database strategies

Please refer to the search history record for full details of the search.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Study
Ayoubkhani, Daniel, Khunti, Kamlesh, Nafilyan, Vahe et al. (2021) Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ (Clinical research ed.) 372: n693
Taquet, Maxime, Geddes, John R, Husain, Masud et al. (2021) 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The lancet. Psychiatry
Thompson, Ellen, Williams, Dylan, Walker, Alex et al. (2021) Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK.
Whitaker M, Elliott J, Chadeau-Hyam M et al. (2021) Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people.

Appendix 6 Evidence tables

Thompson, 2021

Bibliographic Reference	Thompson, Ellen; Williams, Dylan; Walker, Alex; Mitchell, Ruth; Niedzwiedz, Claire; Yang, Tiffany; Huggins, Charlotte; Kwong, Alex; Silverwood, Richard; Gessa, Giorgio Di; Bowyer, Ruth C.E.; Northstone, Kate; Hou, Bo; Green, Michael; Dodgeon, Brian; Doores, Katie; Duncan, Emma; Williams, Frances; Steptoe, Andrew; Porteous, David; McEachan, Rosemary; Tomlinson, Laurie; Goldacre, Ben; Patalay, Praveetha; Ploubidis, George; Katikireddi, Srinivasa Vittal; Tilling, Kate; Rentsch, Christopher; Timpson, Nicholas; Chaturvedi, Nishi; Steves, Claire; =OpenSAFELY, Collaborative; Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK; 2021

Study details

Study design	Meta-analysis
Aims/ review questions	To report the frequency of long COVID among individuals with suspected and test-confirmed COVID-19 and examined associations with sociodemographic and pre-pandemic health risk factors
Country/ Geographical location	UK
Setting(s)	Population based and primary care
Population description	Adults self-reporting COVID-19 infection. COVID-19 cases were defined by self-report, including testing confirmation and health care professional diagnosis. Long COVID was defined as per NICE as either ongoing symptomatic COVID-19 (OSC) or post-COVID-19 syndrome (PCS) using self-reported symptom duration.
Inclusion criteria	Minimum inclusion criteria were pre-pandemic health measures, age, sex, ethnicity plus self-reported COVID-19, and self-reported duration of COVID-19 symptoms.
Exclusion criteria	None stated
Intervention/test/approach	Data were drawn from 10 UK longitudinal studies that had conducted surveys before and during the COVID-19 pandemic comprising five age-homogenous cohorts and five age-heterogeneous cohorts. An additional population-based cohort study to measure long COVID recording in electronic health record (EHR) data from primary care practices was conducted.
Searching methods	No search was conducted. Data were drawn from 10 UK LS that had conducted surveys before and during the COVID-19 pandemic comprising five age-homogenous cohorts and five age-heterogeneous cohorts.

	An additional population-based cohort study to measure long COVID recording in electronic health record (EHR) data from primary care practices was conducted.
Methods of data analysis	Longitudinal study (LS) analysis: Main analyses were conducted in studies with a direct self-reported measure of COVID-19 symptom length. Associations between each factor and both long COVID outcomes (long COVID and PCS) were assessed in separate logistic regression models within each study. We adjusted for a minimal set of confounders across all studies, where relevant: age (adjusted as a continuous variable), sex, and ethnicity. We report odds ratios (ORs) and 95% confidence intervals (CIs). Attrition and survey design were addressed by weighting estimates to be representative of their target population in each included study. To synthesise effect sizes across studies, fixed-effect meta-analysis with restricted maximum likelihood was carried out and repeated with random-effects modelling for comparison. Sensitivity analysis: to mitigate index event bias, inverse probability weights (IPW) were derived for risk of COVID-19. These were derived in each LS separately but following a common approach used previously. Derived weights were then applied in all analysis models as a sensitivity check. EHR analysis: Logistic regression was used to assess whether GP-recorded long COVID was associated with each sociodemographic or pre-pandemic health characteristic. We adjusted for the same set of confounders as used in the LS analyses: age (as categorical variable), sex, ethnicity. In further analyses of age as a risk factor for long COVID in the EHR data, we assigned individuals within 10-year categories an age at the midpoint of each group, then assessed the trend in long COVID frequency with age using linear and non-linear meta-regression.
Methods to investigate heterogeneity	The *I2* statistic was used to report heterogeneity between estimates.
Risk of bias assessment	No risk of bias assessment was reported.
Summary of findings	Longitudinal studies (LS): Females had higher risk than males of having ongoing symptomatic COVID-19 (OSC) and post-COVID-19 syndrome

	(PCS)(at 4+ weeks: OR=1.49; 95%CI: 1.24-1.79; at 12+ weeks: OR=1.60; 95%CI: 1.23-2.07). No clear evidence was found for individuals of non-white ethnicity (compared to individuals of white ethnicity) having differential risk of OSC and PCS combined (OR for symptoms lasting 4+ weeks= 0.80; 95%CI: 0.54-1.19). Non-white ethnicity was associated with lower risk of PCS specifically compared to white ethnicity (OR=0.32; 95%CI: 0.22-0.47) after meta-analysis, but these study-level findings displayed a high degree of heterogeneity (I^2=75%, P<0.001). Across LS, no strong evidence was found for associations of index of multiple deprivation (IMD) with either outcome (OSC or PCS). Having not attained a degree from higher education was associated with lower risk of PCS specifically (OR: 0.73; 95% CI: 0.57-0.94), but not with OSC and PCS in combination (OR: 0.95: 95% CI: 0.80-1.14). When synthesising associations for health characteristics across LS, those with poor or fair pre-pandemic self-reported general health were found to have greater odds of having symptoms for both long COVID-19 outcomes (at 4+ weeks: OR=1.62; 95%CI: 1.25-2.09; at 12+ weeks: OR=1.66; 95%CI: 1.14- 2.40). Greater pre-pandemic psychological distress was also associated with higher risk of both long COVID outcomes (at 4+ weeks: OR=1.45; 95%CI: 1.16-1.82; PCS: OR=1.58; 95%CI: 1.15-2.17). No strong evidence was observed for a linear association of BMI with either outcome. In models to examine the potential importance of a BMI threshold in relation to long COVID, overweight/obesity was associated with increased odds of symptoms lasting for 4+ weeks (OR= 1.24; 95%CI: 1.01-1.53) threshold but not with PCS specifically (OR 0.95, 95% CI: 0.70-1.28). Associations were not found for diabetes, hypertension, or high cholesterol with either outcome, although modest point estimates were on the side of higher long COVID risk in several instances. Asthma was the only specific medical condition associated with increased odds of having symptoms for 4+ weeks (OR=1.31; 95%CI: 1.06-1.62), although the association with PCS specifically was closer to the null (OR=1.13;95%CI: 0.80-1.58). ELECTRONIC HEALTH RECORDS (EHR): In keeping with the LS results, females had higher risk of long COVID than males (OR=1.51; 95%CI:1.41-1.61), while odds were lower in

	individuals of South Asian (compared to (OR=0.75; 95%CI:0.67-0.84) or black ethnicity, relative to white ethnicity (OR=0.66; 95%CI:0.52-0.83). Individuals living in areas with the least deprivation had higher odds of having a long COVID-19 code compared to those in the most deprived IMD quintile. In EHRs, increased odds of having a long COVID-19 code was seen in individuals with pre-existing comorbidities (OR=1.26; 95%CI:1.18-1.35) and psychiatric conditions (OR=1.57; 95%CI:1.47-1.68). Again, as with the population-based studies an increased risk was observed in individuals with a pre-pandemic diagnosis of asthma (OR=1.56; 95%CI:1.46-1.67) and overweight and obesity (OR=1.31, 95%CI:1.21-1.42). No increase in risk was observed for diabetes.
Source of funding	This work was supported by the National Core Studies, an initiative funded by UKRI, NIHR and the Health and Safety Executive. The COVID-19 Longitudinal Health and Wellbeing National Core Study was funded by the Medical Research Council (MC_PC_20030).
Study limitations (Author)	The data are observational, preventing causal conclusions to be drawn on the role of risk factors in long COVID development, and that whilst the authors attempted to address both selection into the samples from study attrition and selecting upon COVID-19 case status (which can induce index event bias), there remains the possibility that potential bias has influenced association estimates. Finally, not all studies had test confirmation of COVID-19 status, and some individuals may have misattributed persistent symptoms to other conditions.
Study limitations (Reviewer)	No predifined inclusion criteria were stated for the included studies. No quality assessment was reported for the included studies. Data for certain risk factors was missing from the EHR sample (e.g. smoking status) preventing comparison between the longitudinal study and EHR data. The data was self-reported, increasing the risk of recall bias.
Other details	

Study arms

Risk factor (N = 13234)

Generic risk factor arm for use with each risk factor in outcome table. N stated as overall sample but adapt to each risk factor.

Reference (N = 13234)

Generic reference arm for use with each risk factor in outcome table. N stated as overall sample but adapt to each risk factor.

Characteristics

Study-level characteristics

Characteristic	Study (N = 6899)
Age Range	19.9 to 63
White % Range	43.8 to 98.4
Non-white ethnic minority Range	1.3 to 50.9
Hospitalised with COVID-19 Range	0.8 to 4.5
% Female Range	55 to 96
Degree educated (%) Range	10 to 50.6
Managerial, admin, professi Range of duration of symptoms (weeks)	18 to 38.9
Intermediate professional Range of duration of symptoms (weeks)	16.6 to 41.9
Manual/Routine professional Range of duration of symptoms (weeks)	19.1 to 42.6
% Not in employment Range	0.3 to 20.5
Age 18-24 years Nominal	184
Age 25-34 years Nominal	515
Age 35-44 years Nominal	897
Age 45-54 years Nominal	1238
Age 55-69 years Nominal	1088

Characteristic	Study (N = 6899)
Age 70-79 years Nominal	193
Age 80 years or older Nominal	74
Female Nominal	2678
Male Nominal	1511
White Nominal	2647
Mixed Nominal	49
South Asian Nominal	340
Black Nominal	73
Index of multiple deprivation quantile 0 Nominal	75
Index of multiple deprivation quantile 1 Nominal	787
Index of multiple deprivation quantile 2 Nominal	850
Index of multiple deprivation quantile 3 Nominal	932
Index of multiple deprivation quantile 4 Nominal	814
Index of multiple deprivation Quantile 5 Nominal	731
Not obese Nominal	2694

Characteristic	Study (N = 6899)
Obese I (BMI 30-34.9) Nominal	787
Obese II (BMI 35-39.9) Nominal	411
Obese III (BMI 40+) Nominal	297
0 comorbidities Nominal	2336
1 comorbidity Nominal	1335
2 or more comorbidities Nominal	518
0 disorders Nominal	2772
1 or more disorders Nominal	1417

Outcomes

Study timepoints

- 4 week (Duration of symptoms lasting 4 weeks or more from onset.)

