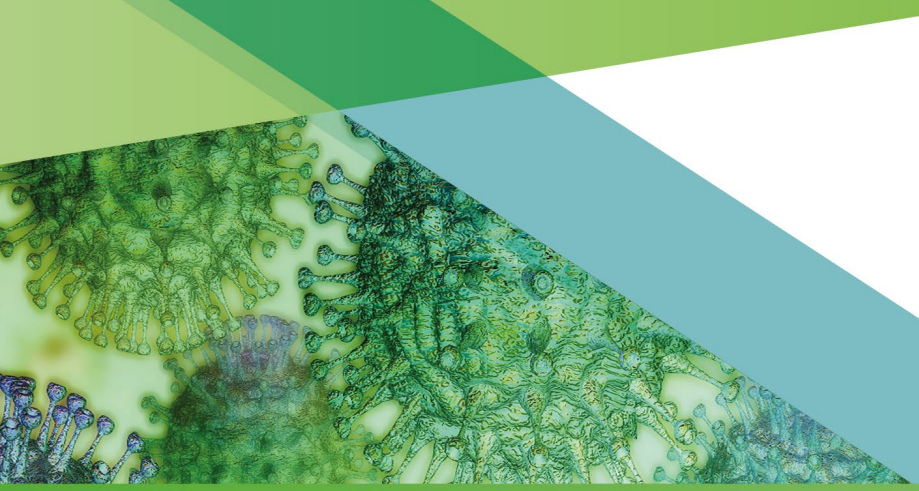


TECHNICAL REPORT

Prevalence of post COVID-19 condition symptoms: a systematic review and meta-analysis of cohort study data, stratified by recruitment setting

27 October 2022

Key facts

- Post COVID-19 condition may pose a threat to healthcare systems already stretched after the acute phase of the COVID-19 pandemic, and its management remains a challenge to healthcare providers. This systematic review of the literature aims to identify reported symptoms of post COVID-19 condition within patient cohorts.
- The primary aim of this systematic review and meta-analysis was to estimate the prevalence of symptoms of post COVID-19 condition, stratified by recruitment setting (community, hospital and Intensive Care Unit (ICU)) as a proxy for disease severity. Only prospective and retrospective cohort studies conducted in Europe, European Union (EU)/European Economic Area (EEA) countries, the United Kingdom, USA, Canada, Australia and New Zealand were considered.
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the certainty of evidence for each outcome of interest. Of 7 125 peer-reviewed studies initially identified, 61 cohort studies from 15 countries were included in the analysis. These studies included 74 213 post COVID-19 condition cases that had been assessed at least 12 weeks after SARS-CoV-2 infection.
- An extremely wide range of physical and psychological symptoms are reported by individuals at least 12 weeks after a SARS-CoV-2 infection.
- Prevalence estimates for five symptoms (fatigue, shortness of breath, depression, headache and dizziness) associated with post COVID-19 condition were supported by evidence scored as high or moderate certainty across both the community and hospital recruitment settings. Each of these five symptoms were noted to be more prevalent among patients recruited in the hospital setting when compared to the community setting, indicating that risk of post COVID-19 condition may be higher among individuals who experience more severe COVID-19 disease.
- Overall, the prevalence of any post COVID-19 condition symptom was estimated at 51% among cohorts recruited in the community setting. However, there was high variability in symptom prevalence estimates between individual studies. This is the result of considerable heterogeneity in cohort study designs developed to investigate post COVID-19 condition, which often lack the control groups necessary to compare symptoms reported among SARS-CoV-2 infected individuals and non-infected individuals.
- Consequently, symptom prevalence estimates must be interpreted with caution as studies lacking non-infected comparator groups may overestimate symptoms specifically attributable to prior SARS-CoV-2 infection. For example, a recently published prospective, population-based, observational cohort study of 76 422 participants in the Netherlands, which corrected for pre-existing symptoms before the onset of COVID-19, as well as symptomatic conditions in a control group, estimates that approximately one in eight people (12.7%) with COVID-19 in the general population will develop post COVID-19 condition, which is far lower than the prevalence estimated in this review.

Suggested citation: European Centre for Disease Prevention and Control. Prevalence of post COVID-19 condition symptoms: A systematic review and meta-analysis of cohort study data stratified by recruitment setting. 27 October 2022. ECDC: Stockholm; 2022.

- While this review may assist policymakers and public health authorities in estimating the burden of post COVID-19 condition and support the planning of rehabilitation services during the post-acute phase of the COVID-19 pandemic, there are important limitations to this work. Due to the time-lag between study design, implementation and publication, results in this systematic review reflect the status quo following the first waves of the pandemic (i.e. pre-Omicron period), where historical variants were in circulation and population-level immunity was markedly different.
- There are still many unknowns in terms of current and future population risk for post COVID-19 condition in the context of increased levels of vaccination and hybrid immunity. Looking ahead, additional large-scale population-based studies with appropriate control groups are required to assess the long-term symptoms specifically attributable to SARS-CoV-2 infection, and their association with a wide range of demographic and clinical risk factors.

Background and rationale

A wide range of long-term effects have been reported following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including a myriad of symptoms and syndromes, often referred to as 'long COVID' [1].

In September 2020, the World Health Organization (WHO) established International Classification of Disease (ICD) codes to facilitate documentation of clinical sequalae following SARS-CoV-2 infection [2]. In response to the wide range of symptom constellations included in varying definitions for 'long COVID', WHO further applied Delphi methodology to develop a consolidated clinical case definition, applying the specific terminology 'post COVID-19 condition':

> 'Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children' [3].

Post COVID-19 condition may pose a threat to healthcare systems that are already stretched after the acute phase of the COVID-19 pandemic, and its management remains a challenge to healthcare providers [4]. Published reviews report over 50 post COVID-19 condition symptoms [5-8], many of which are debilitating and have a strong negative impact on mental health and quality of life [9]. The most prevalent symptoms include fatigue and breathing difficulties, followed by taste and smell disturbances, chest pain, headache, cognitive impairment, memory loss, and sleep disorders [5-8]. It has been noted that post COVID-19 condition symptoms can occur in clusters, while some patients might experience multiple outcomes, and multiple organ systems can be affected simultaneously [5-8].

Given the potential long-term nature of post COVID-19 condition symptoms in some individuals, healthcare systems may face a substantial burden on the services they provide for patient rehabilitation, particularly in primary care.

Scope of this document

This systematic review and meta-analysis aims to identify reported post COVID-19 condition symptoms, estimate their prevalence and determine if COVID-19 disease severity has an impact on symptom prevalence for patient cohorts. To improve the comparability of results and usefulness for European clinicians and policymakers, only prospective and retrospective cohort studies conducted in Europe, EU/EEA countries, the United Kingdom, USA, Canada, Australia, and New Zealand were considered as they have similar healthcare resources.

