National Institute for Health and Care Excellence

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

[I] Evidence reviews for signs and symptoms (update)

NICE guideline NG188

November 2021

Guideline version (Final)

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COVID-19 rapid evidence review: Signs, symptoms and prevalence

November 2021

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 signs, symptoms and prevalence, 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 questions 4 and 5

4. What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health) among people who have symptoms of COVID-19 for 4 to 12 weeks?

5. What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability among people who have symptoms of COVID-19 beyond 12 weeks?

The review protocol is shown in Appendix 2.

Included studies

There were 10 systematic reviews identified from the weekly surveillance searches that reported on persisting signs and symptoms following acute COVID-19 illness. The reviews were compared to assess applicability using the following factors:

- Quality of the review, which was assessed using ROBIS
- Applicability of the systematic review to the review protocol
- Recency of literature search dates
- Overlap of primary studies. Choosing the most comprehensive systematic review will minimise overlap.
- Outcomes reported

The 3 highest quality and most applicable systematic reviews were included in the review. The other 7 reviews were excluded, and details can be found in the excluded studies list (Appendix 8). The systematic reviews included a range of 28-45 studies with some overlap across the reviews. Each review had different approach to analysis. Nassarie 2021 narratively analysed a mixed population of people with persisting symptoms for at least 60 days with either previous suspected or laboratory confirmed COVID-19 illness. Domingo 2021 only analysed people with previous laboratory confirmed SARS-CoV-2 infection with persisting symptoms for at least 4 weeks. Symptoms were meta-analysed by timepoint (4-12 weeks or 12+ weeks). Michelen 2021 analysed a mixed population of people with either previous suspected or laboratory confirmed COVID-19 illness but only included those with persisting symptoms of more than 12 weeks. Details of the systematic reviews are described in Table 1.

In addition, 3 large cohort studies published after the search dates of the systematic reviews were included in the review. Details of the cohort studies are described in Table 2.

Table 1 Included systematic reviews for review questions 4 and 5

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

Nasserie 2021 Published Search date March 2021	People with persisting symptoms related to COVID-19 who were previously inpatients or outpatients (mean age <60 years)	At least 60 days after diagnosis, symptom onset or hospital admission At least 30 days from recovery of acute illness or hospital discharge	45 studies reporting 84 clinical signs or symptoms Prevalence of symptoms measured as median frequency (IQR)	Narrative The study authors had concerns that there was too much heterogeneity to conduct a meta-analysis
Domingo 2021 Pre-print Search date January 2021 Living review	People with laboratory confirmed SARS-CoV-2 infection reported the prevalence of long-term symptoms (age not reported)	4 weeks or more from COVID-19 diagnosis	28 studies reporting on 63 symptoms Prevalence of symptoms presented at 4-12 weeks and 12+ weeks Hospitalised or non-hospitalised for some symptoms	Meta-analysis for outcomes with two or more studies Subgroup analysis to explore heterogeneity Still moderate to high heterogeneity within some subgroups
Michelen 2021 Pre-print Search date March 2021 Included non-English Language papers Living review	People with suspected, laboratory confirmed and/or clinically diagnosed COVID-19 reporting ongoing symptoms (age not reported)	12 or more weeks after COVID-19 illness	32 studies reporting on 61 symptoms Prevalence of symptoms as subgroups of hospitalised or non-hospitalised (where possible)	Meta-analysis for outcomes with two or more studies Subgroup analysis to explore heterogeneity Heterogeneity was still evident

Table 2: Included cohort studies for review questions 4 and 5

Study details	Population	Approach	Prevalence 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	Estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33.62% (95% CI 33.17–34.07) Most common diagnosis was mood, anxiety or psychotic disorder (any) 23.98% (23.58–24.38)
Whittaker 2021 Retrospective cohort Pre-print	46,687 COVID-19 cases (aged ≥18 years) diagnosed between 1st August to 17th October 2020	Data source was from 1,383 general practices contributing to CPRD Aurum. Aimed to identify event rates of new	The largest differences between hospitalised and community patients were respectively noted

	who were either hospitalised (n= 1415) or non-hospitalised (n=45,272) and followed up for 3 months	symptoms, diseases, prescriptions and healthcare utilisation in hospitalised and non-hospitalised individuals.	for rates per 100,000 person-weeks [95%CI] of • breathlessness: 536 [432 to 663] v. 85 [77 to 93]; • joint pain 295 [221 to 392] v. 168 [158 to 179]; • cough: 150 [101 to 224] v. 50 [44 to 56]; • chest pain: 157 [107 to 231] v. 50 [44 to 56]; and • fatigue: 102 [63 to 163] v. 44 [39 to 50]
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.	Two stable clusters of participants were identified based on symptom profiles at 12 weeks. Cluster L1 (“tiredness cluster”) experienced high prevalence of tiredness co-occurring with muscle aches, difficulty sleeping and shortness of breath. Cluster L2 (“respiratory cluster”) experienced high prevalence of respiratory symptoms including shortness of breath, tight chest and chest pain.

Key results

Evidence from 3 systematic reviews described symptoms reported by participants from at least 4 weeks from onset of acute COVID-19 or hospital discharge. The signs and symptoms reported in at least 2 of the systematic reviews are reported in Tables 3 to 11.

Table 3: Signs and symptoms reported in systematic reviews: Systemic symptoms

Sign or symptom	Nasserie 2021	Domingo 2021	Domingo 2021	Michelen 2021
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks**
Fatigue	40% (31 to 57%) Median frequency (IQR) (25 studies)	51% (39% to 64%) Prevalence % (95% CI) (9 studies)	47% (27% to 68%) Prevalence % (95% CI) (3 studies)	30.97% (23.91% to 39.03% Proportion % (95% CI) (17 studies)
Dizziness	None reported	6% (0% to 5%) Prevalence % (95% CI) (1 study)	6% (5% to 7%) Prevalence % (95% CI) (1 study)	4.5% (2.53% to 7.86% Proportion % (95% CI) (5 studies)
Fever	1% (0 to 3%) Median frequency (IQR) (10 studies)	1% (0% to 5%) Prevalence % (95% CI) (4 studies)	0% (0% to 1%) Prevalence % (95% CI) (3 studies)	1.08% (0.24% to 4.66% Proportion % (95% CI) (7 studies)

Table 4: Signs and symptoms reported in systematic reviews: Cardiopulmonary symptoms

Sign or symptom	Nasserie 2021	Domingo 2021	Domingo 2021	Michelen 2021
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks**

Dyspnoea	36% (27.6% to 50%) Median frequency (IQR) (26 studies)	38% (27% to 51%) Prevalence % (95% CI) (10 studies)	22% (12% to 35%) Prevalence % (95% CI) (4 studies)	25.06% (17.86% to 33.97%) Proportion % (95% CI) (20 studies)
Chest pain	13.1% (10.8% to 18%) Median frequency (IQR) (11 studies)	9% (4% to 19%) Prevalence % (95% CI) (2 studies)	5% (2% to 12%) Prevalence % (95% CI) (1 study)	6.36% (3.15% to 12.42%) Proportion % (95% CI) (11 studies)
Palpitations	None reported	11% (5% to 16%) Prevalence % (95% CI) (1 study)	9% (8% to 11%) Prevalence % (95% CI) (1 study)	9.67% (5.95% to 15.34% Proportion % (95% CI) (8 studies)

Table 5: Signs and symptoms reported in systematic reviews: Upper respiratory symptoms

Sign or symptom	**Nasserie 2021**	**Domingo 2021**	**Domingo 2021**	**Michelen 2021**
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks**
Blocked nose	None reported	15% (10% to 20%) Prevalence % (95% CI)	None reported	4.99% (2.73% to 8.92% Proportion % (95% CI)

		(1 study)		(3 studies)
Cough	16.9% (14.4% to 25.1%) Median frequency (IQR) (18 studies)	28% (22% to 35%) Prevalence % (95% CI) (6 studies, any type of cough)	6% (4% to 8%) Prevalence % (95% CI) (2 studies, dry cough only)	8.17% (4.85% to 13.44%) Proportion % (95% CI) (16 studies)
Sore throat	None reported	7% (5% to 10%) Prevalence % (95% CI) (2 studies)	4% (2 to 8%) Prevalence % (95% CI) (2 studies)	4.7% (2.42% to 8.91% Proportion % (95% CI) (5 studies)
Voice change	None reported	20% (12% to 28%) Prevalence % (95% CI) (1 study)	None reported	8.21% (4.17% to 14.21% Proportion % (95% CI) (1 study)