Risk factors associated with symptoms lasting 4 weeks or more

Outcome	4 week, Risk factor vs Reference
Female compared to males, longitudinal studies Odds ratio/95% CI	1.49 (1.24 to 1.79)
Female compared to males, electronic health records (EHR) Odds ratio/95% CI	1.51 (1.41 to 1.61)
Longitudinal studies, non-white versus white Odds ratio/95% CI	0.8 (0.54 to 1.19)
EHR Mixed ethnicity versus white Odds ratio/95% CI	1.01 (0.76 to 1.34)

Outcome	4 week, Risk factor vs Reference
EHR South Asian versus white Odds ratio/95% CI	0.75 (0.67 to 0.84)
EHR Black versus white Odds ratio/95% CI	0.66 (0.52 to 0.66)
Index of Multiple Deprivation (IMD)	
Longitudinal studies per 1 IMD point Odds ratio/95% CI	0.99 (0.95 to 1.03)
EHR IMD quintile 2 vs 1 Odds ratio/95% CI	1.21 (1.09 to 1.33)
EHR IMD quintile 3 vs 1 Odds ratio/95% CI	1.43 (1.3 to 1.57)
EHR IMD quintile 4 vs 1 Odds ratio/95% CI	1.36 (1.23 to 1.5)
EHR IMD quintile 5 vs 1 Odds ratio/95% CI	1.4 (1.27 to 1.55)
Poor overall health self-rated health exposure in the LS meta-analysis, and comorbidities in EHR	
LS meta-analysis Odds ratio/95% CI	1.62 (1.25 to 2.09)
EHR Odds ratio/95% CI	1.26 (1.18 to 1.35)
LS meta-analysis Odds ratio/95% CI	1.46 (1.17 to 1.83)
EHR Odds ratio/95% CI	1.57 (1.47 to 1.68)
Overweight and obesity	
LS meta-analysis Odds ratio/95% CI	1.24 (1.01 to 1.53)

Outcome	4 week, Risk factor vs Reference
EHR Odds ratio/95% CI	1.31 (1.21 to 1.42)
Diabetes	
LS meta-analysis Odds ratio/95% CI	1.38 (0.85 to 2.23)
EHR Odds ratio/95% CI	1.05 (0.95 to 1.16)
Asthma	
LS meta-analysis Odds ratio/95% CI	1.32 (1.07 to 1.62)
EHR Odds ratio/95% CI	1.56 (1.46 to 1.67)

Critical appraisal - ROBIS checklist: Signs, symptoms and risk

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Unclear
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Unclear
Synthesis and findings	Concerns regarding the synthesis and findings	Unclear
Overall study ratings	Overall risk of bias	Moderate

Ayoubkhani, 2021

Bibliographic Reference	Ayoubkhani, Daniel; Khunti, Kamlesh; Nafilyan, Vahe; Maddox, Thomas; Humberstone, Ben; Diamond, Ian; Banerjee, Amitava; Post-covid syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study.; BMJ (Clinical research ed.); 2021; vol. 372; n693

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not provided
Study start date	01-Jan-2020
Study end date	31-Aug-2020

Aim of the study	To estimate the excess morbidity after severe COVID-19 disease, reflecting an urgent need for such evidence by policy makers.
Country/ Geographical location	UK
Study setting	We used the Hospital Episode Statistics Admitted Patient Carerecords for England up to 31 August 2020 and the General Practice Extraction Service Data for Pandemic Planning and Research (GDPPR)18 up to 30 September 2020. Death registrations from the Office for National Statistics were linked for deaths up to 30 September 2020 and registered by 7 October 2020
Population description	Individuals with COVID-19 after discharge from hospital.
Inclusion criteria	Individuals were included if they had a hospital episode from 1 January to 31 August 2020 with a primary diagnosis of COVID-19, (ICD-10) codes U07.1 (virus identified) and U07.2 (virus not identified); that is, by a positive laboratory test or clinical diagnosis.
Exclusion criteria	Individuals with COVID-19 were excluded if they were not discharged alive by 31 August 2020 or their date of birth or sex was not known. The index date was set to the date of discharge after the first hospital episode with COVID-19 as the primary diagnosis.
Intervention/test/approach	Individuals were followed up from the index date to 30 September 2020 or the date of death (whichever was earlier) for all cause mortality, all cause hospital readmission (admission after discharge for patients and admission after the index date for controls), respiratory disease, major adverse cardiovascular event (a composite of heart failure, myocardial infarction, stroke, and arrhythmia), diabetes (type 1 or 2), chronic kidney disease stages 3-5 (including dialysis and kidney transplant), and chronic liver disease. Diagnoses of respiratory disease, major adverse cardiovascular event, diabetes, chronic kidney disease, and chronic liver disease were identified from primary care and hospital records, except for the arrhythmia component of major adverse cardiovascular event for which primary care data were not available (although diagnoses made in hospital were recorded).
Comparator (where applicable)	Candidate controls were individuals in the general population who: did not meet the inclusion criteria for COVID-19; had not died before 1 January 2020; and had at least one GDPPR record between 1 January 2019 (one year before the start of the follow-up period) and 30 September 2020 (end of the study). They applied the GDPPR criterion to ensure the controls were currently active patients within the NHS (eg, they had not emigrated without deregistering from their general practice). Each control had the same index date as their matched patient. They selected controls from the general population rather than matching to non-covid hospital

	admissions to determine the increased risk after hospital admission for COVID-19 versus no hospital admission for COVID-19 (that is, compared with the expected risk for people with similar personal and clinical characteristics in the general population.
Methods for population selection/allocation	They matched patients to controls on potential confounders of the relation between hospital admission for COVID-19 and outcomes, established from electronic health records over a 10 year look back period (1 January 2010 to 31 December 2019). Personal factors recorded were age, sex, ethnicity, region, and deprivation. Comorbidities included the diagnoses listed above and hypertension. and cancer, identified from diagnoses made in primary care and in hospital (with primary and secondary ICD10 codes for the hospital diagnoses). They also included smoking status and body mass index in the matching set as risk factors. They broadly categorised age (<50, 50- 69, ≥70) and body mass index (<25, 25 to <30, ≥30) to facilitate exact matching, which would not have been possible with continuous variables.
Methods of data analysis	Distributions for baseline characteristics were compared between individuals with COVID-19 and a random 0.5% sample of the general population with $\chi 2$ tests and standardised differences in proportions, where a standardised difference or more than 10% indicated a large imbalance between groups. Patients were matched 1:1 to controls with coarsened exact matching, resulting in a perfect balance of joint distributions across the full range of (coarsened) variables included in the matching set, derived from 10 years of records. Matched pairs were discarded if the control died before the corresponding patient's index date. All covariates were categorised before matching, including an unknown category comprising individuals with missing values. The size of the pool of candidate controls (about 50 million individuals) precluded the use of multiple imputation. They computed rates of death, readmission, and multiorgan dysfunction after discharge from hospital per 1000 person years in patients and controls, deriving rate ratios from these rates. They estimated rates for all diagnoses (new onset diagnoses and exacerbation of pre-existing conditions) and only new onset diagnoses (that is, no previous diagnosis for the condition over the 10 year look back period). All rates were stratified by sex, age group (<70, ≥70), and ethnic group (white, non-white). The threshold of 70 years was chosen for age stratified analyses as the government of the United Kingdom has consistently stated that individuals aged 70 or more have a higher risk of severe illness from COVID-19 (eg, in the government's definition of the clinically vulnerable population in social distancing guidelines). Individuals with

	missing information for ethnicity were omitted from all analyses stratified by ethnic group. Patients were further stratified based on whether they were admitted to an intensive care unit during their hospital stay. Sensitivity analysis investigated possible residual confounding by age, smoking status, and body mass index after matching because we had to use coarse versions of the variables to ensure a sufficient match rate. They assessed the robustness of our main results by adjusting for a second order polynomial of age and non-coarsened versions of smoking status and body mass index in a Poisson regression of outcome counts, including the natural logarithm of person years as an offset term.
Attrition/loss to follow-up	None
Summary of results	Admission to hospital for covid-19COVID-19 was associated with an increased risk of readmission and death after discharge compared with individuals with similar personal and clinical characteristics in the general population over the same period. After admission to hospital for covid-19COVID-19, 29% were readmitted and 12% died within a mean follow-up of 140 days. Rates of multiorgan dysfunction after discharge were raised in individuals with covid-19COVID-19 compared with those in the matched control group, suggesting extrapulmonary pathophysiology. Diabetes and major adverse cardiovascular events were particularly common, whether incident or prevalent disease. Thirdly, the absolute risk of death, readmission, and multiorgan dysfunction after discharge was greater for individuals aged 70 or more than for those aged less than 70, and for individuals of white ethnic background than non-white individuals. Compared with outcome rates that might be expected to occur in these groups in the general population, however, younger patients and ethnic minority individuals had greater relative risks than those aged 70 or more and those in the white ethnic group, respectively. In the secondary analysis, they found that individuals discharged from the intensive care unit after covid-19COVID-19 experienced greater rates of death and readmission than those not admitted to the intensive care unit. Rates of all outcomes after discharge were greater in individuals with COVID-19 aged 70 or more than in those <70. Of 86 955 individuals in hospital with COVID-19 during the study period, 53,795 (61.9%) had been discharged alive by the end of the study. After excluding individuals whose age or

sex was not known and those who could not be matched to a control, 47780 patients with COVID-19 (4745 admitted to the intensive care unit and 43,035 not requiring admission to the intensive care unit) were included in the analysis, representing 90.8% of those discharged alive with known age and sex. Mean follow-up was 140 days (standard deviation 50 days, maximum 253 days) for patients with COVID-19 and 153 days (33 days, 253 days) for controls.

At baseline, individuals with covid-19 had a mean age of 64.5 (standard deviation 19.2) and 54.9% were men. Compared with the general population, individuals in hospital with COVID-19 were more likely to be: male, aged 50 or more, living in a deprived area, a former smoker, and overweight or obese. Individuals with COVID-19 were also more likely to be comorbid than the general population, with a higher prevalence of previous admission to hospital and of all measured pre-existing conditions (most notably hypertension, major adverse cardiovascular event, respiratory disease, and diabetes).