Target audience

The target audiences for this document are EU/EEA national public health institutes and ministries of health in the EU/EEA, as well as public health experts and decision-makers at national and subnational level.

Methodology

The systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [10] and MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [11]. The protocol of this systematic review was pre-reviewed and approved by the European Centre for Disease Prevention and Control (ECDC).

Outcomes and inclusion/exclusion criteria

The primary aim of this meta-analysis was to estimate the prevalence of symptoms of post COVID-19 condition, stratified by recruitment setting (community, hospital and Intensive care unit (ICU)) as a proxy for disease severity. Only prospective and retrospective cohort studies conducted in Europe, including EU/EEA countries, the United Kingdom, USA, Canada, Australia, and New Zealand were considered eligible, provided that (a) they evaluated patients with a confirmed SARS-CoV-2 diagnosis based on WHO's COVID-19 case definition [12] in one of the following settings: community, hospital or ICU; (b) they defined post COVID-19 condition as at least 12 weeks after SARS-CoV-2 infection. Only cohort studies were included and all other study designs (i.e. case-control, cross-sectional) were excluded. Non-English language publications were excluded.

Screening and data extraction

Relevant peer-reviewed studies published in English between January 2020 and 14 February 2022 were identified within Medline (OVID) and EMBASE (OVID). Subject headings relating to post COVID-19 condition and cohort study design terms were used to develop a comprehensive search strategy. The reference lists of all studies and reviews included were also screened to identify additional relevant studies. Full texts of potentially eligible studies were evaluated independently by two reviewers. Disagreements or uncertainties during the screening stages were resolved through discussion and consensus.

A structured form was used to record adjusted data from each eligible study, including details on study design, the baseline characteristics of participants, enrolment setting, follow-up duration, risk factors and post COVID-19 condition symptoms. Data were extracted independently by two reviewers and cross-checked by a third reviewer. Information was extracted to identify potential overlapping populations across studies and in this case, data from the study with the larger population and a more rigorously described methodology was prioritised.

Assessing evidence certainty

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the certainty in the body of evidence for each outcome of interest [13]. In line with GRADE recommendations for the assessment of evidence of prognostic factors, all study outcomes were initially ascribed a score of high certainty and subsequently rated down on the basis of study limitations, such as inconsistency, indirectness or imprecision of the results, or evidence of publication bias, and/or rated up for methodologically rigorous studies with large observed effects.

Statistical analysis

Meta-analyses were conducted to estimate pooled relative risks with 95% confidence intervals (CI) for each post COVID-19 condition symptom, stratifying by recruitment setting. In anticipation of significant clinical and methodological heterogeneity in the meta-analyses, logistic regression models with random effects were applied. All variables analysed were dichotomous and analysed as Odds Ratios (OR) and 95% CI. Heterogeneity was quantified using the I^2 statistic, with values above 75% considered to represent considerable heterogeneity. To facilitate interpretability of the results, and in line with recommendations by GRADE [13], the absolute Risk Differences (RD) per 1 000 COVID-19 patients with a corresponding 95% CI are also presented. For meta-analyses including at least 15 studies, funnel plots were used to assess for the presence of publication bias.

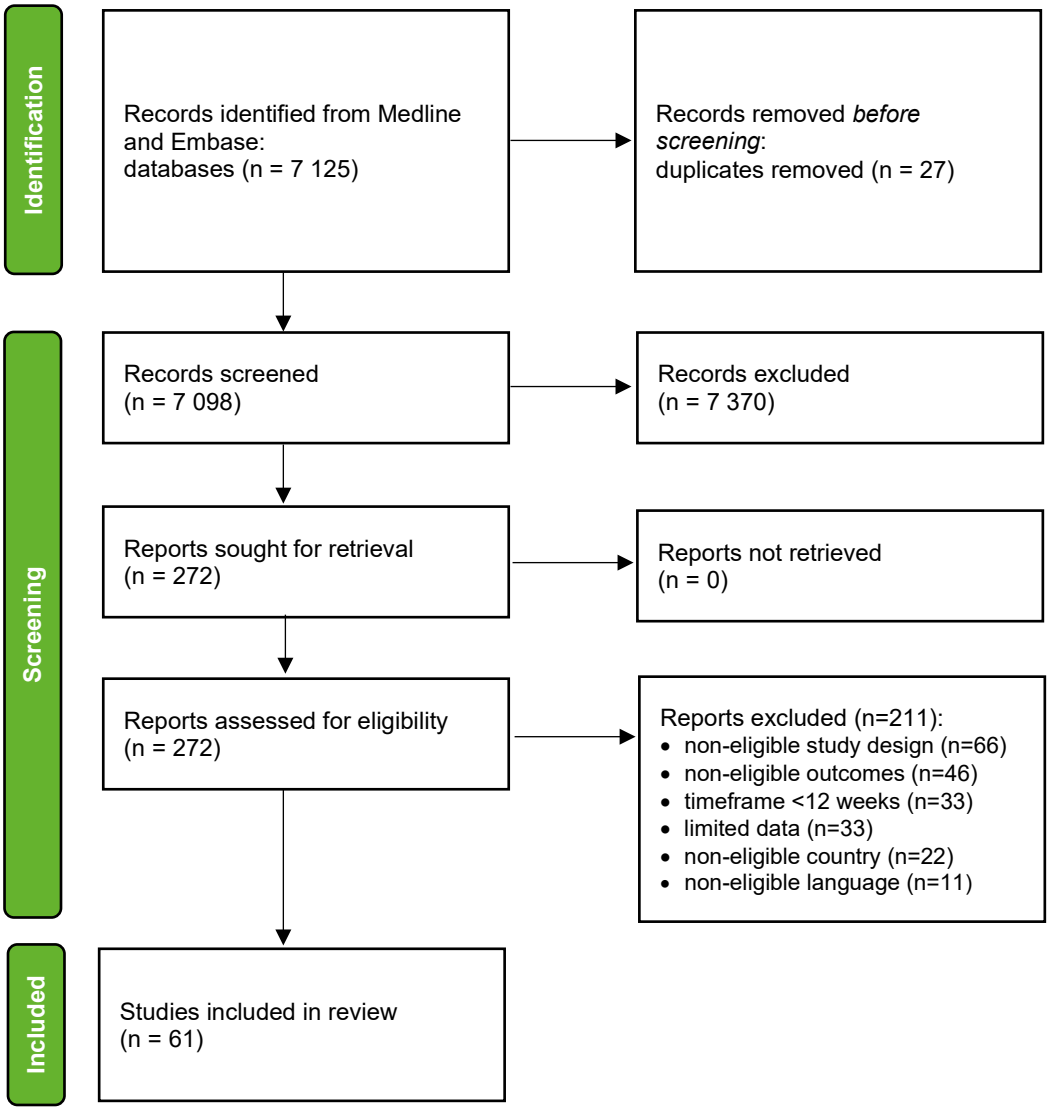
Results

Overview of included studies

A total of 7 125 peer-reviewed studies were identified through comprehensive electronic searches across Medline and EMBASE. After removing duplicates, 7 098 passed to the title and abstract review process. Subsequently, 272 studies were found to meet the inclusion criteria and further screened for eligibility based on their full-text assessment. After full-text screening, 211 studies were excluded for the following reasons: a) non-eligible study design (n=66), b) non-eligible outcomes (n=46), c) timeframe <12 weeks following SARS-CoV-2 infection (n=33), d) limited data (n=33), e) non-eligible country (n=22), and f) non-eligible language (n=11). Sixty-one studies were considered in the analysis (see PRISMA flowchart in Figure 1).