Table 6: Signs and symptoms reported in systematic reviews: Gastrointestinal symptoms

Sign or symptom	**Nasserie 2021**	**Domingo 2021**	**Domingo 2021**	**Michelen 2021**
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks**
Nausea	None reported	1% (0% to 3%) Prevalence % (95% CI) (1 study)	4% (1% to 8%) Prevalence % (95% CI)	None reported

			(1 study)	
Vomiting	None reported	<1% (0% to 2%) Prevalence % (95% CI) (1 study)	2% (1% to 4%) Prevalence % (95% CI) (1 study, vomiting or nausea)	6.69% (1.64% to 23.59% Proportion % (95% CI) (4 studies, vomiting or nausea)
Diarrhoea	None reported	5% (3% to 7%) Prevalence % (95% CI) (3 studies)	2% (1% to 4%) Prevalence % (95% CI) (2 studies)	4% (2.07% to 7.57% Proportion % (95% CI) (10 studies)
Appetite problems	None reported	10% (7% to 13%) Prevalence % (95% CI) (3 studies)	2% (1% to 4%) Prevalence % (95% CI) (2 studies)	17.49 (4.13 to 51.04) Proportion % (95% CI) (3 studies)
Abdominal pain	None reported	4% (1% to 6%) Prevalence % (95% CI) (1 study)	3% (2% to 5%) Prevalence % (95% CI) (1 study)	2.33% (0.54% to 9.42% Proportion % (95% CI) (4 studies)
Weight loss	None reported	12% (6% to 17%) Prevalence % (95% CI) (1 study)	None reported	20.99% (8.09% to 44.51% Proportion % (95% CI) (2 studies)

Table 7: Signs and symptoms reported in systematic reviews: Musculoskeletal symptoms

Sign or symptom	Nasserie 2021	Domingo 2021	Domingo 2021	Michelen 2021

	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks	Population: COVID-19 positive reporting ongoing symptoms 12+ weeks	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks
Joint pain	None reported	19% (14% to 25%) Prevalence % (95% CI) (3 studies)	9% (8% to 11%) Prevalence % (95% CI) (3 studies)	9.39% (5.72% to 15.03% Proportion % (95% CI) (9 studies)
Muscle pain	None reported	22% (16% to 28%) Prevalence % (95% CI) (1 study)	5% (2% to 12%) Prevalence % (95% CI) (3 studies)	11.29% (6.17% to 19.75% Proportion % (95% CI) (12 studies)
Worsened mobility	None reported	37% (28% to 46%) Prevalence % (95% CI) (1 study)	None reported	14.42% (4.67% to 36.73% Proportion % (95% CI) (6 studies)

Table 8: Signs and symptoms reported in systematic reviews: Neurological or neuromuscular symptoms

Sign or symptom	Nasserie 2021	Domingo 2021	Domingo 2021	Michelen 2021
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks	Population: COVID-19 positive reporting ongoing symptoms 12+ weeks	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks
Headache	None reported	12% (10% to 15%)	4% (2% to 10%)	4.88% (2.30% to 10.06%

		Prevalence % (95% CI) (3 studies)	Prevalence % (95% CI) (3 studies)	Proportion % (95% CI) (11 studies)
Walking difficulties	None reported	15% (13% to 18%) Prevalence % (95% CI) (2 studies)	7% (6% to 8%) Prevalence % (95% CI) (1 study)	4.2% (2.02% to 8.53% Proportion % (95% CI) (3 studies)
Smell dysfunction	23.6% (12.4% to 40.7%) Median frequency (IQR) (12 studies)	13% (12% to 36%) Prevalence % (95% CI) (5 studies)	14% (9% to 22%) Prevalence % (95% CI) (3 studies)	15.17% (10.75% to 20.97%) Proportion % (95% CI) (19 studies)
Taste dysfunction	15.6% (10.1% to 23.9%) Median frequency (IQR) (13 studies)	7% (5% to 11%) Prevalence % (95% CI) (3 studies)	10% (7% to 15%) Prevalence % (95% CI) (3 studies)	13.52% (8.96% to 19.89%) Proportion % (95% CI) (17 studies)
Vision disturbance	None reported	None reported	4% (2% to 6%) Prevalence % (95% CI) (1 study)	4.78% (3.32% to 6.83% Proportion % (95% CI) (2 studies)

Table 9: Signs and symptoms reported in systematic reviews: Psychological symptoms

Sign or symptom	**Nasserie 2021**	**Domingo 2021**	**Domingo 2021**	**Michelen 2021**
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing**

				symptoms at 12 or more weeks
Anxiety	22.1% (10% to 29.6%) Median frequency (IQR) (10 studies)	29% (16% to 48%) Prevalence % (95% CI) (2 studies)	23% (21% to 25%) Prevalence % (95% CI) (1 study, anxiety or depression)	18.73% (8.89% to 32.25% Proportion % (95% CI) (7 studies)
Depression	None reported	22% (19% to 25%) Prevalence % (95% CI) (2 studies)	None reported	8.06% (4.14% to 15.1% Proportion % (95% CI) (6 studies)
PTSD	None reported	22% (14% to 34%) Prevalence % (95% CI) (3 studies)	17% (8% to 27%) Prevalence % (95% CI) (1 study)	9.14% (3.66% to 21.04% Proportion % (95% CI) (6 studies)
Sleep disturbance	None reported	36% (10% to 74%) Prevalence % (95% CI) (2 studies)	26% (24% to 29%) Prevalence % (95% CI) (1 study)	18.15% (9.61% to 31.63% Proportion % (95% CI) (9 studies)

Table 10: Signs and symptoms reported in systematic reviews: Neurocognitive symptoms

Sign or symptom	**Nasserie 2021**	**Domingo 2021**	**Domingo 2021**	**Michelen 2021**
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing**

				symptoms at 12 or more weeks
Memory problem	28.3% (18.6% to 35.8%) Median frequency (IQR) (5 studies)	19% (17% to 22%) Prevalence % (95% CI) (2 studies)	None reported	17.94% (5.26% to 46.25% Proportion % (95% CI) (5 studies)
Concentration difficulties	22% to 28% Range (4 studies)	25% (22% to 28%) Prevalence % (95% CI) (2 studies)	None reported	25.98% (20.96% to 31.73%) Proportion % (95% CI) (2 studies)
Cognitive impairment	17.6% (15% to 21.6%) Median frequency (IQR) (6 studies)	24% (18% to 21%) Prevalence % (95% CI) (2 studies)	None reported	17.77% (0.08% to 98.23%) Proportion % (95% CI) (3 studies)
Confusion	None reported	9% (5% to 13%) Prevalence % (95% CI) (1 study)	2% (1% to 4%) Prevalence % (95% CI) (1 study)	2.71% (1.93% to 3.79% Proportion % (95% CI) (2 studies)

Table 11: Signs and symptoms reported in systematic reviews: Other symptoms

Sign or symptom	Nasserie 2021	Domingo 2021	Domingo 2021	Michelen 2021
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks	**Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks**	**Population: COVID-19 positive reporting ongoing symptoms 12+ weeks**	**Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks**

Hair loss	None reported	10% (8% to 12%) Prevalence % (95% CI) (1 study)	22% (20% to 24%) Prevalence % (95% CI) (1 study)	14.34% (5.33% to 33.23% Proportion % (95% CI) (5 studies)
Decreased quality of life	None reported	53% (43% to 63%) Prevalence % (95% CI) (1 study)	None reported	36.76% (18.43% to 59.93% Proportion % (95% CI) (3 studies)

Most commonly reported symptoms

Of the symptoms commonly reported across the reviews, there were several that were more prevalent than others. These were fatigue, dyspnoea, cough, sleep disturbances, anxiety and depression, cognitive impairment, and difficulty concentrating.

In addition to the systematic reviews, Taquet 2021 estimated the incidence of 14 neurological and psychiatric outcomes 6 months after a confirmed diagnosis of COVID-19 to be 33.62% (95% 33.17 to 34.07) of which 12.84% (95% CI 12.36 to 13.33) was a first diagnosis. The most common diagnosis was mood, anxiety or psychotic disorder (any) 23.98% (95% CI 23.58–24.38).

Symptom prevalence over time

There was variation in symptoms prevalence at 4-12 weeks and 12+ weeks. Symptoms such as fatigue were commonly reported at both 4-12 weeks (51%) and 12 + weeks (47% and 31%). Concentration difficulties also remained prevalent over time (25% at 4-12 weeks and 26% at 12+ weeks).