Standardised differences in baseline characteristics between patients and controls were generally below 10%, and most were zero because of the use of exact matching. Individuals aged less than 30 and those whose smoking status or body mass index, or both, were not known, were more common in patients than in controls (as we matched on coarsened versions of these variables). Sensitivity analyses investigating the effect of adjusting for these variables showed minimal change in estimated rate ratios of multiorgan dysfunction between patients and controls, even when stratified by personal characteristics, indicating the absence of residual confounding after matching.

Rates of death, readmission, and multiorgan dysfunction in individuals with covid-19 after discharge from hospital

Of 47,780 individuals in hospital with COVID-19 over the study period, 29.4% were readmitted and 12.3% died after discharge. These events occurred at rates of 766 (95% confidence interval 753 to 779) readmissions and 320 (312 to 328) deaths per 1000 person years, which were 3.5 (3.4 to 3.6) and 7.7 (7.2 to 8.3) times greater, respectively, than those in matched controls. Respiratory disease was diagnosed in 14,140 individuals (29.6%) after discharge, with 6085 of these being new onset diagnoses; the resulting rates of 770 (95% confidence interval 758 to 783) and 539 (525 to 553) per 1000 person years, respectively, were 6.0 (5.7 to 6.2) and 27.3 (24.0 to 31.2) times greater than those in controls.

Diabetes, major adverse cardiovascular event, chronic kidney disease, and chronic liver disease were diagnosed after

discharge in 4.9%, 4.8%, 1.5%, and 0.3% of individuals with COVID-19, respectively, occurring at rates of 127 (122 to 132) for diabetes, 126 (121 to 131) for major adverse cardiovascular event, 39 (36 to 42) for chronic kidney disease, and 7 (6 to 9) for chronic liver disease diagnoses per 1000 person years. The investigators saw a similar pattern when only new onset diagnoses were considered, but at lower rates of 29 (26 to 32) for diabetes, 66 (62 to 70) for major adverse cardiovascular event, 15 (13 to 17) for chronic kidney disease and 4 (3 to 5) for chronic liver disease diagnoses per 1000 person years. Those with COVID-19 were diagnosed with major adverse cardiovascular event, chronic liver disease, chronic kidney disease, and diabetes after discharge from hospital 3.0 (2.7 to 3.2), 2.8 (2.0 to 4.0), 1.9 (1.7 to 2.1), and 1.5 (1.4 to 1.6) times more frequently, respectively, than in the matched control group. Rates of death, readmission, and multiorgan dysfunction after discharge from hospital remained substantially increased in individuals with COVID-19 compared with matched controls, after stratifying by admission to the intensive care unit versus no admission to the intensive care unit. Individuals who needed to be admitted to the intensive care unit had higher rates of respiratory disease and diabetes after discharge, but lower rates of death, readmission, and major adverse cardiovascular event, than those who did not need to be admitted to the intensive care unit.

In sensitivity analyses, comparisons between outcome rates for patients and controls were robust when only laboratory confirmed diagnoses of COVID-19 were included, representing 80.2% of all patients with COVID-19 in the study. We also explored the robustness of our findings when 4865 patients with covid-19 (9.2%) that were unmatched, and therefore excluded from our main analysis, were added to the study population. The investigators found that outcome rates in the matched population could have slightly underestimated the rates in the full population of patients with COVID-19 who were discharged. The estimates presented in their main results could therefore be conservative.

Rate ratios of death, readmission, and multiorgan dysfunction after discharge across demographic characteristics

Rates of all outcomes after discharge were greater in individuals with COVID-19 aged 70 or more than in those aged less than 70, whereas rates of all outcomes other than diabetes were greater in the white ethnic group than in the non-white group. Rate ratios comparing patients with COVID-19 and matched controls were greater in individuals aged less than 70 than those aged 70 or more for all outcomes, however. The largest differences in rate ratios were for death (14.1 (95% confidence interval 11.0 to 18.3) for age <70 years v 7.7 (7.1 to 8.3) for ≥70) and respiratory disease (10.5 (9.7 to

	11.4) for age <70 v 4.6 (4.3 to 4.8) for ≥70). Ethnic differences in rate ratios were greatest for respiratory disease (11.4 (9.8 to 13.3) for individuals in the non-white group v 5.2 (5.0 to 5.5) in the white ethnic group). Differences in rate ratios between men and women were generally small.
Source of funding	The study received no external funding.
Study limitations (Author)	Like all observational studies, residual confounding is possible. Limited events in the control group meant we could not disaggregate rate ratios stratified by age and ethnicity beyond age less than 70 versus 70 or older and white versus non-white groups, despite likely variations in outcomes within these groups. Performing multiple imputation for missing values was not practical because of the size of the study dataset; instead we adopted the missing indicator approach, which could cause some bias in non-randomised studies. The hospital admission threshold might be lower in individuals with recent COVID-19 disease than in the general population, and rates of diagnoses in general might have decreased indirectly because of the pandemic, particularly in people not admitted to hospital with COVID-19. They could not access testing data so some individuals with COVID-19 who did not require admission to hospital might have been matched in the control group. Unlikely to fully capture the lived experiences of individuals with post-COVID-19 syndrome who were possibly asymptomatic and untested at the time of infection. Multiorgan post-covid manifestations have been identified in individuals not admitted to hospital, who were beyond the scope of our study. They did not capture symptoms such as fatigue, disturbances in taste and smell, and anxiety, widely reported in post-covid syndrome.
Study limitations (Reviewer)	Nothing additional to add.

Study arms

COVID-19 cases (N = 47780)

control group (N = 47780)

Characteristics

Study-level characteristics

Characteristic	Study (N = 47780)
Age Mean (SD)	64.5 (19.2)
Gender Men No of events	n = 26245 ; % = 54.9

Study timepoints

- 140 day (Mean follow up was 140 days)

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
Overall bias	Overall risk of bias	High *(Retrospective cohort study with a matched control group. Prone to selection bias.)*

Taquet, 2021

Bibliographic Reference	Taquet, Maxime; Geddes, John R; Husain, Masud; Luciano, Sierra; Harrison, Paul J; 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records.; The lancet. Psychiatry; 2021

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not reported
Study start date	20-Jan-2020
Study end date	13-Dec-2020
Aim of the study	They aimed to provide robust estimates of incidence rates and relative risks of neurological and psychiatric diagnoses in patients in the 6 months following a COVID-19 diagnosis.
Country/ Geographical location	USA
Study setting	A mixture of hospitals, primary care, and specialist providers.
Population description	The primary cohort was defined as all patients who had a confirmed diagnosis of COVID-19. They also constructed two matched control cohorts: patients diagnosed with influenza and patients diagnosed with any respiratory tract infection including influenza. They excluded patients with a diagnosis of COVID-19 or a positive test for SARS-CoV-2 from the control cohorts.

Inclusion criteria	As above for 'population description'. Also, the cohorts included all patients older than 10 years who had an index event on or after Jan 20, 2020 (the date of the first recorded COVID-19 case in the USA), and who were still alive at the time of the main analysis (Dec 13, 2020).
Exclusion criteria	As above for 'population description': They excluded patients with a diagnosis of COVID-19 or a positive test for SARS-CoV-2 from the control cohorts. For outcomes that are chronic illnesses (e.g. dementia or Parkinson's disease), they excluded patients who had the diagnosis before the index event.
Intervention/test/approach	They used a set of established and suspected risk factors for COVID-19 and for more severe COVID-19 illness: age, sex, race, ethnicity, obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, substance use disorder, ischaemic heart disease and other forms of heart disease, socioeconomic deprivation, cancer (and haematological cancer in particular), chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving an immune mechanism. To capture these risk factors in patients' health records, they used 55 variables. Cohorts were matched for all these variables. For outcomes that tend to recur or relapse (eg, ischaemic strokes or psychiatric diagnoses), they estimated separately the incidence of first diagnoses (ie, excluding those who had a diagnosis before the index event) and the incidence of any diagnosis (ie, including patients who had a diagnosis at some point before the index event). For other outcomes (eg, Guillain-Barré syndrome), they estimated the incidence of any diagnosis. Finally, to assess the overall risk of neurological and psychiatric outcomes after COVID-19, they estimated the incidence of any of the 14 outcomes, and the incidence of a first diagnosis of any of the outcomes. This is lower than the sum of incidences of each outcome because some patients had more than one diagnosis. They investigated whether the neurological and psychiatric sequelae of COVID-19 were affected by the severity of the illness. The incidence of outcomes was estimated separately in four subgroups: first, in those who had required hospitalisation within a time window from 4 days before their COVID-19 diagnosis (taken to be the time it might take between clinical presentation and confirmation) to 2 weeks afterwards; second, in those who had not required hospitalisation during that window; third, in those who had been admitted to an intensive therapy unit (ITU) during that window; and fourth, in those who were diagnosed with delirium or other forms of altered mental status during that

	window; we use the term encephalopathy to describe this group of patients. Differences in outcome incidence between these subgroups might reflect differences in their baseline characteristics. Therefore, for each outcome, they estimated the HR between patients requiring hospitalisation (or ITU) and a matched cohort of patients not requiring hospitalisation (or ITU), and between patients with encephalopathy and a matched cohort of patients without encephalopathy. Finally, HRs were calculated for patients who had not required hospitalisation for COVID-19, influenza, or other respiratory tract infections. To provide benchmarks for the incidence and risk of neurological and psychiatric sequelae, patients after COVID-19 were compared with those in four additional matched cohorts of patients diagnosed with health events selected to represent a range of acute presentations during the same time period. These additional four index events were skin infection, urolithiasis, fracture of a large bone, and pulmonary embolism. They assessed the robustness of the differences in outcomes between cohorts by repeating the analysis in three scenarios: one including patients who had died by the time of the analysis, another restricting the COVID-19 diagnoses to patients who had a positive RNA or antigen test (and using antigen test as an index event), and another comparing the rates of sequelae of patients with COVID-19 with those observed in patients with influenza before the pandemic (ie, in 2019 or 2018). Finally, to test whether differences in sequelae between cohorts could be accounted for by differences in extent of follow-up, we counted the average number of health visits that each cohort had during the follow-up period.
Comparator (where applicable)	They constructed two matched control cohorts: patients diagnosed with influenza and patients diagnosed with any respiratory tract infection including influenza. They excluded patients with a diagnosis of COVID-19 or a positive test for SARS-CoV-2 from the control cohorts.
Methods for population selection/allocation	They used The TriNetX Analytics Network, a federated network recording anonymised data from electronic health records in 62 health-care organisations, primarily in the USA, comprising 81 million patients. The health-care organisations are a mixture of hospitals, primary care, and specialist providers, contributing data from uninsured and insured patients. These organisations warrant that they have all necessary rights, consents, approvals, and authority to provide the data to TriNetX, so long as their name remains anonymous as a data source and their data are used for research purposes. By use of the TriNetX user interface, cohorts can be created on the basis of inclusion and exclusion