The 61 cohort studies included 74 213 post COVID-19 condition cases that were assessed at least 12 weeks after SARS-CoV-2 infection, with the sample ranging from 13 to 57 748 patients with SARS-CoV-2 within each study. With regard to geographical region, 12 studies were undertaken in Italy [14-25], eight in Spain, seven in France [26-32], five in Denmark [33-37], three in Germany [38-40], three in the Netherlands [41-44], three in Norway [45-47], three in Switzerland [48-50], two in Sweden [51,52], three in the UK [53-55], one in Turkey [56], seven in the US [57-63], two in Canada [64,65] and two in Australia [66,67]. For COVID-19 diagnosis, RT-PCR was used in 58 studies, clinical diagnosis or serological/antibody tests were applied in three [59,60,63] and clinical and serological methods were used in nine studies as a complement to RT-PCR [16,30,35,42,44,50,54,55,68]. The follow-up duration among all studies ranged from three to 12 months. An overview of the studies included is available in Annex 1.

Figure 1. PRISMA flowchart

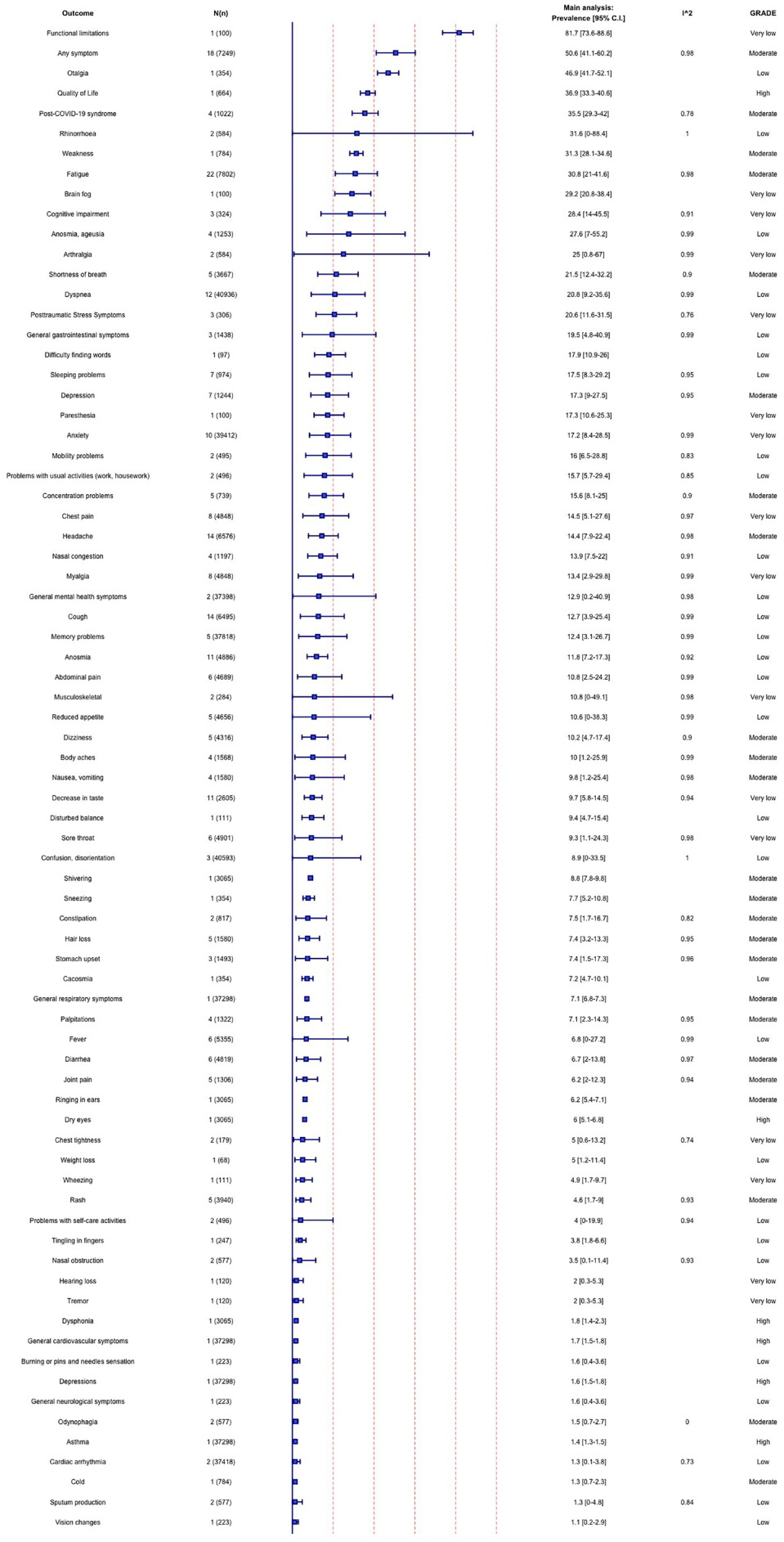


Prevalence of post COVID-19 condition symptoms

A detailed overview of prevalence estimates and for each reported post COVID-19 condition symptom, by recruitment setting, is provided in Figure 2 (community setting), Figure 3 (hospital setting) and Figure 4 (ICU setting).

Overall, the prevalence of any post COVID-19 condition symptom was estimated at 50.6% (95% CI: 41.1–60.2, moderate certainty) among cohorts recruited in the community setting; 66.5% (95% CI: 56.0–76.3, moderate certainty) among cohorts recruited in the hospital setting; and 73.8% (95% CI: 62.3–83.9, low certainty) among cohorts recruited in the ICU setting. However, when interpreting these estimates it is critical to remember that most of the studies lack non-infected comparator groups, which may lead to over-estimation of those symptoms specifically attributable to prior SARS-CoV-2 infection.