Other commonly reported symptoms appear to be reported less frequently over time. Cough was much more prevalent at 4-12 weeks (28%) compared to 12 or more weeks (6% and 8%). Sleep disturbance was more prevalent at 4-12 weeks (36%) compared to 12 or more weeks (18% and 26%). This was similar for anxiety and depression. In contrast, hair loss was less prevalent at 4-12 weeks (10%) but more studies reported this symptoms at 12 or more weeks (14% or 22%).

Symptom clusters

Whitaker 2021 (REACT 2) attempted to determine clusters of symptoms using symptom persistence reported at 12 weeks. They identified 2 stable clusters of

symptoms. Cluster 1 was the “tiredness cluster” in which people experience high prevalence of tiredness co-occurring with muscle aches, difficulty sleeping and shortness of breath. Cluster 2 was the “respiratory cluster” in which people experienced high prevalence of respiratory symptoms including shortness of breath, tight chest and chest pain.

Subgroups

Hospitalised vs non-hospitalised for acute COVID-19 illness

Where data allowed, subgroup analysis was carried out in the reviews based on whether patients had been hospitalised or not for their acute illness. For fatigue there was higher prevalence in those who had previously been hospitalised (59% at 4-12 weeks; 37.1% and 63% at 12+ weeks) compared to those who had not been hospitalised (16% at 4-12 weeks and 24.6% at 12+ weeks). This was similar for dyspnoea. (Hospitalised 57% at 4-12 weeks and 29% at 12+ weeks; non-hospitalised 24% at 4-12 weeks and 13.72% at 12+ weeks).

This was further supported by Whittaker 2021 which found that the largest differences between hospitalised and community patients was noted for breathlessness, joint pain, cough, chest pain and fatigue, with the higher prevalence seen for hospitalised patients after 3 months.

Strengths and limitations

Review authors noted that study design limitations prevented them from addressing issues such as duration of persistent symptoms or the percentage of symptoms that resolved. There was limited data on persistence of symptoms by initial severity of illness. There was a lack of standardised definitions or instruments used to measure symptoms across the studies which meant that the same symptoms could be measured in different ways. This may explain in part why there were particularly high levels of heterogeneity across the studies. Other possible explanations of heterogeneity could be due to setting, population and follow up time. The lack of control group in the studies or symptom prevalence before COVID-19 were also highlighted limitations in the evidence.

The evidence included mostly adults who were hospitalised or treated for moderate-to-severe COVID-19. Therefore, there was no evidence on the prevalence of long-term effects in children or in individuals who presented with mild COVID symptoms in the acute stage.

All 3 included systematic reviews carried out a risk of bias assessment of their included studies. The studies were generally considered across all reviews to be of moderate to high risk of bias. This mostly due to attrition in the studies, generalisability concerns, methods of participation selection due the nature of the study designs, and the majority of the studies being self-reported outcomes and the

greater risk of recall bias. The 3 additional cohort studies were also judged to be high risk of bias for the same reasons.

Domingo 2021 carried out a modified GRADE approach to assess the body of evidence for prevalence outcomes. They used this approach to assess the certainty of evidence for 63 symptoms. They rated 3/63 (5%) symptoms as moderate certainty, 25/63 (40%) as low certainty and 35/63 (55%) symptoms as very low certainty. However, they did not report reasons for downgrading the evidence.

GRADE profiles are reported in Appendix 7.

Expert panel discussion

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

Benefits and harms

The panel discussed the importance of identifying the most common symptoms that present in people experiencing long term effects of COVID-19. Knowing the most common symptoms will help clinicians to recognise post-COVID-19 syndrome as a possible diagnosis. However, they were mindful that the most common symptoms will not always be present and should not be used as strict criteria for diagnosis as this could mean people who present atypically may be missed. Although the panel acknowledged that new, ongoing or recurring symptoms 12 weeks or more from acute illness onset might be more indicative of post-COVID-19 syndrome, they also thought it important to consider symptoms presenting earlier. This is to ensure symptoms that could indicate an acute complication are assessed as early as possible.

Expert witness testimony advised that many adults with new or ongoing symptoms after acute COVID-19 were experiencing anxiety caused by unnecessary investigations and referrals to different specialists. Therefore, the panel advised that the NICE guideline that shared decision making should be signposted to. The panel agreed there should not be a recommendation cautioning against unnecessary investigations or referrals because there was already under-referral to dedicated clinics or MDTs.

The panel suggested that a dedicated clinic or integrated multidisciplinary assessment service should investigate adults with ongoing symptoms after acute COVID-19. This is to increase coordinated and rapid care. It is also to prevent referral to a series of different specialists and many unnecessary and/or repeated investigations, which can cause anxiety for people and their families. This was the advice from expert witness testimony for adults.

Certainty of the evidence

The panel recognised that the evidence base is still considered to be moderate to very low quality. All studies were considered to be of moderate to high risk of bias due to the ways the studies were conducted. The panel were also mindful that it when considering prevalence data, it is important to know the denominator when interpreting the percentages. This varied across all studies. However, it is clear from the evidence that some symptoms such as fatigue and shortness of breath are reported consistently across studies and the panel commonly see them in clinical practice, which increases the certainty around these symptoms. The panel also acknowledged that some symptoms may be under-reported in the literature. In their experience, patients may not report a symptom, such as sleep disturbance, unless directly asked. They were mindful that the way participants were asked about their symptoms in the studies could impact on how symptoms were reported.

Preferences and values

The input of patients to the expert group discussion was 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 people experiencing fear and anxiety because they do not know what to expect or who to contact for support. This fear and anxiety can be intensified by patients' experience of having their symptoms dismissed when seeking help. Determining the main signs and symptoms of post-COVID-19 syndrome will help address these concerns.

Resource and other considerations

Ongoing persistent symptoms can impact on an individual's ability to perform usual work activities. Healthcare workers have been considered at high risk of contracting

SARS-CoV-2 infection. This could potentially mean a higher prevalence of long-term effects of COVID-19 in this population which may impact on resources within the NHS.

Other considerations

The panel discussed that older people may present with atypical symptoms that could be overlooked. For example, older people can present with gradual decline, deconditioning, worsening frailty or dementia and may not be eating and drinking which can have a variety of causes. It would be reasonable to consider post-COVID-19 syndrome as a cause of these symptoms.

For evidence on signs and symptoms in children and young people, please see separate evidence review.

Appendix 1 Methods used to develop the guidance

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

Appendix 2 Review protocols

Review question 4

What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 for a duration of 4 to 12 weeks?

Criteria	**Notes**
Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) from 4 to 12 weeks after the onset of acute COVID-19 illness.
Interventions/service configuration/information and support [delete/amend as appropriate]	Not applicable
Comparators	Not applicable
Outcomes	Prevalence of symptoms or clusters of symptoms (ongoing physical and mental health) reported 4-12 weeks following onset of acute COVID-19 illness including, but not limited to: Signs and symptoms: • respiratory symptoms such as chronic cough, shortness of breath, cardiovascular symptoms and disease such as chest tightness, tachycardia, palpitations, protracted loss or change of smell and taste • mental health problems including but not limited to depression, anxiety and PTSD symptoms and cognitive difficulties • Neuropsychiatric or psychiatric symptoms • Neurological symptoms including weakness, numbness, continuing headaches, seizures,

	cognitive symptoms visual loss, autonomic symptoms, vestibular symptoms • Myalgia or joint pain • Evidence of end organ damage across a range of organs • gastrointestinal disturbance with diarrhoea • fatigue, weakness and sleeplessness • skin rashes • evidence of systemic inflammation Conditions • Autonomic conditions • Respiratory conditions such as lung inflammation and fibrosis • Cardiovascular conditions such as myocarditis and heart failure • liver and kidney dysfunction • clotting disorders and thrombosis • Lymphadenopathy • neurological disorders including neuropathy
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. • Systematic reviews of observational studies • Prospective and retrospective observational studies • Descriptive studies; case series, case reports • Mixed method study designs
Countries	Any
Timepoints	Any
Other exclusions	None

Review question 5

What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 beyond 12 weeks?