	criteria, matched for confounding variables with a built-in propensity score-matching algorithm, and compared for outcomes of interest over specified time periods.
Methods of data analysis	They used propensity score matching to create cohorts with matched baseline characteristics, done within the TriNetX network. Propensity score with 1:1 matching used a greedy nearest neighbour matching approach with a calliper distance of 0·1 pooled SDs of the logit of the propensity score. Any characteristic with a standardised mean difference between cohorts lower than 0·1 was considered well matched.20 The incidence of each outcome was estimated by use of the Kaplan-Meier estimator. Comparisons between cohorts were made with a log-rank test. We calculated HRs with 95% CIs using a proportional hazard model wherein the cohort to which the patient belonged was used as the independent variable. The proportional hazard assumption was tested with the generalised Schoenfeld approach. When the assumption was violated, the time varying HR was assessed with natural cubic splines fitted to the log cumulative hazard. Statistical analyses were done in R, version 3.4.3, except for the log-rank tests, which were done within TriNetX. Statistical significance was set at two-sided p-value <0·05.
Attrition/loss to follow-up	None
Summary of results	They assessed the probability of the major neurological and psychiatric outcomes in patients diagnosed with COVID-19 compared with the matched cohorts diagnosed with other respiratory tract infections and with influenza. Most diagnostic categories were more common in patients who had COVID-19 than in those who had influenza HR = 1.44 (1·40–1·47) for any diagnosis; HR = 1.78 (1.68–1.89) for any first diagnosis and those who had other respiratory tract infections HR = 1.16 (1.14–1.17) for any diagnosis; 1.32 (1.27–1.36) for any first diagnosis). Hazard rates were also higher in patients who were admitted to ITU than in those who were not HR = 1.58 (1.50–1.67 for any diagnosis; HR = 2.87 (2.45–3.35) for any first diagnosis). HRs were significantly greater than 1 for all diagnoses for patients who had COVID-19 compared with those who had influenza, except for parkinsonism and Guillain-Barré syndrome, and significantly greater than 1 for all diagnoses compared with patients who had respiratory tract infections. Similar results were observed when patients who had COVID-19 were compared with those who had one of the four other index events, except when an outcome had a predicted relationship with the comparator condition (eg, intracranial haemorrhage was more common in association with fracture of a large bone). There were no violations of the proportional hazards assumption for most of the neurological outcomes over the 6 months of follow-up (appendix pp 15, 35). The only exception was for intracranial haemorrhage and ischaemic stroke in

	patients who had COVID-19 when compared with patients who had other respiratory tract infections (p=0.012 for intracranial haemorrhage and p=0.032 for ischaemic stroke). For the overall psychiatric disorder category (ICD-10 F20–48), the HR did vary with time, declining but remaining significantly higher than 1, indicating that the risk was attenuated but maintained 6 months after COVID-19 diagnosis. HRs for COVID-19 diagnosis compared with the additional four index events showed more variation with time, partly reflecting the natural history of the comparator condition (appendix, pp 16–19, 36). They explored the effect of COVID-19 severity in four ways. First, they restricted analyses to matched cohorts of patients who had not required hospitalisation. HRs remained significantly greater than 1 in this subgroup, with an overall HR for any diagnosis of 1.47 (1.44–1.51) for patients who had COVID-19 compared with patients who had influenza, and 1.16 (1.14–1.17) compared with those who had other respiratory tract infections. For a first diagnosis, the HRs were 1.83 (1.71–1.96) versus patients who had influenza and 1.28 (1.23–1.33) versus those who had other respiratory tract infections. Second, we calculated HRs for the matched cohorts of patients with COVID-19 requiring hospitalisation versus those who did not require hospitalisation (44,927 matched patients). This comparison showed greater hazard rates for all outcomes in the hospitalised group than in the non-hospitalised group, except for nerve, nerve root, or plexus disorders, with an overall HR of 1.33 (1.29–1.37) for any diagnosis and 1.70 (1.56–1.86) for any first diagnosis. Third, they calculated HRs for the matched cohorts of patients with COVID-19 requiring ITU admission versus those not requiring ITU admission (8942 patients), with a HR of 1.58 (1.50–1.67) for any diagnosis and 2.87 (2.45–3.35) for any first diagnosis. Fourth, we calculated HRs for the matched cohorts of patients with COVID-19 who had encephalopathy diagnosed during acute illness versus those who did not (6221 patients). HRs for all diagnoses were greater for the group who had encephalopathy than for the matched cohort who did not, with an overall HR of 1.85 (1.73–1.98) for any diagnosis and 3.19 (2.54–4.00) for any first diagnosis. They inspected other factors that might influence the findings. The results regarding hospitalisation, ITU admission, or encephalopathy (which they had defined as occurring up to 14 days after diagnosis) could be confounded by admissions due to an early complication of COVID-19 rather than to COVID-19 itself. This was explored by excluding outcomes during this period, with the findings remaining similar, albeit with many HRs being reduced. Additionally, COVID-19 survivors had fewer health-care visits during the 6-month period compared with the other cohorts. Hence the higher incidence of many

	diagnoses was not simply due to having had more diagnostic opportunities. The increased rates of neurological and psychiatric sequelae were robust in all three sensitivity analyses: when patients who had died by the time of the analysis were included, when the COVID-19 diagnosis was confirmed by use of an RNA or antigen test, and when the sequelae were compared with those observed in patients who had influenza in 2019 or 2018. The severity of COVID-19 had a clear effect on subsequent neurological diagnose. Overall, COVID-19 was associated with increased risk of neurological and psychiatric outcomes, but the incidences and HRs of these were greater in patients who had required hospitalisation, and markedly so in those who had required ITU admission or had developed encephalopathy, even after extensive propensity score matching for other factors (eg, age or previous cerebrovascular disease). However, the incidence and relative risk of neurological and psychiatric diagnoses were also increased even in patients with COVID-19 who did not require hospitalisation. Some specific neurological diagnoses merit individual mention. The risk of cerebrovascular events (ischaemic stroke and intracranial haemorrhage) was elevated after COVID-19, with the incidence of ischaemic stroke rising to almost one in ten (or three in 100 for a first stroke) in patients with encephalopathy. 2·66% of patients older than 65 years and 4·72% who had encephalopathy received a first diagnosis of dementia within 6 months of having COVID-19. Whether COVID-19 is associated with Guillain-Barré syndrome remains unclear - their data were equivocal, with HRs increased with COVID-19 compared with other respiratory tract infections but not with influenza, and increased compared with three of the four other index health events. The findings regarding anxiety and mood disorders showed that the HR remained elevated, although decreasing, at the 6-month period. They also observed a significantly increased risk of psychotic disorders. Substance use disorders and insomnia were also more common in COVID-19 survivors than in those who had influenza or other respiratory tract infections (except for the incidence of a first diagnosis of substance use disorder after COVID-19 compared with other respiratory tract infections). Therefore, as with the neurological outcomes, the psychiatric sequelae of COVID-19 appear widespread and to persist up to, and probably beyond, 6 months. Compared with neurological disorders, common

	psychiatric disorders (mood and anxiety disorders) showed a weaker relationship with the markers of COVID-19 severity in terms of incidence or HRs. This might indicate that their occurrence reflects, at least partly, the psychological and other implications of a COVID-19 diagnosis rather than being a direct manifestation of the illness. HRs for most neurological outcomes were constant, and hence the risks associated with COVID-19 persisted up to the 6-month timepoint. They estimated the diagnostic incidence of the neurological and psychiatric outcomes of the primary cohort in the 6 months after a COVID-19 diagnosis. In the whole cohort, 33.62% (33.17–34.07) of patients received a diagnosis. For the cohort subgroups, these estimates were 38.73% (37.87–39.60) for patients who were hospitalised, 46.42% (44.78–48.09) for those admitted to ITU, and 62.34% (60.14–64.55) for those diagnosed with encephalopathy. A similar, but more marked, increasing trend was observed for patients receiving their first recorded neurological or psychiatric diagnosis.
Source of funding	NIHR Oxford Health Biomedical Research Centre.
Study limitations (Author)	Their findings have weaknesses inherent to an electronic health records study, such as the unknown completeness of records, no validation of diagnoses, and sparse information on socioeconomic and lifestyle factors. These issues primarily affect the incidence estimates, but the choice of cohorts against which to compare COVID-19 outcomes influenced the magnitude of the HRs. The analyses regarding encephalopathy (delirium and related conditions) deserve a note of caution. Even among patients who were hospitalised, only about 11% received this diagnosis, whereas much higher rates would be expected. Under-recording of delirium during acute illness is well known and probably means that the diagnosed cases had prominent or sustained features; as such, results for this group should not be generalised to all patients with COVID-19 who experience delirium. They also note that encephalopathy is not just a severity marker but a diagnosis in itself, which might predispose to, or be an early sign of, other neuropsychiatric or neurodegenerative outcomes observed during follow-up. The timing of index events was such that most infections with influenza and many of the other respiratory tract infections occurred earlier on during the pandemic, whereas the incidence of COVID-19 diagnoses increased over time. The effect of these timing differences on observed rates of sequelae is unclear but, if anything, they are likely to make the HRs an underestimate because COVID-19 cases were diagnosed at a time when all other diagnoses were made at a lower rate in the population. Some patients in the comparison cohorts are likely to have had undiagnosed COVID-19; this would also tend to make their HRs an underestimate.

	Finally, a study of this kind can only show associations; efforts to identify mechanisms and assess causality will require prospective cohort studies and additional study designs.
Study limitations (Reviewer)	Nothing further to add.