Figure 2. Prevalence of post COVID-19 condition symptoms for patients recruited in the community setting



Outcome	N(n)	Main analysis: Prevalence [95% C.I.]	I^2	GRADE
Functional limitations	1 (100)	81.7 [73.6-88.6]		Very low
Any symptom	18 (7249)	50.6 [41.1-60.2]	0.98	Moderate
Otalgia	1 (354)	46.9 [41.7-52.1]		Low
Quality of Life	1 (664)	36.9 [33.3-40.6]		High
Post-COVID-19 syndrome	4 (1022)	35.5 [29.3-42]	0.78	Moderate
Rhinorrhoea	2 (584)	31.6 [0-88.4]	1	Low
Weakness	1 (784)	31.3 [28.1-34.6]		Moderate
Fatigue	22 (7802)	30.8 [21-41.6]	0.98	Moderate
Brain fog	1 (100)	29.2 [20.8-38.4]		Very low
Cognitive impairment	3 (324)	28.4 [14-45.5]	0.91	Very low
Anosmia, ageusia	4 (1253)	27.6 [7-55.2]	0.99	Low
Arthralgia	2 (584)	25 [0.8-67]	0.99	Very low
Shortness of breath	5 (3667)	21.5 [12.4-32.2]	0.9	Moderate
Dyspnea	12 (40936)	20.8 [9.2-35.6]	0.99	Low
Posttraumatic Stress Symptoms	3 (306)	20.6 [11.6-31.5]	0.76	Very low
General gastrointestinal symptoms	3 (1438)	19.5 [4.8-40.9]	0.99	Low
Difficulty finding words	1 (97)	17.9 [10.9-26]		Low
Sleeping problems	7 (974)	17.5 [8.3-29.2]	0.95	Low
Depression	7 (1244)	17.3 [9-27.5]	0.95	Moderate
Paresthesia	1 (100)	17.3 [10.6-25.3]		Very low
Anxiety	10 (39412)	17.2 [8.4-28.5]	0.99	Very low
Mobility problems	2 (495)	16 [6.5-28.8]	0.83	Low
Problems with usual activities (work, housework)	2 (496)	15.7 [5.7-29.4]	0.85	Low
Concentration problems	5 (739)	15.6 [8.1-25]	0.9	Moderate
Chest pain	8 (4848)	14.5 [5.1-27.6]	0.97	Very low
Headache	14 (6576)	14.4 [7.9-22.4]	0.98	Moderate
Nasal congestion	4 (1197)	13.9 [7.5-22]	0.91	Low
Myalgia	8 (4848)	13.4 [2.9-29.8]	0.99	Very low
General mental health symptoms	2 (37398)	12.9 [0.2-40.9]	0.98	Low
Cough	14 (6495)	12.7 [3.9-25.4]	0.99	Low
Memory problems	5 (37818)	12.4 [3.1-26.7]	0.99	Low
Anosmia	11 (4886)	11.8 [7.2-17.3]	0.92	Low
Abdominal pain	6 (4689)	10.8 [2.5-24.2]	0.99	Low
Musculoskeletal	2 (284)	10.8 [0-49.1]	0.98	Very low
Reduced appetite	5 (4656)	10.6 [0-38.3]	0.99	Low
Dizziness	5 (4316)	10.2 [4.7-17.4]	0.9	Moderate
Body aches	4 (1568)	10 [1.2-25.9]	0.99	Moderate
Nausea, vomiting	4 (1580)	9.8 [1.2-25.4]	0.98	Moderate
Decrease in taste	11 (2605)	9.7 [5.8-14.5]	0.94	Very low
Disturbed balance	1 (111)	9.4 [4.7-15.4]		Low
Sore throat	6 (4901)	9.3 [1.1-24.3]	0.98	Very low
Confusion, disorientation	3 (40593)	8.9 [0-33.5]	1	Low
Shivering	1 (3065)	8.8 [7.8-9.8]		Moderate
Sneezing	1 (354)	7.7 [5.2-10.8]		Moderate
Constipation	2 (817)	7.5 [1.7-16.7]	0.82	Moderate
Hair loss	5 (1580)	7.4 [3.2-13.3]	0.95	Moderate
Stomach upset	3 (1493)	7.4 [1.5-17.3]	0.96	Moderate
Cacosmia	1 (354)	7.2 [4.7-10.1]		Low
General respiratory symptoms	1 (37298)	7.1 [6.8-7.3]		Moderate
Palpitations	4 (1322)	7.1 [2.3-14.3]	0.95	Moderate
Fever	6 (5355)	6.8 [0-27.2]	0.99	Low
Diarrhea	6 (4819)	6.7 [2-13.8]	0.97	Moderate
Joint pain	5 (1306)	6.2 [2-12.3]	0.94	Moderate
Ringing in ears	1 (3065)	6.2 [5.4-7.1]		Moderate
Dry eyes	1 (3065)	6 [5.1-6.8]		High
Chest tightness	2 (179)	5 [0.6-13.2]	0.74	Very low
Weight loss	1 (68)	5 [1.2-11.4]		Low
Wheezing	1 (111)	4.9 [1.7-9.7]		Very low
Rash	5 (3940)	4.6 [1.7-9]	0.93	Moderate
Problems with self-care activities	2 (496)	4 [0-19.9]	0.94	Low
Tingling in fingers	1 (247)	3.8 [1.8-6.6]		Low
Nasal obstruction	2 (577)	3.5 [0.1-11.4]	0.93	Low
Hearing loss	1 (120)	2 [0.3-5.3]		Very low
Tremor	1 (120)	2 [0.3-5.3]		Very low
Dysphonia	1 (3065)	1.8 [1.4-2.3]		High
General cardiovascular symptoms	1 (37298)	1.7 [1.5-1.8]		High
Burning or pins and needles sensation	1 (223)	1.6 [0.4-3.6]		Low
Depressions	1 (37298)	1.6 [1.5-1.8]		High
General neurological symptoms	1 (223)	1.6 [0.4-3.6]		Low
Odynophagia	2 (577)	1.5 [0.7-2.7]	0	Moderate
Asthma	1 (37298)	1.4 [1.3-1.5]		High
Cardiac arrhythmia	2 (37418)	1.3 [0.1-3.8]	0.73	Low
Cold	1 (784)	1.3 [0.7-2.3]		Moderate
Sputum production	2 (577)	1.3 [0-4.8]	0.84	Low
Vision changes	1 (223)	1.1 [0.2-2.9]		Low

Figure 3. Prevalence of post COVID-19 condition symptoms for patients recruited in the hospital setting