Criteria	**Notes**
Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) continuing after 12 weeks from the onset of acute COVID-19 illness
Interventions/service configuration/information and support [delete/amend as appropriate]	Not applicable
Comparators	Not applicable

Outcomes	Prevalence of symptoms or clusters of symptoms (ongoing physical and mental health) reported 12+ weeks following onset of acute COVID-19 illness including, but not limited to: Signs and symptoms: • respiratory symptoms such as chronic cough, shortness of breath, cardiovascular symptoms and disease such as chest tightness, tachycardia, palpitations, protracted loss or change of smell and taste • mental health problems including but not limited to depression, anxiety and PTSD symptoms and cognitive difficulties • Neuropsychiatric or psychiatric symptoms • Neurological symptoms including weakness, numbness, continuing headaches, seizures, cognitive symptoms visual loss, autonomic symptoms, vestibular symptoms • Myalgia or joint pain • Evidence of end organ damage across a range of organs • gastrointestinal disturbance with diarrhoea • fatigue, weakness and sleeplessness • skin rashes • evidence of systemic inflammation Conditions • Autonomic conditions • Respiratory conditions such as lung inflammation and fibrosis • Cardiovascular conditions such as myocarditis and heart failure

	• liver and kidney dysfunction • clotting disorders and thrombosis • Lymphadenopathy • neurological disorders including neuropathy
Settings	Any

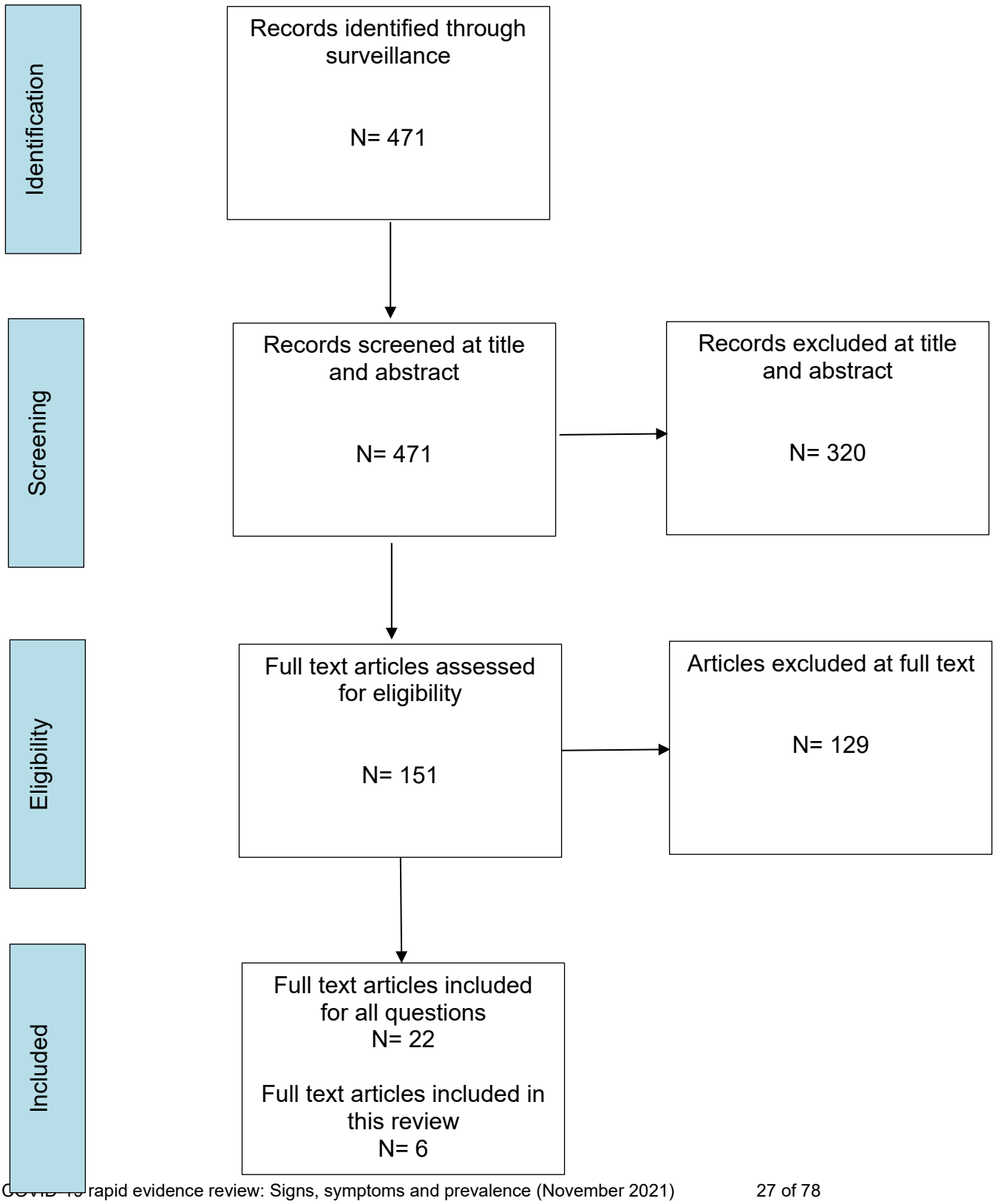
Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised 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. • Systematic reviews of observational studies • Prospective and retrospective observational studies • Descriptive studies; case series, case reports • Mixed method study designs
Countries	Any
Timepoints	Any
Other exclusions	None

Appendix 3 Literature search strategy

See methods and processes chapters for more information.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Study
Domingo Francesca, Reyes, Waddell Lisa, A, Cheung Angela, M et al. Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review. medrxiv preprint
Michelen, Melina, Manoharan, Lakshmi, Elkheir, Natalie et al. Characterising long-term covid-19: a rapid living systematic review. medrxiv preprint
Nasserie, Tahmina; Hittle, Michael; Goodman, Steven N (2021) Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA network open 4(5): e2111417
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
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.
Whittaker Hannah, R, Gulea, Claudia, Koteci, Ardita et al. Post-acute COVID-19 sequelae in cases managed in the community or hospital in the UK: a population based study. medrxiv preprint

Appendix 6 Evidence tables

Domingo Francesca, 2021

Bibliographic Reference	Domingo Francesca, Reyes; Waddell Lisa, A; Cheung Angela, M; Cooper Curtis, L; Belcourt Veronica, J; Zuckermann Alexandra M., E.; Corrin, Tricia; Ahmad, Rukshanda; Boland, Laura; Laprise, Claudie; Idzerda, Leanne; Khan, Anam; Garcia Alejandra, Jaramillo; Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review; medrxiv preprint; 2021

Study details

Study design	Systematic review
Aims/ review questions	The objective of this living systematic review is to document the prevalence of post COVID-19 conditions (4-12 and >12 weeks), including the frequency of symptoms, sequelae and difficulties individuals living with post COVID-19 conditions have conducting usual activities
Search date	15-Jan-2021
Country/ Geographical location	Not applicable
Setting(s)	Community/primary care
Population description	People with laboratory confirmed SARS-CoV-2 infection or COVID-19 clinically diagnosed by a health professional and reported the prevalence of long-term symptoms or sequelae 4 weeks or more from COVID-19 diagnosis
Inclusion criteria	• Primary studies published since January 1st, 2020 in English or French • Studies needed to have 50 or more participants
Exclusion criteria	• Pre-print and non-peer reviewed articles • Primary studies that recruited participants specifically because they reported long-term effects 4 or more weeks after COVID-19 diagnosis
Intervention/test/approach	Not applicable
Comparator (where applicable)	Not applicable
Searching methods	• Adapted the systematic review search strategy conducted by NICE (COVID-19 rapid guideline: managing the long-term effects of COVID-19) • Searched after the NICE search dates (October 22 2020 to January 15 2021) • Searched Embase, Medline, PsycINFO, and Cochrane Central. • All studies included in the NICE review and any French articles they excluded were eligible for inclusion