Study arms

Individuals who had COVID-19 (N = 236379)

Individuals who had influenza (N = 105579)

Individuals who had other respiratory tract infections (non-covid, but including influenza) (N = 236038)

Characteristics

Study-level characteristics

Characteristic	Study (N = 236379)
Age (years) Mean (SD)	46 (19.7)
% Female Nominal	55.6
White Nominal	57.2
Black or African American Nominal	18.8
Hispanic or Latino Nominal	16
Overweight and obesity Nominal	18.1
Hypertensive disease Nominal	30
Type 2 diabetes Nominal	15.5
Asthma Nominal	10.6
Nicotine dependence Nominal	7.2

Characteristic	Study (N = 236379)
Substance use disorder Nominal	10.5
Ischaemic heart diseases Nominal	8.9
Other forms of heart disease Nominal	18
Chronic kidney disease Nominal	6.7
Neoplasms Nominal	19.1

Outcomes

Study timepoints

- 180 day

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
Overall bias	Overall risk of bias	High *(Retrospective cohort study with matched control groups. Prone to selection bias.)*

Whitaker, 2021

Bibliographic Reference	Whitaker M; Elliott J; Chadeau-Hyam M; Riley S; Darzi A; Cooke G; Ward H; Elliott P; Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people; 2021

Study details

Study design	Retrospective cohort study
Aim of the study	To estimate symptom prevalence and investigate co-occurrence of symptoms among participants in the community reporting symptoms lasting 12 weeks or more following suspected or confirmed COVID-19.
Country/ Geographical location	UK
Study setting	Community: Random population sample of adults in England who had COVID-19.
Population description	Adults in the community who had COVID-19 in the past.
Inclusion criteria	Same as above.

Exclusion criteria	Individuals who had missing data.
Intervention/test/approach	Random population samples of adults in England were invited to take part every 2–4 months using the National Health Service (NHS) patient list to achieve similar numbers of participants in each of 315 lower-tier local authority (LTLA) areas. Participants registered via an online portal or by telephone. Those registered were sent a test kit by post that included a self-administered point-of-care lateral flow immunoassay (LFIA) test with instructions and a link to an online video. Participants completed a survey (online/telephone) upon completion of their self-test. Participants provided information on demographics, household composition, whether or not they thought that they had had COVID-19, whether or not they had had a PCR test, co-morbidities, symptoms related to COVID-19, severity of symptoms, and duration of any of a list of 29 symptoms.18 In addition, we asked participants to report any other symptoms in free text. Personalised invitations were sent to between 560,000 and 600,000 individuals aged 18 years and above in each of rounds three to five of the REACT-2 study, carried out from 15 to 28 September 2020 (round 3), 27 October to 10 November 2020 (round 4) and 25 January to 8 February 2021 (round 5). Registrations closed after ~190,000 people had signed up at each round.
Comparator (where applicable)	There was no comparator.
Methods for population selection/allocation	As above.
Methods of data analysis	They obtained prevalence estimates for reporting of one or more of the 29 symptoms by sex, age and other characteristics, at time of suspected or confirmed COVID-19, and for persistence of symptoms at four and 12 weeks. Their main analyses focused on individual symptoms reported as lasting for 12 weeks (84 days) or more. Prevalence estimates were weighted by sex, age, ethnicity, LTLA population and index of multiple deprivation, to take account of the sampling design that gave approximately equal numbers of participants in each LTLA, and differential response rates, to obtain prevalence estimates that were representative of the population of England as a whole. They used logistic regression (univariable, and sex, age adjusted) to investigate the associations of demographic and lifestyle factors with persistence of symptoms at 12 weeks or more, and gradient boosted tree models to investigate predictive ability (area under the curve, AUC) changes from adding variables to the model for persistent symptoms at 12 weeks or more. To identify a more specific set of persistent symptoms associated with history of COVID-19, in sensitivity analyses, they carried out variable selection in a 30% subset of

	symptomatic participants: in univariable models, they identified a subset of persistent symptoms (12 or more weeks) that were positively associated with a reported prior positive PCR test, and estimated the population prevalence of persistence of one or more of these symptoms. They also repeated the logistic and gradient boosted tree modeling with this subset of symptoms as outcome variables. Generalised additive models (GAMs) were constructed with likelihood of symptom persistence at 12 weeks or more modelled as a smoothed function of sex and age. A default thin plate spline was used and the smoothed functions were plotted to visualise the relationship between risk of persistent symptoms and age. They used free-text analysis to identify single and co-occurring words to indicate other symptoms recorded by participants, and plotted these in a network. To identify symptom clusters segmenting participants, two binary matrices were constructed for presence or absence (1 or 0) of each of the 29 surveyed symptoms at (i) time of symptom onset and (ii) 12 weeks after, for each participant. Clustering was performed, separately, both row-wise (to identify groups of participants with similar symptoms) and column-wise (to group symptoms based on their co-occurrence) using the CLustering LARge Applications (CLARA) extension of the Partitioning Around Medoids (PAM) algorithm, implemented in the R package fpc.20 Briefly, PAM searches for the most representative data points to become cluster centroids by minimising the sum of dissimilarities between data points and their assigned centroids. CLARA uses a sampling approach to reduce the computational burden for large data sets. They used Hamming distance as a measure of dissimilarity between participants (row-wise clustering) and symptoms (column-wise clustering). They determined the optimal number of clusters using the average silhouette width. They used two methods to assess cluster stability. First, they bootstrapped and re-clustered 100 times, then quantified the difference between bootstrapped and non-bootstrapped clusters using the Jaccard coefficient, which can range from 0 (no overlap) to 1 (perfect overlap). Second, they removed each symptom in turn, re-clustered, then calculated the average proportion of non-overlap (APN) between these and whole-dataset clusters as a proxy for the individual variable importance and contribution to the population segmentation. To further describe patterns of symptom co-occurrence, they took the cross-product of the symptom matrix at symptom onset and at 12 weeks to find pairwise symptom co-occurrence counts, and visualised them as heatmaps.
Attrition/loss to follow-up	None

Summary of results	A total of 508,707 people took part in REACT-2 rounds three to five and completed surveys. The weighted prevalence of self-reported COVID-19 was 19.2% [19.1,19.3] with 92,116 people reporting one or more of 29 symptoms, of whom 76,155 (82.7%) reported a valid date of symptom onset 12 weeks or more before their survey date. Of those self-reporting COVID-19, 28,713/76,155 (37.7%) experienced at least one symptom for 12 weeks or more and 11,241 (14.8%) experienced at least three symptoms for the same period. This gives a weighted population prevalence of persistent symptoms of 5.75% (5.68, 5.81) for one and 2.22% (2.18, 2.26) for three or more symptoms for England to early February 2021. Almost a third of people with at least one symptom lasting 12 weeks or more (8,771/28,713 [30.5%]) reported having had severe COVID-19 symptoms ("significant effect on my daily life") at the time of their illness, giving a weighted prevalence overall of people with persistent symptoms at 12 weeks who had reported severe symptoms of 1.72% (1.69,1.76). The proportion of people with one or multiple symptoms declined over time since infection. There was a rapid drop-off by four weeks, a further, smaller drop by 12 weeks, but then little evidence of further decline over time up to ~22 weeks for both men and women, with higher prevalence of symptoms at each time point among women. **Factors associated with persistent symptoms** Among symptomatic people, the persistence of one or more symptoms for 12 weeks or more was higher in women than men (age-adjusted OR: 1.51 [1.46,1.55]), and increased with age, with a linear increase of 3.5 percentage points per decade of life. With adjustment for sex and age, persistent symptoms were associated with self-reported overweight (OR: 1.16 [1.12, 1.21]) and obesity (OR: 1.53 [1.47,1.59]) compared with normal weight individuals, smoking (OR: 1.35 [1.28,1.41]), vaping (OR: 1.26 [1.18,1.34]) and hospitalisation with COVID-19 (OR: 3.46 [2.93,4.09]), while Asian ethnicity (OR: 0.80 [0.74,0.88]) was associated with lower risk of persistent symptoms compared to people of white ethnicity. There was a higher proportion with persistent symptoms among those with low incomes at 51.0% (49.5, 52.4) compared with high incomes at 28.7% (27.2, 30.4) and among people living in the most deprived areas at 42.6% (41.5, 43.6) compared with the most affluent areas at 34.7% (34.0, 35.3). Prevalence of persistent symptoms at 12 or more weeks was around 50% or more among people reporting co-morbidities, ranging up to 67.9% (65.6,70.1) for "other lung condition".

	In addition to the 29 symptoms enquired about on the questionnaire, 8,370 respondents gave free-text descriptions of other symptoms, of whom 1,860 reported symptoms that persisted for 12 weeks or more. Free-text analysis of co-occurring words indicated common additional symptoms which were not in our survey, including brain-fog, hair-loss, blood-pressure, heart-palpitations, severe-joint-pain. **Clustering analysis** In clustering analysis, two stable clusters of participants were identified based on symptom profiles at 12 weeks. Participants in Cluster L1 (“tiredness cluster”) experienced high prevalence of tiredness, which co-occurred with muscle aches, difficulty sleeping and shortness of breath. Participants in Cluster L2 (“respiratory cluster”) experienced high prevalence of respiratory symptoms including shortness of breath and tight chest, as well as chest pain. A higher proportion of people in the respiratory cluster reported severe symptoms at the time of their COVID-19 illness (43.5%, [42.0,44.9]) than in the tiredness cluster (27.4%, [26.7,28.1]). Participants reported high prevalence of persistent symptoms lasting 12 weeks or more. Estimates ranged from 5.8% of the population experiencing one or more persistent symptoms post-COVID-19 (corresponding to over 2 million adults in England), to 2.2% for three or more persistent symptoms (just under a million adults in England), and 1.7% with one or more symptoms lasting at least 12 weeks in people who reported severe COVID-19 symptoms affecting their daily life at the time of their illness. They found a linear association between age and persistent symptoms in people with symptomatic COVID-19. Their finding is conditional on symptomatic COVID-19, reflecting the fact that older age groups in the community have lower infection rates than younger people and are more likely to be asymptomatic. Their identification of two stable and well-differentiated symptom clusters at 12 weeks supports the characterisation of Long COVID as a diverse set of overlapping conditions.
Source of funding	Department of Health and Social Care in England.
Study limitations (Author)	Their open free-text question identified a number of symptoms not included in their questionnaire including “brain fog”, “palpitations” and “hair loss”. However, as the study was based on self-reported data and because many of the symptoms are common and not specific to COVID-19, they may have overestimated the prevalence of persistent symptoms. A further limitation is the retrospective study design, which introduces the possibility of recall bias. Nonetheless, in earlier analyses they have shown that participant reports of date of

	onset of their symptoms produce an epidemic curve that very closely tracks the epidemic. Respondents were restricted to reporting a single date of (initial) symptom onset which does not allow for delayed onset of some symptoms, nor does it allow for the reporting of relapsing symptoms which appear to be a feature of Long COVID. A further limitation, despite the high response rate for a community surveillance study, is the possibility of participation bias as the REACT-2 study included a home antibody self-test; it is plausible that people with persistent symptoms may have been more likely to participate in order to ascertain their antibody status.
Study limitations (Reviewer)	Nothing further to add.