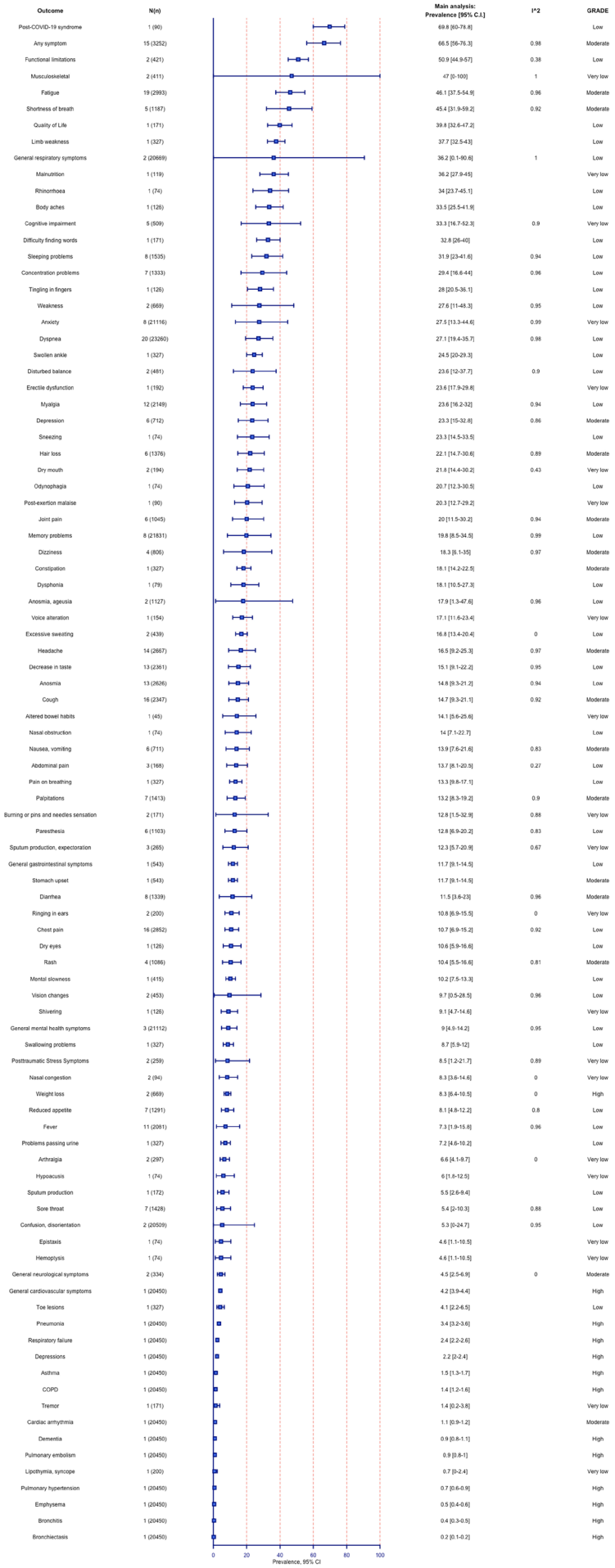
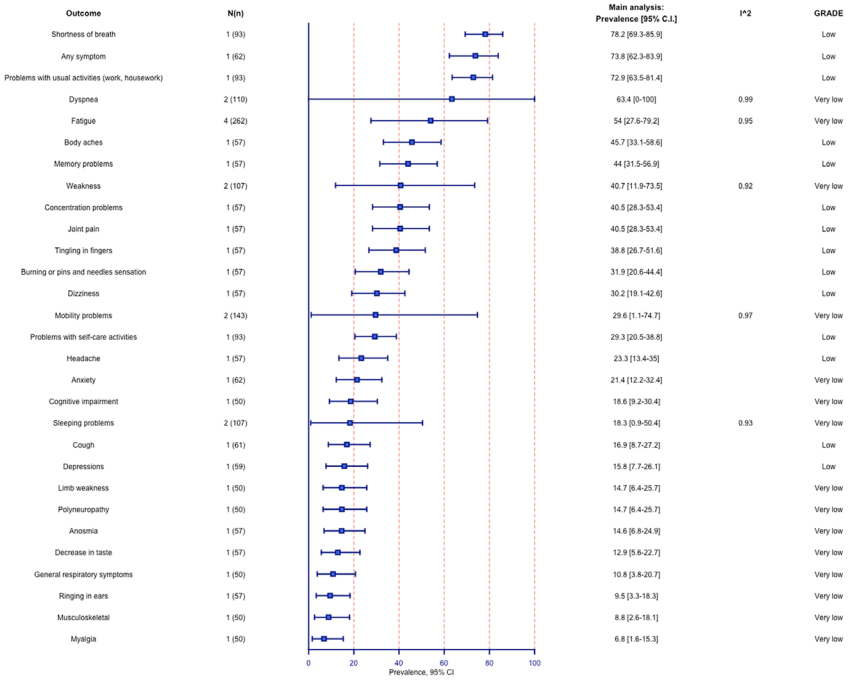


Figure 4. Prevalence of post COVID-19 condition symptoms for patients recruited in the ICU setting



Considering only prevalence estimates supported by evidence of high or moderate certainty, the most frequently reported symptoms from patients recruited in the community setting were quality of life (36.9%; 95% CI: 33.3–40.6), general weakness (31.3%; 95% CI: 28.1–34.6), fatigue (30.8%; 95% CI: 21.0–41.6), shortness of breath (20.9%; 95% CI: 12.1–31.3), depression (17.3%; 95% CI: 9.0–27.5), concentration problems (15.6%; 95% CI: 8.1–25.0), headache (14.4%; 95% CI: 7.9–22.4), dizziness (10.2%; 95% CI: 4.7–17.4) and body aches (10.0%; 95% CI: 1.2–25.9). The remaining conditions were either identified at a prevalence <10% or supported by evidence of lower certainty.

Considering only prevalence estimates supported by evidence of high or moderate certainty, the most frequently reported symptoms from patients recruited in the hospital setting were: fatigue (46.1%; 95% CI: 37.5–54.9), shortness of breath (45.4%; 95% CI: 31.9–59.2), depression (23.3%; 95% CI: 15.0–32.8), hair loss (22.1%; 95% CI: 14.7–30.6), joint pain (20.0%; 95% CI: 11.5–30.2), dizziness (18.3%; 95% CI: 6.1–35.0), constipation (18.1%; 95% CI: 14.2–22.5), headache (16.5%; 95% CI: 9.2–25.3), cough (14.7%; 95% CI: 9.3–21.1), nausea and vomiting (13.9%; 95% CI: 7.6–21.6), palpitations (13.2%; 95% CI: 8.3–19.2), stomach upset (11.7%; 95% CI: 9.1–14.5), diarrhoea (11.5%; 95% CI: 3.6–23.0) and rash (10.4%; 95% CI: 5.5–16.6). The remaining conditions were either identified at a prevalence <10% or supported by evidence of lower certainty.

No studies performed in the ICU setting reported prevalence estimates supported by evidence scored as high or moderate certainty.