	• A complementary grey literature search was conducted in January 2021
Methods of data analysis	• The primary synthesis focused on outcomes in individuals who had laboratory-confirmed COVID-19 to minimise likelihood of capturing long-term sequelae from unrelated conditions • Short- (4-12 weeks) and long-term (>12 weeks) outcomes were synthesised separately • Where multiple outcomes were available, results from the longest follow-up time point were used • Meta-analyses were conducted for outcomes with two or more studies using a random effects model where appropriate • Subgroup analyses were determined *a priori* if data were available and were considered for key outcomes to explore heterogeneity. • Additional narrative syntheses were conducted for the outcomes in the clinically-diagnosed population but heterogeneity was not explored.
Methods to investigate heterogeneity	• Use of *a priori subgroups* in key outcomes were used to explore heterogeneity • Based on sub-group analyses for fatigue and shortness of breath, stratifying results by level of care received during the acute stage of COVID-19 infection (i.e. admitted to ICU, hospitalised, non-hospitalised), appeared to explain some of the heterogeneity • However, there was still moderate to high heterogeneity within some subgroups (e.g. hospitalised populations). • Differences in how outcomes were measured and the thresholds used by each study to indicate an adverse outcome may also have contributed to differences in prevalence estimates across studies. • Measurement of outcomes at different points or periods of follow-up within the short or long-term may also have contributed to differences in prevalence estimates across studies.
Risk of bias assessment	• Modified version of the Joanna Briggs Institute critical appraisal tool for prevalence studies to assess risk of bias for each outcome • Certainty in the body of evidence was assessed by modified GRADE • Adapted the GRADE framework for assessment of incidence estimates in the context of prognostic studies to assess prevalence estimates • Of the 28 studies, we assessed 19 to be at moderate risk of bias and nine to be at high risk of bias • The most common sources of potential biases were from participant selection (i.e. convenience samples or

	study population was not representative of the target population) and poor objectivity/validity of outcome measurement (i.e. many outcomes were self-reported or obtained using non-validated measures) • GRADE assessment of 63 outcomes: moderate certainty in 3/63 (5%), low certainty in 25/63 (40%) and very low certainty 35/63 (55%)
Source of funding	Funding for the conduct of this review is provided by the Public Health Agency of Canada
Study limitations (Author)	• The only studies that were eligible for inclusion in the review that were published prior to October 2020 were studies that were included in the NICE review, or French–language studies that were excluded from that review. • Inclusion of only English and French articles that may have introduced a language bias, however only 17 potentially relevant articles were excluded on the basis of language • Modified GRADE approach used has yet to be validated • There were evidence gaps or limited data for many outcomes in this systematic review. • The majority of evidence included adults or individuals who were hospitalised or treated for moderate-to-severe COVID-19 so the prevalence of long-term effects in children, in individuals who were asymptomatic or presented with mild COVID symptoms in the acute stage may not be sufficiently represented. • There were few studies identified reporting long-term effects beyond 12 weeks post-infection. • Many studies had small sample sizes (<200 participants) or were at risk of bias due to the selection of participants and outcome measures used. • The lack of contemporaneous control groups meant that it was not possible to determine whether symptoms were due to COVID-19. Other possible contributing factors could include the presence of pre-existing symptoms or conditions prior to COVID-19 infection, effects of treatment received or effects of being hospitalized or admitted to the ICU, and effects due to the pandemic itself (e.g., barriers to seeking treatment, psychosocial impacts).
Study limitations (Reviewer)	No additional limitations identified.

Outcomes

Study timepoints

- 4 week (4-12 weeks)
- 12 week (12 or more weeks)

One or more symptoms

Outcome	Study, 4 week	Study, 12 week
Persistence or presence of one or more symptoms at follow-up Evidence from 3 studies (4 -12 weeks); 4 studies (12+ weeks) Prevalence (%)	83%	56%
Persistence or presence of one or more symptoms at follow-up Evidence from 3 studies (4 -12 weeks); 4 studies (12+ weeks) 95% CI	65% to 93%	34% to 75%

Symptoms

Outcome	Study, 4 week	Study, 12 week
Fatigue Evidence from 9 studies (4-12 weeks); 3 studies (12+ weeks) Prevalence (%)	51%	47%
Fatigue Evidence from 9 studies (4-12 weeks); 3 studies (12+ weeks) 95% CI	39% to 64%	27% to 68%
Fatigue (Non-hospitalised) Evidence from 1 study (4-12 weeks) Prevalence (%)	16%	NR
Fatigue (Non-hospitalised) Evidence from 1 study (4-12 weeks) 95% CI	11% to 21%	NR
Fatigue (Hospitalised) Evidence from 6 studies (4-12 weeks); 1 study (12+ weeks) Prevalence (%)	59%	63%
Fatigue (Hospitalised) Evidence from 6 studies (4-12 weeks); 1 study (12+ weeks) 95% CI	50% to 68%	60% to 65%
Shortness of breath Evidence from 10 studies (4-12 weeks); 4 studies (12+ weeks) Prevalence (%)	38%	22%

Outcome	Study, 4 week	Study, 12 week
Shortness of breath Evidence from 10 studies (4-12 weeks); 4 studies (12+ weeks) 95% CI	27% to 51%	12% to 35%
Shortness of breath (Non-hospitalised) Evidence from 1 study (4-12 weeks); 1 study (12+ weeks) Prevalence (%)	24%	16%
Shortness of breath (Non-hospitalised) Evidence from 1 study (4-12 weeks); 1 study (12+ weeks) 95% CI	18% to 30%	13% to 20%
Shortness of breath (Hospitalised with moderate to severe COVID 19 or COVID-19 pneumonia) Evidence from 3 studies (4-12 weeks) Prevalence (%)	57%	NR
Shortness of breath (Hospitalised with moderate to severe COVID 19 or COVID-19 pneumonia) Evidence from 3 studies (4-12 weeks) 95% CI	29% to 81%	NR
Cough (any type) Evidence from 6 studies (4-12 weeks) Prevalence (%)	28	NR
Cough (any type) Evidence from 6 studies (4-12 weeks) 95% CI	22% to 35%	NR
Dry cough Evidence from 2 studies (12+ weeks) Prevalence (%)	NR	6%
Dry cough Evidence from 2 studies (12+ weeks) 95% CI	NR	4% to 8%
Productive cough Evidence from 2 studies (12+ weeks) Prevalence (%)	NR	5%
Productive cough Evidence from 2 studies (12+ weeks) 95% CI	NR	3% to 7%

Outcome	Study, 4 week	Study, 12 week
General pain/discomfort Evidence from 2 studies (4-12 weeks); 1 study (12+ weeks) Prevalence (%)	40%	27%
General pain/discomfort Evidence from 2 studies (4-12 weeks); 1 study (12+ weeks) 95% CI	24% to 58%	25% to 29%
Sleep disturbances or difficulties Evidence from 2 studies (4-12 weeks); 1 study (12+ weeks) Prevalence (%)	36%	26%
Sleep disturbances or difficulties Evidence from 2 studies (4-12 weeks); 1 study (12+ weeks) 95% CI	10% to 74%	24% to 29%
Anxiety Evidence from 2 studies (4-12 weeks Prevalence (%)	29%	NR
Anxiety Evidence from 2 studies (4-12 weeks 95% CI	16% to 48%	NR
Anxiety or depression Evidence from 2 studies (4-12 weeks); 1 study (12+weeks) Prevalence (%)	22%	23%
Anxiety or depression Evidence from 2 studies (4-12 weeks); 1 study (12+weeks) 95% CI	19% to 25%	21% to 25%
Depression or PTSD Evidence from 1 studies (12+ weeks) Prevalence (%)	NR	22%
Depression or PTSD Evidence from 1 studies (12+ weeks) 95% CI	NR	12% to 32%
Hair loss Evidence from 1 study (4-12 weeks); 1 study (12+ weeks) Prevalence (%)	10%	22%

Outcome	Study, 4 week	Study, 12 week
Hair loss Evidence from 1 study (4-12 weeks); 1 study (12+ weeks) 95% CI	8% to 12%	20% to 24%
Still felt ill or not back to full health Evidence from 3 studies (4-12 weeks) Prevalence (%)	52%	NR
Still felt ill or not back to full health Evidence from 3 studies (4-12 weeks) 95% CI	35% to 68%	NR
Cognitive impairment Evidence from 2 studies Prevalence %	24%	NR
Cognitive impairment Evidence from 2 studies 95% CI	18% to 21%	NR
Memory problems Evidence from 2 studies Prevalence %	19%	NR
Memory problems Evidence from 2 studies 95% CI	17% to 22%	NR
Difficulty concentrating Evidence from 2 studies Prevalence %	25%	NR
Difficulty concentrating Evidence from 2 studies 95% CI	22% to 28%	NR

Complications from COVID-19

Outcome	Study, 4 week	Study, 12 week
Impaired pulmonary function Evidence from 1 study (12+ weeks) Prevalence (%)	NR	42%
Impaired pulmonary function Evidence from 1 study (12+ weeks) 95% CI	NR	31% to 53%