Study arms

Individuals who had COVID-19 (N = 508707)

Characteristics

Study-level characteristics

Characteristic	**Study (N =** 28713)
Age 18-24 years % symptomatic	30.2
Age 25-34 years % symptomatic	30.9
Age 35-44 years % symptomatic	32.7
Age 45-54 years % symptomatic	39.1
Age 55-64 years % symptomatic	42.7
Age 65-74 years % symptomatic	46.3
Age 74+ years % symptomatic	52.8
% Female Nominal	41.5
Asian	30.2

Characteristic	Study (N = 28713)
% symptomatic	
Black % symptomatic	37.6
Mixed % symptomatic	39.1
Other % symptomatic	37.7
White % symptomatic	37.9

Outcomes

Study timepoints

- 12 week

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
Overall bias	Overall risk of bias	High *(Retrospective cohort study. Prone to selection bias and recall bias.)*

Appendix 7 GRADE profiles

Risk factors: Adults experiencing symptoms beyond the duration of acute COVID-19

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Risk factor: Female sex (follow-up: 4 weeks)							
6525 (9 observational studies)	very serious[a]	serious[b]	not serious	not serious	none	Very low	Odds ratio 1.49 (CI 95% 1.24 — 1.79)
Risk factor: Hospitalisation (follow-up: 12 weeks)							
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Low	Odds ratio 3.46 (CI 95% 2.93 — 4.09)
Risk factor: Vaping (follow-up: 12 weeks)							
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Low	Odds ratio 1.26 (CI 95% 1.18 — 1.34)
Risk factor: Smoking (follow-up: 12 weeks)							

Certainty assessment							Summary of findings
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Low	Odds ratio 1.35 (CI 95% 1.28 — 1.41)
Risk factor: Obesity (follow-up: 12 weeks)							
0 (1 observational study)	very serious[c]	not serious	not serious	not serious	none	Low	Odds ratio 1.53 (CI 95% 1.47 — 1.59)
Risk factor: Female sex (follow-up: 12 weeks)							
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Very low	Odds ratio 1.51 (CI 95% 1.46 — 1.55)
Risk factor: Non-white ethnicity (follow-up: 4 weeks)							
5607 (7 observational studies)	very serious[a]	not serious	not serious	serious[d]	none	Very low	Odds ratio 0.80 (CI 95% 0.54 — 1.19)
Risk factor: Asian ethnicity (follow-up: 12 weeks)							
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Very low	Odds ratio 0.80 (CI 95% 0.74 — 0.88)
Risk factor: Poor pre-pandemic mental health (follow-up: 4 weeks)							

Certainty assessment							Summary of findings
5467 (9 observational studies)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 1.46 (CI 95% 1.17 — 1.83)
Risk factor: Poor general health (follow-up: 4 weeks)							
4429 (7 observational studies)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 1.62 (CI 95% 1.25 — 2.09)
Risk factor: Asthma (follow-up: 4 weeks)							
4525 (9 observational studies)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 1.32 (CI 95% 1.07 — 1.62)
Risk factor: Overweight or obese (follow-up: 12 weeks)							
4327 (8 observational studies)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 1.25 (CI 95% 1.01 — 1.55)
Risk factor: Overweight (follow-up: 12 weeks)							
(1 observational study)	very serious[c]	not serious	not serious	not serious	none	Very low	Odds ratio 1.16 (CI 95% 1.12 — 1.21)

CI: confidence interval; **OR:** odds ratio

Explanations

a. Risk of bias assessment not reported but most studies used self-reported outcomes that increases recall bias.
b. Significant heterogeneity (I2 >50%)
c. Study rated as high risk of bias due to the retrospective study design and high probability of recall bias
d. 95% CI crosses the line of no effect

Appendix 8 Excluded studies

Study	Reason for exclusion
Addison, Alfred B, Wong, Billy, Ahmed, Tanzime et al. (2021) Clinical Olfactory Working Group Consensus Statement on the Treatment of Post Infectious Olfactory Dysfunction. The Journal of allergy and clinical immunology	- Indirect evidence
Aemaz Ur Rehman, Muhammad, Farooq, Hareem, Ali, Muhammad Mohsin et al. (2021) The Association of Subacute Thyroiditis with COVID-19: a Systematic Review. SN comprehensive clinical medicine: 1-13	- Covered in included systematic review
Al-Aly, Ziyad; Xie, Yan; Bowe, Benjamin (2021) High-dimensional characterization of post-acute sequalae of COVID-19. Nature	- Covered in included systematic review
Alemanno, Federica, Houdayer, Elise, Parma, Anna et al. (2021) COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. PloS one 16(2): e0246590	-Sample size less than 10,000
Aminian, Ali, Bena, James, Pantalone, Kevin M et al. (2021) Association of Obesity with Post-Acute Sequelae of COVID-19 (PASC). Diabetes, obesity & metabolism	- Sample size less than 10,000
Arnold David, T, Milne, Alice, Stadon, Louise et al. Are vaccines safe in patients with Long COVID? A prospective observational study. medrxiv preprint	- Duplicate
Augustin, Max, Schommers, Philipp, Stecher, Melanie et al. (2021) Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. The Lancet regional health. Europe 6: 100122	- Sample size less than 10,000
Augustin, Max, Schommers, Philipp, Stecher, Melanie et al. Recovered not restored: Long-term health consequences after mild COVID-19 in non-hospitalized patients. medrxiv preprint	- Duplicate
Badenoch James, B, Rengasamy Emma, R, Watson Cameron, J et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. medrxiv preprint	- Covered in included systematic review
Baricich, Alessio, Borg, Margherita B, Cuneo, Daria et al. (2021) Midterm functional sequelae and implications in rehabilitation after COVID19. A cross-sectional study. European journal of physical and rehabilitation medicine	- Sample size less than 10,000
Bell Melanie, L, Catalfamo Collin, J, Farland Leslie, V et al. Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. medrxiv preprint	- Sample size less than 10,000
Bellan, Mattia, Soddu, Daniele, Balbo, Piero Emilio et al. (2021) Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA network open 4(1): e2036142	- Sample size less than 10,000

Biadsee, Ameen, Dagan, Or, Ormianer, Zeev et al. (2021) Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients. American journal of otolaryngology 42(4): 103065	- Sample size less than 10,000
Brackel, Caroline L H, Lap, Coen R, Buddingh, Emilie P et al. (2021) Pediatric long-COVID: An overlooked phenomenon?. Pediatric pulmonology	- Duplicate
Bultas, Margaret W and Fuller, Kelli (2021) Multisystem Inflammatory Syndrome in Children and COVID-19 Infections. NASN school nurse (Print): 1942602x211021136	- Study design: Narrative review with no data
Bultas, Margaret W and Fuller, Kelli (2021) Multisystem Inflammatory Syndrome in Children and COVID-19 Infections. NASN school nurse (Print): 1942602x211021136	- Study design: Narrative review with no data
Cabrera Martimbianco, Ana Luiza, Pacheco, Rafael Leite, Bagattini, Angela Maria et al. (2021) Frequency, signs and symptoms, and criteria adopted for long COVID: a systematic review. International journal of clinical practice: e14357	- Duplicate
Cabrera Martimbianco, Ana Luiza, Pacheco, Rafael Leite, Bagattini, Angela Maria et al. (2021) Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. International Journal of Clinical Practice	- Covered in included systematic review
Carenzo, Luca, Dalla Corte, Francesca, Haines, Ryan W et al. (2021) Return to Work After Coronavirus Disease 2019 Acute Respiratory Distress Syndrome and Intensive Care Admission: Prospective, Case Series at 6 Months From Hospital Discharge. Critical care medicine	- Study design: Case series (Prevalence)
Cennamo, Gilda, Reibaldi, Michele, Montorio, Daniela et al. (2021) Optical coherence tomography angiography features in post COVID-19 pneumonia patients: a pilot study. American journal of ophthalmology	- Scoping assessment - no impact on current recommendations
Chowdhury Zahin, Amin-Chowdhury, Harris Ross, J, Aiano, Felicity et al. Characterising long COVID more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. medrxiv preprint	- Sample size less than 10,000
Clarke, Jonathan, Flott, Kelsey, Crespo Roberto, Fernandez et al. Assessing the Safety of Home Oximetry for Covid-19: A multi-site retrospective observational study. medrxiv preprint	- Population: Acute Covid-19
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	- Not relevant to review protocols
Cousyn, L, Sellem, B, Palich, R et al. (2021) Olfactory and gustatory dysfunctions in COVID-	- Sample size less than 10,000

19 outpatients: a prospective cohort study. Infectious diseases now	
D'Cruz, R.F., Perrin, F., Waller, M. et al. (2021) Clinical, radiological, functional and psychological characteristics of severe COVID-19 pneumonia survivors: A prospective observational cohort study. Thorax 76(suppl1): a34-a35	- Study design: Conference abstract
Damanti, Sarah, Ramirez, Giuseppe Alvise, Bozzolo, Enrica Paola et al. (2021) 6-Month Respiratory Outcomes and Exercise Capacity of COVID-19 Acute Respiratory Failure Patients Treated With CPAP. Internal medicine journal	- Sample size less than 10,000
DARLEY David, R, Dore, Gregory, Byrne, Anthony et al. Limited recovery from post-acute sequelae of SARS-CoV-2 (PASC) at eight months of a prospective cohort. medrxiv preprint	- Sample size less than 10,000
Daugherty, Sarah E, Guo, Yinglong, Heath, Kevin et al. (2021) Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ (Clinical research ed.) 373: n1098	- Covered within included primary study
Davis Hannah, E, Assaf Gina, S, McCorkell, Lisa et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. medrxiv preprint	- Sample size less than 10,000
Daynes, Enya, Gerlis, Charlotte, Chaplin, Emma et al. Early experiences of rehabilitation for patients post-COVID to improve fatigue, breathlessness exercise capacity and cognition. medrxiv preprint	- Intervention: Rehabilitation on discharge
Daynes, Enya, Gerlis, Charlotte, Chaplin, Emma et al. (2021) Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. Chronic respiratory disease 18: 14799731211015691	- Intervention: Rehabilitation on discharge
Dennis, Andrea, Wamil, Malgorzata, Alberts, Johann et al. (2021) Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ open 11(3): e048391	- Sample size less than 10,000
Desgranges, Florian, Tadini, Eliana, Munting, Aline et al. Post-COVID-19 syndrome in outpatients: a cohort study. medrxiv preprint	- Sample size less than 10,000
Divanoglou, Anestis, Samuelsson, Kersti, Sj?dahl, Rune et al. Rehabilitation needs and mortality associated with the Covid-19 pandemic: a population-based study of all hospitalised and home-healthcare individuals in a Swedish healthcare region. medrxiv preprint	- Sample size less than 10,000
Donegani, Maria Isabella, Miceli, Alberto, Pardini, Matteo et al. (2021) Brain Metabolic Correlates of Persistent Olfactory Dysfunction after SARS-Cov2 Infection. Biomedicines 9(3)	- Study aim: Pathophysiology/mechanisms
Estiri, Hossein, Strasser, Zachary, Brat, Gabriel et al. Evolving Phenotypes of non-hospitalized Patients that Indicate Long Covid. medrxiv preprint	- Covered within included primary study