Prevalence estimates for five post COVID-19 condition symptoms (fatigue, shortness of breath, depression, headache and dizziness) were supported by evidence scored as high or moderate certainty across both the community and hospital recruitment settings. Each of these five symptoms were noted to be more prevalent among patients recruited in the hospital setting than the community setting (Table 1).

Table 1. Estimated prevalence of post COVID-19 condition symptoms reported among patients recruited in both the community and hospital setting

Post COVID-19 condition symptom	Community setting prevalence	Hospital setting prevalence
Fatigue	**30.8%** 95% CI: 21.0–41.6	**46.1%** 95% CI: 37.5–54.9
Shortness of breath	**20.9%** 95% CI: 12.1–31.3	**45.4%** 95% CI: 31.9–59.2
Depression	**17.3%** 95% CI: 9.0–27.5	**23.3%** 95% CI: 15.0–32.8
Headache	**14.4%** 95% CI: 7.9–22.4	**16.5%** 95% CI: 9.2–25.3
Dizziness	**10.2%** 95% CI: 4.7–17.4	**18.3%** 95% CI: 6.1–35.0

Considering only prevalence estimates supported by evidence scored as moderate or high certainty (See Figures 2 and 3).

Discussion

Key findings

This systematic review and meta-analysis has identified an extremely wide range of physical and psychological symptoms reported by individuals at least 12 weeks after a SARS-CoV-2 infection. Overall, the prevalence of any post COVID-19 condition symptom was estimated at ~51% (moderate certainty) among cohorts recruited in the community setting; ~67% (moderate certainty) among cohorts recruited in the hospital setting; and ~74% (low certainty) among cohorts recruited in the ICU setting. Prevalence estimates for five post COVID-19 condition symptoms (fatigue, shortness of breath, depression, headache and dizziness) were supported by evidence scored as high or moderate certainty across both the community and hospital recruitment settings. Using cohort recruitment setting as a proxy for COVID-19 severity, each of these five symptoms were noted to be more prevalent among patients recruited in the hospital setting than the community setting, indicating that risk of post COVID-19 condition may be higher among individuals who experience more severe COVID-19 disease.

Symptom prevalence estimates reported here must be interpreted with caution as the majority of the included studies lack non-infected comparator groups. Absence of a non-infected comparator group may lead to overestimation of those symptoms attributed to prior SARS-CoV-2 infection. For example, Ballering et al. recently published a prospective, population-based, observational cohort study of 76 422 participants in the Netherlands, which corrected for pre-existing symptoms before the onset of COVID-19, as well as symptomatic conditions in a matched control group during the study period 31 March 2020 to 2 August 2021. They estimate that approximately one in eight people (12.7%) with COVID-19 in the general population will develop post COVID-19 condition, which is far lower than the prevalence estimated in this review [69]. In addition, Subramanian et al. report on a retrospective, matched cohort study, using a large UK-based primary care database to determine symptoms associated with confirmed SARS-CoV-2 infection beyond 12 weeks in non-hospitalised adults and the risk factors associated with developing persistent symptoms. For the study period 31 January 2020 to 15 April 2021 they compared 486 149 cases with 1 944,580 matched controls, identifying a total of 62 symptoms significantly associated with SARS-CoV-2 infection after 12 weeks. Among patients with a minimum of 12 weeks' follow-up, 20 864 of 384 137 (5.4%) patients infected with SARS-CoV-2 and 65 293 of 1 501 689 (4.3%) patients with no recorded evidence of SARS-CoV-2 infection reported at least one of the symptoms included in the WHO case definition for post COVID-19 condition (aHR 1.26, 95% CI 1.25–1.28) [70].

The findings of this systematic review align with the results of other published reviews which suggest post COVID-19 condition is primarily characterised by fatigue, weakness, dyspnoea, and cognitive impairment, along with other less-frequent symptoms, which may be relapsing-remitting in nature and have a negative impact on quality of life [5-9,71-75]. As observed in this meta-analysis, other reviews report high variability in symptom prevalence estimates between individual studies. This is the result of considerable heterogeneity in cohort study designs developed to investigate post COVID-19 condition, which often lack the control groups necessary to compare symptoms reported among SARS-CoV-2 infected individuals and non-infected individuals.

Risk factors for post COVID-19 condition remain poorly characterised. By using recruitment setting as a proxy for COVID-19 severity, this review has established that risk of post COVID-19 condition may be higher among individuals who experience more severe COVID-19 disease. However, this finding is likely to be confounded by factors (e.g. age and pre-existing conditions or symptoms) that increase the likelihood of experiencing a severe COVID-19 outcome. Using their matched primary care cohort, Subramanian et al. additionally investigated risk factors associated with developing persistent COVID-19 symptoms. Risk factor analysis included 384 137 individuals infected with SARS-CoV-2 with a minimum of 12 weeks' follow-up. When using the WHO definition of post COVID-19 condition, several sociodemographic and clinical risk factors were significantly associated with increased reporting incidence: female sex, socioeconomic deprivation, smoking history, BMI (overweight or obese) and the existence of comorbidities (including COPD, benign prostatic hyperplasia, fibromyalgia and anxiety) [70]. Socioeconomic deprivation, smoking history, high BMI and the existence of comorbidities are all strong predictors of severe COVID-19 outcomes following SARS-CoV-2 infection [76]. SARS-CoV-2 is known to impact the function of multiple tissues and organ systems, primarily the respiratory tract but also the brain, endothelium, heart, kidney, and liver [77,78]. Although post COVID-19 condition symptomatology can be attributed to organ injuries that occurred during the acute phase of SARS-CoV-2 infection, there is emerging evidence that some patients who only experience mild or moderate acute symptoms can develop long-term complications unrelated to organ dysfunction incurred during the first exposure [79]. Further research, using adequate control groups, is required to better quantify the relationship between COVID-19 symptom severity and risk of post COVID-19 condition.

Study limitations

There are important limitations to this work. Given the considerable heterogeneity in study designs and the lack of control groups in the cohort studies included, prevalence estimates for several reported symptom outcomes were deemed to be of low certainty, with high variability, as noted by their I^2, and should be interpreted with caution [80,81].

Due to the time-lag between study design, implementation and publication, results in this systematic review reflect the status quo following the first waves of the pandemic (i.e. the pre-Omicron period), where historical variants were in circulation and population-level immunity was markedly different. Results presented in this systematic

review are not stratified by vaccination or prior infection status, meaning no conclusions can be drawn on the potential protective effect of immunity - which is critical, given current high levels of vaccination and experienced reinfection - on the risk of developing post COVID-19 condition symptoms [82-84].

These data do not objectively quantify the severity or duration of reported symptoms and future studies will need to address this in order to inform a more global assessment of the burden of disease for individuals as well as healthcare systems [72].