Critical appraisal - ROBIS checklist: Signs, symptoms and risk

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

Michelen, 2021

Bibliographic Reference	Michelen, Melina; Manoharan, Lakshmi; Elkheir, Natalie; Cheng, Vincent; Dagens, Drew; Hastie, Claire; Hara Margaret, O'Hara; Suett, Jake; Burls, Amanda; Foote, Carol; Carson, Gail; Olliaro Piero, L; Sigfrid, Louise; Stavropoulou, Charitini; Cinatl, Jindrich; Dikic, Ivan; Davies, Paul; Kulathu, Yogesh; Characterising long-term covid-19: a rapid living systematic review; medrxiv preprint; 2021

Study details

Study design	Systematic review
Aims/ review questions	To synthesise and continually update the evidence on the character and prevalence of Long COVID
Search date	17-Mar-2021
Country/ Geographical location	Not applicable
Setting(s)	Not applicable
Population description	People with suspected, laboratory confirmed and/or clinically diagnosed COVID-19 who report symptoms 12 or more weeks post COVID-19
Inclusion criteria	• Peer-reviewed studies with at least 100 people • No language restrictions
Exclusion criteria	• Reviews and opinion pieces • Studies that included <100 people or where follow-up was unclear or < 12 weeks post-onset
Intervention/test/approach	Not applicable
Comparator (where applicable)	Not applicable
Searching methods	• Searched MEDLINE and CINAHL (EBSCO), Global Health (OVID), WHO Global Research Database on

	COVID-19, and Lit COVID from 1 January 2020 to 17th March 2021 • Searched Google Scholar screening the first 500 titles • References of systematic reviews were searched
Methods of data analysis	• Symptom proportions were presented by different settings (hospitalised, non-hospitalised or a mix if no subset data was available) • Proportion of symptoms and 85% Ci were estimated using the exact method. • If there were 2 or more studies, a meta-analysis was performed using a random intercept logistic regression model with Hartung-Knapp modification due to heterogeneity and skewed sample sizes. • Meta-regression was conducted where there were more than 10 studies reporting on a symptom.
Methods to investigate heterogeneity	• Heterogeneity was measured using the I2 statistic • Subgroup analysis was conducted to explore the modification of the factors on proportion of symptoms • Sensitivity analysis was conducted to examine impact of high risk of bias studies • Publication bias was explored with funnel plots.
Risk of bias assessment	• The included studies were assessed for risk of bias using a validated modified version of an existing tool (referenced but not described) • 12 studies were assessed as high risk of bias, 22 moderate and 5 low risk of bias • Most studies had a high risk of bias with regards to the generalisability of their results to the wider population with COVID-19 • Recruitment process in the studies and response rates were often not well-described. • Several studies applied different data collection methods. • Most studies used validated measures that were not designed to detect symptoms arising from COVID-19 • Only 4 studies included a comparative control group.
Summary of findings	**Signs and symptoms** • Most common symptoms are reported in outcome tables. • Although high I2 values (>80%) observed, they resulted from narrow dispersions in the estimates and well-separated estimates and confidence intervals between studies. The differences between these symptoms and the heterogeneity within them is likely to be due to other factors e.g. study settings, populations and different measurement tools used.

	• There was a diverse array of less prevalent symptoms (usually <20%) reported, including systemic, musculoskeletal, neurological, and psychological symptoms such as sweating, chest pain, sore throat, anxiety and headaches. • In several symptoms and signs, the heterogeneity of the results was found to be associated with the level of hospitalisation. hospital settings, location of studies and follow up time.
Source of funding	• Supported by the UK Foreign, Commonwealth and Development Office and Wellcome and the Bill & Melinda Gates Foundation. • The results presented have been obtained with the financial support of the EU FP7 project PREPARE (602525)
Study limitations (Author)	• The studies included were highly heterogenous due to difference in their study designs, settings, population, follow up time and symptom ascertainment methods • Studies used inconsistent terminology describing symptoms and limited details and stratification on pre-existing co-morbidities, severity of COVID-19 and treatment methods. • The lack of case-control studies prevents direct attribution of symptoms solely to COVID-19
Other details	The study team included members who have been affected by long term COVID-19 sequalae and a patient support group with global reach.

Outcomes

Symptoms

Outcome	**Study**
Weakness Evidence from 2 studies (n/N 186/513) Proportion (%)	41.2%
Weakness Evidence from 2 studies (n/N 186/513) 95% CI	25.43% to 59.01%
General malaise Evidence from 2 studies (n/N 292/672) Proportion (%)	32.68%
General malaise Evidence from 2 studies (n/N 292/672) 95% CI	14.91% to 57.36%

Outcome	Study
Fatigue Evidence from 17 studies (n/N 2207/6039) Proportion (%)	30.97%
Fatigue Evidence from 17 studies (n/N 2207/6039) 95% CI	23.91% to 39.03%
Fatigue (Non-hospitalised) Evidence from 4 studies (n/N 200/813) Proportion (%)	24.6
Fatigue (Non-hospitalised) Evidence from 4 studies (n/N 200/813) 95% CI	20.11% to 29.72%
Fatigue (Hospitalised) Evidence from 11 studies (n/N 1762/4147) Proportion (%)	37.1%
Fatigue (Hospitalised) Evidence from 11 studies (n/N 1762/4147) 95% CI	26.54% to 49.06%
Concentration impairment Evidence from 2 studies (n/N 66/254) Proportion (%)	25.98%
Concentration impairment Evidence from 2 studies (n/N 66/254) 95% CI	20.96 % to 31.73%
Breathlessness Evidence from 20 studies (n/N 1297/5523) Proportion %	25.06%
Breathlessness Evidence from 20 studies (n/N 1297/5523) 95% CI	17.86% to 33.97%
Breathlessness (Non-hospitalised) Evidence from 4 studies (n/N 151/1084) Proportion %	13.72%
Breathlessness (Non-hospitalised) Evidence from 4 studies (n/N 151/1084)	8.51% to 21.37%

Outcome	Study
95% CI	
Breathlessness (Hospitalised) Evidence from 14 studies (n/N 765/3148) Proportion %	28.68%
Breathlessness (Hospitalised) Evidence from 14 studies (n/N 765/3148) 95% CI	18.48% to 41.64%
Reduced quality of life Evidence from 3 studies (n/N 340/807) Proportion %	36.76%
Reduced quality of life Evidence from 3 studies (n/N 340/807) 95% CI	18.43% to 59.93%
Cough Proportion %	8.17%
Cough 95% CI	4.85% to 13.44%

Critical appraisal - ROBIS checklist: Signs, symptoms and risk

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

Nasserie, 2021

Bibliographic Reference	Nasserie, Tahmina; Hittle, Michael; Goodman, Steven N; Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review.; JAMA network open; 2021; vol. 4 (no. 5); e2111417

Study details

Study design	Systematic review

Aims/ review questions	What are the frequency and variety of persistent symptoms after COVID-19 infection?
Search date	11-Mar-2021
Country/ Geographical location	Bangladesh, UK, Italy, France, China, Spain, USA, Germany, Netherlands, Norway, Canada, Austria, Ireland, and Turkey
Population description	• People with persisting symptoms related to COVID-19 who were previously inpatients or outpatients • Persistent symptoms were defined as those persisting for at least 60 days after diagnosis, symptom onset, or hospital admission or at least 30 days after recovery from acute illness or hospital discharge
Inclusion criteria	• English language • Cohort studies that reported the prevalence of persistent symptoms among individuals with SARS-CoV-2 infection • Clearly defined and sufficient follow-up • Defined time zero (ie, the beginning of the follow-up interval) as symptom onset, COVID-19 diagnosis, or hospitalisation owing to infection had to include a minimum of 2 months of follow-up • Studies that defined time zero as recovery from the acute illness or hospital discharge had to include a minimum of 1 month of follow-up
Exclusion criteria	• Case reports • Case series • Where symptoms were defined only at the time of infection and/or hospitalisation
Intervention/test/approach	Not applicable
Comparator (where applicable)	Not applicable
Searching methods	• A systematic search of PubMed and Web of Science for articles published between January 1, 2020, and March 11, 2021 • Search terms included COVID-19, SARS-CoV-2, coronavirus, 2019-nCoV, long-term, after recovery, long-haul, persistent, outcome, symptom, follow-up, and longitudinal
Methods of data analysis	• A descriptive approach to analysis was taken due to the heterogeneity of study designs • The median and interquartile range (IQR) were reported for outcomes with 5 or more estimates, and individual values were reported for outcomes with 4 or fewer estimates. • Did not report 95% CIs for the reported percentages because they were not directly relevant to inferences