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	- For consideration at future update pending further data
Fair Health (2021) A Detailed Study of Patients with Long-Haul COVID: An Analysis of Private Healthcare Claims.	- No data to extract
Faverio, Paola, Luppi, Fabrizio, Rebora, Paola et al. Six-month pulmonary impairment after severe COVID-19: a prospective, multicenter follow-up study. medrxiv preprint	- Scoping assessment - no impact on current recommendations
Froidure, Antoine, Mahsouli, Amin, Liistro, Giuseppe et al. (2021) Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respiratory medicine 181: 106383	- Sample size less than 10,000
Frontera Jennifer, A., Yang, Dixon, Lewis, Ariane et al. A Prospective Study of Long-Term Outcomes Among Hospitalized COVID-19 Patients with and without Neurological Complications. medrxiv preprint	- Sample size less than 10,000
Gaber T A-Z, K; Ashish, A; Unsworth, A (2021) Persistent post-covid symptoms in healthcare workers. Occupational medicine (Oxford, England)	-Sample size less than 10,000
Galal, islam, Hussein Aliae AR, Mohamed-Hussein, Amin - Mariam, T et al. Determinants of Persistent Post COVID-19 symptoms: Value of a Novel COVID-19 symptoms score. medrxiv preprint	-Sample size less than 10,000
Ganesh, Ravindra, Grach Stephanie, L, Bierle Dennis, M et al. The Female Predominant Persistent Immune Dysregulation of the Post COVID Syndrome: A Cohort Study. medrxiv preprint	- Sample size less than 10,000
Ghosn, Jade, Piroth, Lionel, Epaulard, Olivier et al. (2021) Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Sample size less than 10,000
Giovannetti, Guido, De Michele, Lucrezia, De Ceglie, Michele et al. (2021) Lung ultrasonography for long-term follow-up of COVID-19 survivors compared to chest CT scan. Respiratory medicine 181: 106384	- Scoping assessment - no impact on current recommendations
Gobbi, M, Brunani, A, Arreghini, M et al. (2021) Nutritional status in post SARS-Cov2 rehabilitation patients. Clinical nutrition (Edinburgh, Scotland)	- Scoping assessment - no impact on current recommendations
Guler, Sabina A, Ebner, Lukas, Beigelman, Catherine et al. (2021) Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. The European respiratory journal	- Sample size less than 10,000

Hallam F, Rankin R BJ (2021) Rehabilitation of adults who are hospitalised due to acute COVID-19 or Long COVID: physiotherapy service delivery.	- Study design: Expert opinion
Heightman, Melissa, Prashar, Jai, Hillman, Toby et al. Post-COVID assessment in a specialist clinical service: a 12-month, single-centre analysis of symptoms and healthcare needs in 1325 individuals. medrxiv preprint	- Sample size less than 10,000
Hirschtick, Jana L, Titus, Andrea R, Slocum, Elizabeth et al. (2021) Population-based estimates of post-acute sequelae of SARS-CoV-2 infection (PASC) prevalence and characteristics. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- Sample size less than 10,000
Holmes, Elaine, Wist, Julien, Masuda, Reika 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	- Scoping assessment - no impact on current recommendations
Hopkins, C, Surda, P, Vaira, L A et al. (2020) Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. Rhinology	- Sample size less than 10,000
Horn, Mathilde, Wathelet, Marielle, Fovet, Thomas et al. (2020) Is COVID-19 Associated With Posttraumatic Stress Disorder?. The Journal of clinical psychiatry 82(1)	- Sample size less than 10,000
Hoshijima, Hiroshi, Mihara, Takahiro, Seki, Hiroyuki et al. Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. medrxiv preprint	- Covered in included systematic review
Humphreys, H., Kilby, L., Kudiersky, N. et al. (2021) Long COVID and the role of physical activity: a qualitative study. BMJ Open 11(3): 047632	- Qualitative studies: Separate search conducted by SIGN
Hunter, A., Hodgson, L., Leckie, T. et al. (2020) Socially distanced rehabilitation: A potential new normal for post-critical care recovery?. Intensive Care Medicine Experimental 8(suppl2)	- Scoping assessment - no impact on current recommendations
Hylton, H., Pfeffer, P.E., Robson, C. et al. (2021) Rapid design and implementation of a personalised holistic post-COVID recovery and rehab app. Thorax 76(suppl1): a236	- Study design: Conference abstract
Iftikhar, Hina; Doherty, Warren L; Sharp, Charles (2021) Long-term COVID-19 complications: a multidisciplinary clinic follow-up approach. Clinical medicine (London, England) 21(suppl2): 3-4	- Intervention: Rehabilitation on discharge
Iqbal, Ayman, Iqbal, Kinza, Arshad Ali, Shajeea et al. (2021) The COVID-19 Sequelae: A Cross-Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. Cureus 13(2): e13080	- Sample size less than 10,000

Iqbal, Fahad M, Lam, Kyle, Sounderajah, Viknesh et al. (2021) Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine 36: 100899	- Covered in included systematic review
Ismael, Flavia, Bizario, Joao C S, Battagin, Tatiane et al. (2021) Post-infection depressive, anxiety and post-traumatic stress symptoms: A prospective cohort study in patients with mild COVID-19. Progress in neuro-psychopharmacology & biological psychiatry: 110341	-Sample size less than 10,000
Iwu, C.J.; Iwu, C.D.; Wiysonge, C.S. (2021) The occurrence of long COVID: A rapid review. Pan African Medical Journal 38: 1-12	- Review of studies covered in development
Jacobs, Laurie G, Gourna Paleoudis, Elli, Lesky-Di Bari, Dineen et al. (2020) Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PloS one 15(12): e0243882	- Sample size less than 10,000
Jewson, Jacob; McNamara, Alice; Fitzpatrick, Jane (2020) Life after COVID-19: The importance of a safe return to physical activity. Australian journal of general practice 49	- Supporting evidence
Ladds, Emma, Rushforth, Alex, Wieringa, Sietse et al. (2020) Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. BMC health services research 20(1): 1144	- Qualitative studies: Separate search conducted by SIGN
Ladds, Emma, Rushforth, Alex, Wieringa, Sietse et al. (2021) Developing services for long COVID: lessons from a study of wounded healers. Clinical medicine (London, England) 21(1): 59-65	- Qualitative studies: Separate search conducted by SIGN
Lemhofer, Christina, Gutenbrunner, Christoph, Schiller, Jorg et al. (2021) Assessment of rehabilitation needs in patients after COVID-19: Development of the COVID-19-rehabilitation needs survey. Journal of rehabilitation medicine	- Study design: Narrative review with no data
Li, Jian'an, Xia, Wenguang, Zhan, Chao et al. Effectiveness of a telerehabilitation program for COVID-19 survivors (TERECO) on exercise capacity, pulmonary function, lower limb muscle strength, and quality of life: a randomised controlled trial. medrxiv preprint	- Scoping assessment - no impact on current recommendations
Lopez-Leon, Sandra, Wegman-Ostrosky, Talia, Perelman, Carol et al. (2021) More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv : the preprint server for health sciences	- Covered in included systematic review
Mahmud, Reaz, Rahman, Md Mujibur, Rassel, Mohammad Aftab et al. (2021) Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. PloS one 16(4): e0249644	- Sample size less than 10,000
Makaronidis, Janine, Firman, Chloe, Magee, Cormac G et al. (2021) Distorted chemosensory perception and female sex associate with	- Sample size less than 10,000

persistent smell and/or taste loss in people with SARS-CoV-2 antibodies: a community based cohort study investigating clinical course and resolution of acute smell and/or taste loss in people with and without SARS-CoV-2 antibodies in London, UK. BMC infectious diseases 21(1): 221	
Malik, Jahanzeb, Zaidi Syed Muhammad, Jawad, Ishaq, Uzma et al. Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review. medrxiv preprint	- Covered in included systematic review
Mandal, Swapna, Barnett, Joseph, Brill, Simon E et al. (2020) 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax	- Sample size less than 10,000
Martin, Ines, Braem, Fred, Baudet, Lia et al. (2021) Follow-up of functional exercise capacity in patients with COVID-19: It is improved by telerehabilitation. Respiratory medicine 183: 106438	- Scoping assessment - no impact on current recommendations
Mattioli, Flavia, Stampatori, Chiara, Righetti, Francesca et al. (2021) Neurological and cognitive sequelae of Covid-19: a four month follow-up. Journal of neurology	- Sample size less than 10,000
Meije, Y, Duarte-Borges, A, Sanz, X et al. (2021) Long-term outcomes of patients following hospitalization for COVID-19: a prospective observational study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Sample size less than 10,000
Miller, Faith, Nguyen, Vincent, Navaratnam Annalan, MD et al. Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales. medrxiv preprint	- Duplicate
Miskowiak, K W, Johnsen, S, Sattler, S M et al. (2021) Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 46: 39-48	- Sample size less than 10,000
Montefusco, Laura, Ben Nasr, Moufida, D'Addio, Francesca et al. (2021) Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. Nature metabolism	- Scoping assessment - no impact on current recommendations
Moradi, Yaser, Mollazadeh, Farzin, Karimi, Parivash et al. (2020) Psychological disturbances of survivors throughout COVID-19 crisis: a qualitative study. BMC psychiatry 20(1): 594	- Qualitative studies: Separate search conducted by SIGN
Moreno-Perez, Oscar, Merino, Esperanza, Leon-Ramirez, Jose-Manuel et al. (2021) Post-acute COVID-19 Syndrome. Incidence and risk factors: a Mediterranean cohort study. The Journal of infection	- Sample size less than 10,000