This study primarily reports on data from adult cohorts, with very limited data from paediatric populations. As recognised in the WHO clinical case definition, post COVID-19 condition may present differently in children as symptoms are more challenging to communicate and document among very young paediatric populations [34]. More data is needed from paediatric and adolescent cohorts, where the presence of control groups is of even greater importance [85-87].

To improve the comparability of results and usefulness for European clinicians and policymakers, only prospective and retrospective cohort studies conducted in Europe, EU/EEA countries, the United Kingdom, USA, Canada, Australia, and New Zealand were considered as they have similar healthcare resources. Consequently, these results may not be generalisable to other areas of the globe. However, similar results have been noted in different geographical areas [71].

Summary

This systematic review and meta-analysis identified an extremely wide range of physical and psychological symptoms reported by individuals at least 12 weeks after a SARS-CoV-2 infection. Given the potential long-term nature and breadth of post COVID-19 condition symptoms in some individuals, healthcare systems may face a substantial burden on the services they provide for patient rehabilitation, particularly in primary care, where integrated care models will be required [88].

While this review may assist policymakers and public health authorities in estimating the burden of post COVID-19 condition and supporting the planning of rehabilitation services during the post-acute phase of the COVID-19 pandemic, there are still many unknowns in terms of current and future population risk in the context of increased levels of vaccination and hybrid immunity. Looking ahead, additional large-scale population-based studies with appropriate control groups are required to assess which long-term symptoms are specifically attributable to SARS-CoV-2 infection and their association with a wide range of demographic and clinical risk factors.

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Acknowledgements

Chrysa Chatzopoulou, Katerina Papathanasaki and Konstantinos Skouloudakis for their assistance in data archiving.

Funding

This report was commissioned by ECDC from the PREP-EU Consortium under Framework Contract ECDC/2019/001 Lot 1B.

Role of the Funding Agency: The funder contributed to the definition of the scope of the review and commented on the protocol and draft manuscript and was not involved in conducting the systematic review. ECDC provided intellectual input throughout the project and arranged for an internal peer review.

Data sharing statement

Data sharing is not applicable to this article as no new data were created or analysed in this study. All data were extracted from peer-reviewed studies, which were identified from the literature and have been appropriately referenced within the article.

Declaration of interests

The authors declare that they have no known competing interests.

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Annex 1. Overview of included studies

First Author/year	Country, city	Hospital	Study design	Setting at enrolment	COVID-19 diagnosis/hospital discharge timeframe	COVID-19 diagnosis method	Follow up
Blomberg 2021	Bergen, Norway	Bergen Municipality Emergency Clinic, Haukeland University Hospital, Haraldsplass Deaconess Hospital	Prospective cohort	Community, hospital	Diagnosis: 28 February to 6 May 2020	RT-PCR	Six months
Sibila 2021	Spain	Hospital Clinic in Barcelona	Prospective cohort	Hospital	Discharged from hospital: 4 March to 27 April 2020	RT-PCR	Three months
Horwitz 2021	US	NYU Langone Health	Prospective cohort	Hospital	Discharged from hospital: 15 April to 30 May 2020	RT-PCR	Six months
Augustin 2021	Germany	Outpatient clinic of the University Hospital Cologne (UHC)	Prospective cohort	Community	SARS-CoV-2 positive: 6 April to 2 December 2020	RT-PCR	4.3 (IQR 3-5) and 6.8 (IQR 6-8) months
Petersen 2021	Denmark, Faroe Islands		Cohort	Community	Diagnosis: 3 March to 22 April 2020	RT-PCR	Mean: 125 (17, 45-153)
Staudt 2021	Germany	RoMed hospitals (Rosenheim, Wasserburg, Bad Aibling)	Cohort	Hospital	Hospitalised: 1 March to 30 June 2020	RT-PCR	10 months/308 days [295; 328]
Diaz-Fuentes 2021	US, Bronx	Post-acute COVID-19 pulmonary clinic	Retrospective cohort	Community, hospital	June to December 2020	RT-PCR	Three months/ 12 weeks (8–16)
Molhave 2021	Denmark	Aarhus University Hospital	Prospective cohort	Hospital	Hospitalised: 1 March to 1 July 2020	RT-PCR	48 weeks/ 350 (IQR 341–380) days
McPeake 2021	Scotland	Five hospitals across Scotland	Prospective cohort	Hospital	July 2020 to December 2020	RT-PCR or a high clinical suspicion of SARS-CoV-2	135 (IQR: 85–181) days
Shah 2020	Canada		Prospective cohort	Hospital	Hospitalised: March to May 2020	RT-PCR	12 (range 8–12) weeks
Mattioli 2021	Italy	University Hospital of Brescia	Prospective cohort	Hospital	Undefined	RT-PCR	Four months
Jovanoski 2021	US	COVID-19 EHR dataset	Retrospective cohort	Hospital, community	Diagnosis: 20 February to 4 July 2020	Clinical, diagnostic tests	>90–≤180 days
Karaarslan 2021	Turkey	Gülhane Training and Research Hospital	Cohort	Hospital (non-ICU)	Discharged from hospital: 18 November 2020 to 30 January 2021	RT-PCR	Three and six months
Leis-Cofino 2021	Spain	University Hospital of Fuenlabrada	Cohort	Hospital	Hospitalised: March to April 2020	RT-PCR	Three months
Leth 2021	Denmark	Aarhus University Hospital	Cohort	Hospital	Hospitalised: 11 March to 15 May 2020	RT-PCR	Three months/12 weeks