	and reported frequencies varied more by design than could be attributed to random error. • Disease severity at baseline was calculated as a weighted mean (the sum of all severity scores multiplied by the proportion of patients with that score). Severity scores were 0 (asymptomatic), 1 (mild to moderate), 2 (severe), and 3 (critical)
Methods to investigate heterogeneity	Not applicable as studies were not pooled due to heterogeneity
Risk of bias assessment	• Used 6 quality criteria based on the National Institutes of Health Quality Assessment Tool for Observational and Cohort Studies to assess study design or features most likely to bias frequency. estimates. • The variable that was most representative of low study quality was attrition, which was reported in 36 of 45 studies • 24 studies (53.3%) either did not report retention or reported retention of 70% or less among patients from the initial eligible sample. • Median retention was 74% (IQR 60% to 83.6%) • Only 6 studies (13.3%) reported retention above 90% • Most studies did not report the demographic characteristics of patients who declined participation. • Almost all studies were of moderate or low quality based only on retention, standardization, and representativeness criteria.
Source of funding	None reported
Study limitations (Author)	• Design limitations among the included studies prevented the authors addressing several issues such as duration of persistent symptoms, the percentage of symptoms that resolved and the long-term trajectory of global quality of life and function. • There was limited data on the persistence of symptoms by initial severity, particularly among outpatients. • It was difficult to compare frequency and severity due to lack of standardised definitions or instruments. • Studies that measured the same symptom in different ways reported substantially different estimates, even within the same study. • Few of the studies examined past history or baseline prevalence of similar symptoms or assessed prevalence in a contemporaneous group that did not have COVID-19, making it difficult to assess the fraction or severity of persistent symptoms that could be associated with COVID-19 infection.
Study limitations (Reviewer)	No additional limitations identified.

Characteristics

Study-level characteristics

Characteristic	Study (N = 9751)
Mean or median age reported in 30 studies (Reported mean or median ages younger than 60 years)	≤60 years
Mean or median age reported in 14 studies (Reported mean or median ages of 50 years or younger)	≤50 years
Male No of events	n = 5266; % = 54
Symptom severity (asymptomatic, mild to moderate, severe or critical) No of studies	19
Symptom severity (mild to moderate) No of studies	2
Symptom severity (severe) No of studies	1
Symptom severity (critical) No of studies	2
Time zero - diagnosis or symptom onset Beginning of follow-up interval reported in the study No of studies	16
Time zero - hospital admission Beginning of follow-up interval reported in the study No of studies	4
Time zero - hospital discharge Beginning of follow-up interval reported in the study No of studies	23
Time zero - recovery from acute illness Beginning of follow-up interval reported in the study No of studies	4

Outcomes

Symptom persistence

Outcome	Study, (N = 9751)
Symptom persistence (median frequency) (%) Median (IQR)	72.5 (55 to 80)

Evidence from 16 studies, most of which comprised patients who were previously hospitalised reporting the persistence of at least 1 symptom among their study population at last follow up.

Symptoms

Outcome	Study, (N = 9751)
Shortness of breath or dyspnoea (median frequency) (%) Evidence from 26 studies; self-reported in 14 studies, validated instruments in 10 studies and combination in 2 studies Median (IQR)	36 (27.6 to 50)
Fatigue or Exhaustion (median frequency) (%) Evidence from 25 studies; most studies (22) did not specify how fatigue was defined Median (IQR)	40 (31 to 57)
Cough (median frequency) (%) Evidence from 18 studies. One other study reported a frequency of 60% but it was not clear why the finding was substantially different Median (IQR)	16.9 (14.4 to 25.1)
Atypical chest pain (median frequency) (%) Evidence from 11 studies Median (IQR)	13.1 (10.8 to 18)
Fever (median frequency) (%) Evidence from 10 studies Median (IQR)	1 (0 to 3)
Anosmia (median frequency) (%) Evidence from 12 studies. Adjusted to examine probability of symptoms persisting if they appeared during acute illness Median (IQR)	23.6 (12.4 to 40.7)
Ageusia or Dysgeusia (median frequency) (%) Evidence from 13 studies. Adjusted to examine probability of symptoms persisting if they appeared during acute illness Median (IQR)	15.6 (10.1 to 23.9)
Depression (median frequency) (%) Evidence from 10 studies; Reported using standardised measures Median (IQR)	14.9 (11 to 18)

Outcome	Study, (N = 9751)
Anxiety (median frequency) (%) Evidence from 10 studies. Reported using standardised measures Median (IQR)	22.1 (10 to 29.6)
Cognitive deficits (median frequency) (%) Evidence from 6 studies Median (IQR)	17.6 (15 to 21.6)
Memory loss (median frequency) (%) Evidence from 5 studies Median (IQR)	28.3 (18.6 to 35.8)
Difficulty concentrating (%) Evidence from 4 studies Range	22 to 28

Critical appraisal - ROBIS checklist: Signs, symptoms and risk

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

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 (eg, 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. 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	The severity of COVID-19 had a clear effect on subsequent neurological diagnoses. 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% (95% CI 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.

	The baseline characteristics of the COVID-19 cohort divided into those who did versus those who did not have a neurological or psychiatric outcome. 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, 95% CI 1·40–1·47 for any diagnosis; 1·78, 1·68–1·89 for any first diagnosis) and those who had other respiratory tract infections (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 (1·58, 1·50–1·67 for any diagnosis; 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. 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. 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 (95% CI 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. 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, 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, they calculated HRs for the matched cohorts of patients with COVID-19 who had encephalopathy diagnosed during acute illness versus those who did not. 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.
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	18.8

Characteristic	Study (N = 236379)
Nominal	
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
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. 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 modelling 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 = 508707)**
18-24 Nominal	30.2

Characteristic	Study (N = 508707)
25-34 Nominal	30.9
35-44 Nominal	32.7
45-54 Nominal	39.1
55-64 Nominal	42.7
65-74 Nominal	46.3
74+ Nominal	52.8
% Female Nominal	41.5
Asian Nominal	30.2
Black Nominal	37.6
Mixed Nominal	39.1
Other Nominal	37.7
White Nominal	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.)*

Whittaker Hannah et al.

Bibliographic Reference	Whittaker Hannah, R; Gulea, Claudia; Koteci, Ardita; Kallis, Constantinos; Morgan Ann, D; Iwundu, Chukwuma; Weeks, Mark; Gupta, Rikisha; Quint Jennifer, K; Post-acute COVID-19 sequelae in cases managed in the community or hospital in the UK: a population based study; medrxiv preprint

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not reported
Study start date	01-Aug-2020
Study end date	17-Oct-2020
Aim of the study	To investigate new primary care-recorded symptoms, diseases, prescriptions and healthcare utilisation in patients post-acute COVID-19 infection, comparing outcomes between those managed in the community and those hospitalised.
Country/ Geographical location	UK
Study setting	Hospital and community
Population description	People with covid-19 who were either hospitalised within two weeks of diagnosis or non-hospitalised.
Inclusion criteria	The study population included individuals aged 18 years or over, registered with a general practice contributing to CPRD Aurum. Cases of COVID-19 were identified from 1st August to 17th October 2020.
Exclusion criteria	Patients with evidence of any investigated outcome preceding their COVID-19 diagnosis were excluded from individual analyses.
Intervention/test/approach	Outcomes were determined for the same cohort at 6 and 12 months prior to diagnosis. This enabled evaluation of outcome patterns pre-COVID-19 (12 months prior), at the beginning of the pandemic (6 months prior), and post- COVID-19, in the same patients. This was important as changes in healthcare utilisation during the pandemic have been recognised and may influence outcome events.
Comparator (where applicable)	They compared post-COVID-19 sequelae between hospitalised and non-hospitalised individuals.
Methods for population selection/allocation	They used the Clinical Practice Research Database (CPRD) Aurum, a nationally representative database of anonymised primary care electronic healthcare records, which holds data on symptoms, diagnoses, prescriptions, test results,