Nehme, Mayssam (2020) COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings. Annals of Internal Medicine	- Sample size less than 10,000
Office for National Statistics (2021) Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 July 2021.	- No data to extract
Parkin, Amy, Davison, Jennifer, Tarrant, Rachel et al. (2021) A Multidisciplinary NHS COVID-19 Service to Manage Post-COVID-19 Syndrome in the Community. Journal of primary care & community health 12: 21501327211010994	- Scoping assessment - no impact on current recommendations
Pearmain, L., Avram, C., Yioe, V. et al. (2021) Patient symptoms following discharge from hospital after COVID-19 pneumonia. Thorax 76(suppl1): a180-a181	- Study design: Conference abstract
Peluso, Michael J, Kelly, J Daniel, Lu, Scott et al. (2021) Rapid implementation of a cohort for the study of post-acute sequelae of SARS-CoV-2 infection/COVID-19. medRxiv : the preprint server for health sciences	- Sample size less than 10,000
Penner, Justin, Abdel-Mannan, Omar, Grant, Karlie et al. (2021) 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. The Lancet. Child & adolescent health	- Duplicate
Perlis, Roy H, Green, Jon, Santillana, Mauricio et al. (2021) Persistence of symptoms up to 10 months following acute COVID-19 illness. medRxiv : the preprint server for health sciences	- Sample size less than 10,000
Pilotto, Andrea, cristillo, viviana, Piccinelli stefano, cotti et al. COVID-19 severity impacts on long-term neurological manifestation after hospitalisation. medrxiv preprint	- Sample size less than 10,000
Pizarro-Pennarolli, Catalina, Sanchez-Rojas, Carlos, Torres-Castro, Rodrigo et al. (2021) Assessment of activities of daily living in patients post COVID-19: a systematic review. PeerJ 9: e11026	- Scoping assessment - no impact on current recommendations
Rao, Sanjay, Benzouak, Tarek, Gunpat, Sasha et al. Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis. medrxiv preprint	- Covered in included systematic review
Rass, Verena, Beer, Ronny, Josef Schiefecker, Alois et al. (2021) Neurological outcome and quality of life three months after COVID-19: a prospective observational cohort study. European journal of neurology	- Sample size less than 10,000
Rass, Verena, Beer, Ronny, Schiefecker, Alois Josef et al. (2021) Neurological outcome and quality of life 3 months after COVID-19: A prospective observational cohort study. European Journal of Neurology	- Duplicate
Raw RK, Kelly CA, Rees J et al. (2021) Previous COVID-19 infection, but not Long-COVID, is associated with increased adverse	- No data to extract

events following BNT162b2/Pfizer vaccination. The Journal of infection	
Rizzo Paolo, Boscolo-Rizzo, Menegaldo, Anna, Fabbris, Cristoforo et al. High prevalence of long-term psychophysical olfactory dysfunction in patients with COVID-19. medrxiv preprint	- Sample size less than 10,000
Rizzo Paolo, Boscolo, Guida, Francesco, Polesel, Jerry et al. Long COVID In Adults at 12 Months After Mild-to-Moderate SARS-CoV-2 Infection. medrxiv preprint	- Sample size less than 10,000
Romero-Duarte, Alvaro, Rivera-Izquierdo, Mario, Guerrero-Fernandez de Alba, Inmaculada et al. (2021) Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. BMC medicine 19(1): 129	- Sample size less than 10,000
Saigal, A., Naidu, S.B., Shah, A.J. et al. (2021) 'Long-COVID': The need for multi-disciplinary working. Thorax 76(suppl1): a33-a34	- Study design: Conference abstract
Salamanna, Francesca, Veronesi, Francesca, Martini, Lucia et al. (2021) Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data. Frontiers in medicine 8: 653516	- Covered in included systematic review
Santiago-Rodriguez, Edda I, Maiorana, Andres, Peluso, Michael J et al. (2021) Characterizing the COVID-19 illness experience to inform the study of post-acute sequalae and recovery: a qualitative study. medRxiv : the preprint server for health sciences	- Qualitative studies: Separate search conducted by SIGN
SCHERLINGER, Marc, Felten, Renaud, Gallais, Floriane et al. Refining long-COVID by a prospective multimodal evaluation of patients with long-term symptoms related to SARS-CoV-2 infection. medrxiv preprint	- Sample size less than 10,000
Shang, Y F, Liu, T, Yu, J N et al. (2021) Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. Journal of internal medicine	- Sample size less than 10,000
Shouman, Kamal, Vanichkachorn, Greg, Cheshire, William P et al. (2021) Autonomic dysfunction following COVID-19 infection: an early experience. Clinical autonomic research : official journal of the Clinical Autonomic Research Society	- Sample size less than 10,000
Sigfrid, Louise, Drake Tom, M, Pauley, Ellen et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. medrxiv preprint	- Sample size less than 10,000
Skyrud Katrine, Damgaard; Telle Kjetil, Elias; Magnusson, Karin Impacts of COVID-19 on long-term health and health care use. medrxiv preprint	- Not relevant to review protocols
Soraas, Arne, Ro, Ragnhild, Kalleberg Karl, T et al. Self-reported Memory Problems Eight	- Covered in included systematic review

Months after Non-Hospitalized COVID-19 in a Large Cohort. medrxiv preprint	
Spotnitz Matthew, E, Hripcsak, George, Ryan Patrick, B et al. Characterizing Post-Acute Sequelae of SARS-CoV-2 Infection across Claims and Electronic Health Record Databases. medrxiv preprint	- Covered in included systematic review
Sudre, Carole H, Murray, Benjamin, Varsavsky, Thomas et al. (2021) Attributes and predictors of long COVID. Nature medicine	- Sample size less than 10,000
Sykes, Dominic L, Holdsworth, Luke, Jawad, Nadia et al. (2021) Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It?. Lung	- Sample size less than 10,000
Tabacof, Laura, Mancuso Jenna, Tosto-Mancuso, Wood, Jamie et al. Post-acute COVID-19 syndrome negatively impacts health and wellbeing despite less severe acute infection. medrxiv preprint	- Sample size less than 10,000
Taquet, M (2020) Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62?354 COVID-19 cases in the USA. The Lancet Psychiatry	- Covered in included systematic review
Tarsitani, Lorenzo, Vassalini, Paolo, Koukopoulos, Alexia et al. (2021) Post-traumatic Stress Disorder Among COVID-19 Survivors at 3-Month Follow-up After Hospital Discharge. Journal of general internal medicine	- Sample size less than 10,000
Todt, Beatriz Costa, Szlejf, Claudia, Duim, Etienne et al. (2021) Clinical outcomes and quality of life of COVID-19 survivors: A follow-up of 3 months post hospital discharge. Respiratory medicine 184: 106453	- Sample size less than 10,000
Townsend, Liam, Moloney, David, Finucane, Ciaran et al. (2021) Fatigue following COVID-19 infection is not associated with autonomic dysfunction. PloS one 16(2): e0247280	- Sample size less than 10,000
Tran, Viet-Thi, Riveros, Carolina, Clepier, Berangere et al. Development and validation of the long covid symptom and impact tools, a set of patient-reported instruments constructed from patients' lived experience. medrxiv preprint	- Scoping assessment - no impact on current recommendations
Trimboli, Pierpaolo, Camponovo, Chiara, Scappaticcio, Lorenzo et al. (2021) Thyroid sequelae of COVID-19: a systematic review of reviews. Reviews in endocrine & metabolic disorders	- Covered in included systematic review
Vaira LA, Hopkins C, Petrocelli M et al. (2021) Efficacy of corticosteroid therapy in the treatment of long- lasting olfactory disorders in COVID-19 patients. Rhinology 59(1): 21-25	- Scoping assessment - no impact on current recommendations
Vanderlind, William Michael, Rabinovitz, Beth B, Miao, Iris Yi et al. (2021) A systematic review of neuropsychological and psychiatric sequalae of COVID-19: implications for treatment. Current opinion in psychiatry 34(4): 420-433	- Covered in included systematic review
Voruz, Philippe, Allali, Gilles, Benzakour, Lamyae et al. Long COVID neuropsychological	- Sample size less than 10,000

deficits after severe, moderate or mild infection. medrxiv preprint	
Walle-Hansen, M M, Ranhoff, A H, Mellingsaeter, M et al. (2021) Health-related quality of life, functional decline, and long-term mortality in older patients following hospitalisation due to COVID-19. BMC geriatrics 21(1): 199	- Sample size less than 10,000
Wallis, T J M, Heiden, E, Horno, J et al. (2021) Risk factors for persistent abnormality on chest radiographs at 12-weeks post hospitalisation with PCR confirmed COVID-19. Respiratory research 22(1): 157	- Sample size less than 10,000
Westerlind, Emma, Palstam, Annie, Sunnerhagen, Katharina S et al. (2021) Patterns and predictors of sick leave after Covid-19 and long Covid in a national Swedish cohort. BMC public health 21(1): 1023	- Covered in included systematic review
Wildwing, T. and Holt, N. (2021) The neurological symptoms of COVID-19: a systematic overview of systematic reviews, comparison with other neurological conditions and implications for healthcare services. Therapeutic Advances in Chronic Disease 12	- Covered in included systematic review
Writing Committee for the COMEBAC Study, Group, Morin, Luc, Savale, Laurent et al. (2021) Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. JAMA	- Sample size less than 10,000
Wu, Qian, Zhong, Lingshan, Li, Hongwei et al. (2021) A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019. Canadian respiratory journal 2021: 6692409	- Sample size less than 10,000
Wynberg, Elke, Willigen Hugo, van, Dijkstra, Maartje et al. Evolution of COVID-19 symptoms during the first 9 months after illness onset. medrxiv preprint	- Sample size less than 10,000
Yusuf, Fauzi, Abubakar, Azzaki, Maghfirah, Desi et al. (2021) Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis. F1000Research 10: 301	- Sample size less than 10,000
Ziauddeen, Nida, Gurdasani, Deepti, Hara Margaret, E et al. Characteristics of Long Covid: findings from a social media surve. medrxiv preprint	- Sample size less than 10,000