First Author/year	Country, city	Hospital	Study design	Setting at enrolment	COVID-19 diagnosis/hospital discharge timeframe	COVID-19 diagnosis method	Follow up
Gonzalez 2021	Spain	Hospital Universitari Arnau de Vilanova and Hospital Universitari Santa Maria in Lleida	Prospective cohort	ICU	Hiospitalised: March to June 2020	RT-PCR	Three months
Ghosn 2021	France	Hospitals in France	Prospective cohort	Hospital	24 January to 10 April 2020	RT-PCR	Three and six months
Nguyen 2021	France	NA	Cohort	Community, hospital	3 March to 27 April 2020	RT-PCR	At least six months
Stephenson 2022	UK	Public Health England (PHE) database	National matched cohort study	Community, hospital	Diagnosed: 1 January to 31 March 2021	RT-PCR	Three months
Messin 2021	France	Nord Franche-Comté Hospital (NFCH)	Retrospective cohort	Hospital	March 2020	RT-PCR	Six months
Sigfrid 2021	UK	ISARIC	Prospective cohort	Hospital	Hospitalised: 7 January to 5 October 2020	RT-PCR, clinical	Three to 12 months
bMattioli 2021	Italy	University Hospital of Brescia	Cohort	HCWs	up to February 2020	RT-PCR	Four months
Bellan 2021	Italy	Azienda Ospedaliero–Universitaria Maggiore della Carità university hospital in Novara	Prospective cohort	Hospital	Discharged: 1 March to 29 June 2020	RT-PCR, bronchoalveolar lavage, serological tests	Three to four months
Taboada 2020	Spain	NA	Prospective cohort	Hospital	Hospitalised: March-April 2020	RT-PCR	Six months
Morin 2021	France	Bicêtre Hospital (Paris-Saclay University hospitals)	Prospective cohort	Hospital	Hospitalised: 1 March to 29 May 2020	RT-PCR, CT	Four months
Kyzar 2021	US	NA	Cohort	Community, hospital	15 April to 23 February 2020	Serum antibody testing	24 to 60 weeks
Mazza 2021	Italy	IRCCS San Raffaele Hospital	Prospective cohort	Community, hospital	Up to 25 February 2020	RT-PCR	Six and 12 months
bBellan 2021	Italy	Azienda Ospedaliero–Universitaria Maggiore della Carità university hospital in Novara	Cohort	Hospital	Discharged: 1 March to 29 June 2020	RT-PCR	12 months/366 days (363–369)
van Veenendaal 2021	Netherlands	University Medical Center Groningen	Prospective cohort	ICU	Admitted to ICU: 19 March to 30 September 2020	RT-PCR	Three and six months
Gerard 2021	France	Nancy Brabois University Hospital	Prospective cohort	Hospital	Hospitalised: 1 March and 29 April 2020	RT-PCR, CT scan	Six months
Becker 2021	Switzerland	University Hospital Basel, and the Kantonsspital Aarau	Prospective cohort	Hospital	Hospitalised: March to June 2020	RT-PCR	12 months
Kozak 2021	Canada	Sunnybrook Health Sciences Centre	Retrospective cohort	Community, hospital	1 January to 8 June 2020	RT-PCR	>90 days
Van de Borst 2021	Netherlands	Radboud University Medical Center, Nijmegen	Prospective cohort	Community, hospital	23 April to 15 July 2020	RT-PCR, clinical diagnosis	Three months

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Noviello 2022	Italy	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan	Controlled cohort	Community, hospital	February to April 2020	RT-PCR	4.8 ± 0.3 months
Maestre-Muniz 2021	Spain	Tomelloso General Hospital	Cohort	Hospital	1 March to 1 June 2020	RT-PCR	One year
Petrocelli 2021	Italy, Bologna	Bellaria and Maggiore Hospital, Bologna	Prospective cohort	Hospital	16 April to 2 May 2020	RT-PCR	Three and six months
Clavario 2021	Italy, Genoa	Outpatient Cardiac Rehabilitation center of Genoa	Prospective cohort	Hospital	Undefined (from March 2020)	RT-PCR	Three months
Menges 2021	Switzerland	N/A	Prospective cohort	Community	Diagnosis: 27 February to 5 August 2020	RT-PCR	7.2 months (5.9 to 10.3)
Buonsenso 2021	Italy	Fondazione Policlinico Universitario A. Gemelli IRCCS	Prospective cohort	Community	Diagnosed: March and November 2020	RT-PCR	>120 days
de Lorenzo 2021	Italy, Milan	San Raffaele University Hospital	Retrospective cohort	Hospital	from 25 February 2020	RT-PCR	Three months
Nersesjan 2021	Denmark	Rigshospitalet, Copenhagen University Hospital	Prospective cohort	Hospital	April to September 2020	RT-PCR, antibody test	Four months
Vanichkachorn 2021	US		Cohort	Community, hospital	April to November 2020	RT-PCR, clinical diagnosis	Mean: 93 days
Blackett 2022	US, NYC	Columbia University Irving Medical Center	Prospective cohort	Community, hospital	April to November 2020	RT-PCR	At least six months
Noel-Savina 2021	France	Toulouse University Hospital	Prospective cohort	Hospital	April to September 2020	RT-PCR	4.3 months
Hellgren 2021	Sweden, Östergötland		Prospective cohort	Hospital	Hospitalisation: 1 March to 31 May 2020	RT-PCR	Four months
Zayet 2021	France	ANOSVID study, Nord Franche-Comté Hospital	Retrospective cohort	Community, hospital	Diagnosis: 1 March 2020 to 31 May 2020	RT-PCR	Nine months
Fortini 2021	Italy, Florence	San Giovanni di Dio Hospital	Prospective cohort	Hospital	Discharged: March to May 2020	RT-PCR	Three to six months
Fortini 2022	Italy, Florence	San Giovanni di Dio Hospital	Prospective cohort	Hospital	Discharged: March to May 2020	RT-PCR	One year
Steinbeis 2022	Germany, Berlin	Charite Universitatsmedizin Berlin	Prospective cohort	Hospital	May June 2020	RT-PCR	Three, six and 12 months
Kanberg 2021	Sweden, Gothenburg	Sahlgrenska University Hospital	Prospective cohort	Hospital	21 February to 5 November 2020	RT-PCR	Median: 225 (187–262) days
Mendez 2022	Spain, Valencia		Prospective cohort	Hospital	8 March to 25 April 2020	RT-PCR	12 (±1) months
Say 2021	Australia, Melbourne	Royal Children's Hospital (RCH)	Prospective cohort	Community, hospital	21 March to 28 October 2020	RT-PCR	Three to six months
Strahm 2022	Switzerland	23 healthcare institutions	Prospective cohort	Community, hospital	Undefined	RT-PCR, Serology test	117 days (93–147 days)

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Wynberg 2021	Netherlands, Amsterdam		Prospective cohort	Community, hospital	11 May 2020 to 1 May 2021	RT-PCR, antigen test	12 weeks
Ares-Blanco 2021	Spain, Madrid	Federica Montseny PHCC	Retrospective cohort	Community, hospital	10 March to 7 April 2020	RT-PCR	>12 weeks
Darley 2021	Australia, Sydney	St Vincent's Hospital	Prospective cohort	Community, hospital	9 March to 28 April 2020	RT-PCR	Eight months
Tortajada 2022	Spain, Valencia	Arnau de Vilanova–Llíria Health Department	Prospective cohort	Hospital	3 March to April 2020	RT-PCR	12 months (mean: 46 weeks)
Peluso 2021	US		Retrospective cohort	Community and hospital	Undefined	NAAT	Four and eight months
Miskowiak 2021	Denmark	Bispebjerg Hospital, IMPACT-COVID study	Prospective cohort	Hospital	March 2020	RT-PCR	3–4 months
Lerum 2021	Norway	Six major hospitals in Norway	Prospective cohort	Hospital	Undefined	RT-PCR	Three months
Soraas 2021	Norway	South-Eastern Norway	Prospective cohort	Community	1 February to 15 April 2020	RT-PCR	126 days ±33