	immunisations, consultations, hospitalisations and specialist referrals for over 39 million patients across the UK, covering approximately 19% of the UK population.
Methods of data analysis	Cox regression analysis was performed to compare outcome event rates between hospitalised and non-hospitalised cohorts. Finally, they examined the frequency of ten outcomes (anxiety, breathlessness, fatigue, muscle pain, chest pain, chest tightness, insomnia, palpitations, lung fibrosis, and bronchodilator prescription) among the non-hospitalised subgroup. The ten outcomes were those for which there was evidence of an increase in event rates post-COVID-19 relative to prior timepoints. All statistical analyses were conducted using Stata 16.
Attrition/loss to follow-up	None
Summary of results	Those hospitalised were older (median age [IQR]: 60 [46 to 74] v. 37 [24 to 53] years), were more likely to be men (52.2% v. 45.2%), overweight or obese (63.1% v 38.9%) and ex- or current smokers (70.8% v. 51.7%) than those not hospitalised. Although hospitalised patients were more likely to have comorbidities, the median number of comorbidities was low in both groups. Median follow-up time was 63 days [IQR 63 to 63] for determining new symptoms and prescriptions post COVID-19 diagnosis and 91 days [IQR 91 to 91] for new diseases. *Symptoms (using NG188 common symptom list):* For most symptoms, hospitalised patients had higher event rates than the community group. These included breathlessness, cough, joint pain, chest pain, fatigue, abdominal pain, nausea, skin rashes, dizziness, fever, diarrhoea, cognitive impairment, and delirium. The largest differences between hospitalised and community patients were respectively noted for rates per 100,000 person-weeks [95%CI] of: • breathlessness: 536 [432 to 663] v. 85 [77 to 93]; • joint pain 295 [221 to 392] v. 168 [158 to 179]; • cough: 150 [101 to 224] v. 50 [44 to 56]; • chest pain: 157 [107 to 231] v. 50 [44 to 56]; and • fatigue: 102 [63 to 163] v. 44 [39 to 50], • with smaller absolute differences for the remaining eight symptoms. There were non-significant differences of general and neuropathic pain, muscle pain, headache, paraesthesia, insomnia, ear/nose/throat symptoms and anorexia. Palpitation rates were the same in both groups post-COVID-19 but higher rates of chest tightness and tinnitus were noted

in the community group, although absolute rates were very low (<10 per person weeks).

Diseases:

Regarding most diseases, hospitalised patients had higher event rates than the community group. These included all cardiovascular and haematological conditions, diabetes, adrenal disease, renal failure and arthritis.

The largest differences between hospitalised and community patients were respectively noted for rates per 100,000 person-weeks [95%CI] of

- diabetes: 303 [225 to 416] v. 36 [32 to 42];
- hypertension: 244 [178 to 344] v. 47 [41 to 53];
- venous thromboembolism (VTE): 185 [130 to 271] v. 10 [8 to 13];
- renal failure: 149 [101 to 230] v. 11 [9 to 14] and
- anaemia: 87 [52 to 155] v. 15 [12 to 18].

Rates of asthma, lung fibrosis, GORD, liver disease, anxiety and depression were not statistically significantly different between groups.

By contrast, absolute rates of lung fibrosis were higher in the community group, although rates were very low (<5 per 100,000 person weeks). There were no events for either thyroid disease or inflammatory bowel disease in either group.

Prescriptions and healthcare utilisation increased in hospital group compared to community group.

Stratification of outcomes by age and sex in community group

Overall, men less than 50 years has lower rates of symptoms, disease and prescriptions.

Differences in age: older adults had higher rates of breathlessness, chest pain, cognitive impairment, dizziness, delirium, muscle pain, cough, diabetes, arthritis, VTE, and opioid, paracetamol, and diuretic prescriptions compared to younger adults.

Older adults also had higher rates of cardiovascular disease, notably in men.

Women had higher rates of fatigue and older women in particular had higher rates of joint pain compared to men.

	Younger women had higher rates of headache and anxiety compared to men and higher rates of skin rash, depression, and sore throat compared to men and older adults.
Source of funding	BREATHE - The Health Data Research Hub for Respiratory Health. National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC).
Study limitations (Author)	Only included COVID-19 patients from wave two, when testing capacity was much higher, thereby limiting potential selection biases. Whilst they cannot ascertain whether symptoms recorded on primary care records were directly due to COVID-19 or other conditions, they did investigate event rates among the same cohorts 6 and 12 months prior to contextualise their findings. Risk of misclassification of diseases and symptoms, an inherent weakness of studies of this nature. They were unable to capture the effect of socioeconomic status as these data are not available in primary care records and accept that this is a limitation. Nor have they been able to consider the severity of their investigated outcomes. Given the relatively short follow-up period, they may be missing some symptoms and diseases which occur later in the trajectory of long-Covid. Likely that they will have missed some cases of new onset symptoms or diseases post-COVID in those patients who choose not to seek medical care and manage symptoms independently with over-the-counter medications. Perceived barriers in primary care accessibility and limited understanding of long Covid among clinicians. These factors may also lead to underreporting and under-recording of symptoms/diseases.
Study limitations (Reviewer)	Nothing further to add.

Study arms

Hospitalised people with covid-19 (N = 1415)

Non-hospitalised people with covid-19 (N = 45272)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 46687)**
18-30 years Nominal	38.6

Characteristic	Study (N = 46687)
31-40 years Nominal	16.6
41-50 years Nominal	15.7
51–60 years Nominal	16
61–70 years Nominal	7.4
71-80 years Nominal	3.3
>80 years Nominal	2.4
% Female Nominal	54.6

Outcomes

Study timepoints

- 63 day (For determining new symptoms and prescriptions.)
- 91 day (For determining new diseases)

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.)*

Appendix 7 GRADE profiles

Signs and Symptoms: Adults experiencing symptoms beyond the duration of acute COVID-19 illness (>4 weeks

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Fatigue (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
1292 (9 observational studies)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 51% 95% CI 39% to 64%
Fatigue (People with a history of laboratory-confirmed COVID-19 (follow-up: 12 weeks)							
1962 (3 observational studies)	serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Very low[a]	Prevalence 47% 95% CI 27% to 68%
Dyspnoea (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
1495 (10 observational studies)	serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Very low[a]	Prevalence 38% 95% CI 27% to 51%
Dyspnoea (People with a history of laboratory-confirmed COVID-19) (follow-up: 12 weeks)							

Certainty assessment							Summary of findings
2373 (4 observational studies)	serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Very low[a]	Prevalence 22% 95% CI 12% to 35%
Cough (any type) (People with a history of laboratory-confirmed COVID-19 (follow-up: range 4 weeks to 12 weeks)							
(6 observational studies)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 28% 95% CI 22% to 35%
Sleep disturbances or difficulties (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
(2 observational studies)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 36% 95% CI 10% to 74%
Sleep disturbances or difficulties (People with a history of laboratory-confirmed COVID-19) (follow-up: 12 weeks)							
(1 observational study)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 36% 95% CI 10% to 74%
Anxiety or depression (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
0 (2 observational studies)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 22% 95% CI 19% to 25%
Anxiety or depression (People with a history of laboratory-confirmed COVID-19) (follow-up: 12 weeks)							

Certainty assessment							Summary of findings
0 (1 observational study)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 23% 95% CI 21% to 25%
Hair loss (People with a history of laboratory-confirmed COVID-19) (follow-up: 12 weeks)							
(1 observational study)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 22% 95% CI 20% to 24%
Cognitive impairment (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
(2 observational studies)	not serious[a]	not serious[a]	not serious[a]	not serious[a]	none	Low[a]	Prevalence 24% 95% CI 18% to 21%
Difficulty concentrating (People with a history of laboratory-confirmed COVID-19) (follow-up: range 4 weeks to 12 weeks)							
(2 observational studies)	not serious	not serious	not serious	not serious	none	Moderate[b]	Prevalence 25% 95% CI 22% to 28%

CI: confidence interval

Explanations

a. The systematic review did not report reasons for downgrading. Overall GRADE rating reported as in paper.
b. The systematic review did not report reasons for upgrading. Overall GRADE rating reported as in paper.

Appendix 8 Excluded studies

The same excluded study list appears in the risk factors evidence review because the same search was performed to cover the same review questions.

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	- Not relevant to review protocols

analysis of 58 million patient records in situ using OpenSAFELY. medrxiv preprint	
Cousyn, L, Sellem, B, Palich, R et al. (2021) Olfactory and gustatory dysfunctions in COVID-19 outpatients: a prospective cohort study. Infectious diseases now	- Sample size less than 10,000
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-	- Sample size less than 10,000

19: first results from the national prospective observational Swiss COVID-19 lung study. The European respiratory journal	
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-	- Sample size less than 10,000

Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. Cureus 13(2): e13080	
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 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	- Sample size less than 10,000
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	- Sample size less than 10,000

factors: a Mediterranean cohort study. The Journal of infection	
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-	- No data to extract

COVID, is associated with increased adverse 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
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