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COVID 19 – KCE CONTRIBUTIONS

EPIDEMIOLOGY OF LONG COVID: A PRELIMINARY REPORT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
aOR	Adjusted odds ratio
COVID-19	Coronavirus Disease-19
DASS 21	Depression Anxiety and Stress Scale 21
DLCO	Diffusing capacity for carbon dioxide
FAS	Fatigue assessment score
ICU	Intensive care unit
IQR	Interquartile range
ITU	Intensive therapy unit
mMRC	modified medical research council
OR	Odds ratio
PCR	Polymerase chain reaction
SARS-Cov-2	Severe acute respiratory syndrome coronavirus-2

1 DISCLAIMER

The current work is based on the available evidence at the moment of writing the report (27/05/2021). There are still major evidence gaps, as studies are ongoing and science requires time to build up. A part of the available literature is not peer-reviewed and hence not necessarily conforms to the high-quality standards for scientific research. This document should be considered as a working paper that will be updated when the final report is published (October-November 2021). This implies that some findings may change over time.

2 KEY POINTS

- **Available evidence on the prevalence of long COVID remains limited and insufficient to formulate sound conclusions. Synthesising the information is challenging since studies are highly heterogeneous and the reported prevalences vary substantially.**
- **There is still no clear widely accepted definition of long COVID. Long COVID encompasses distinct phenotypes (or clusters of symptoms) that can broadly vary and evolve over time. As such, people may experience different patterns of symptoms that could have multiple causes. In specific patient groups (e.g. patients that have been hospitalised in the acute phase), it is important to distinguish those related with permanent organ impairment from those not related with organ damage.**
- **Reported prevalences differ according to the targeted population and follow-up time:**
  - **In studies in which (almost) all included patients were not hospitalised during the acute phase, it is estimated that, between 5 and 36% of them still have symptoms whithin the first 3 months after the onset of the COVID-19. However, in studies in which almost all patients have been hospitalised, higher prevalences are reported (between 39 and 72%).**
  - **Beyond 3 months, studies that predominantly included patients who have not been hospitalised, about 2-21% of them still have symptoms. For those studies including mostly patients that were hospitalised during the acute phase, the reported prevalence is higher and ranges between 51 and 68%.**
  - **Studies with long follow-up are sparse. It appears that symptoms improve over time but at 6 months of follow-up, about 13 to 25% of patients who were not hospitalised may still have at least one symptom. Higher rates reaching 60% have nonetheless been reported in patients who have been hospitalised.**
  - **Current evidence does not precisely allow to distinguish between the prevalence of symptoms following organ damage and symptoms unrelated to organ damage. Since the appearance of symptoms can besides COVID-19 have other non-mutual exclusive underlying causes (hospital stay, post-intensive care syndrome), the prevalence of long COVID might be overestimated.**
- **In the first three months, the most commonly reported persistent symptoms in the group of long COVID patients are fatigue (up to 98%), dyspnoea (up to 93%) and headache (up to 91%). Beyond 3 months, the most frequent symptoms were fatigue (up to 78%), cognitive disorders (up to 55%) and respiratory symptoms such as dyspnoea or dysfunctional breathing (up to 21%). Taste and olfactory dysfunction improve over time but may persist in the long run for a minority of patients. The type of symptoms does not seem to differ between patients who were hospitalised versus those who were not hospitalised during the acute phase. In addition to the symptoms, an impact on activities of daily life and (social) functioning is reported.**
- **The risk factors to develop long COVID are still unclear. Studies that aimed to identify risk factors are limited and considerably heterogeneous. Up to now, there is no study with large and sufficiently long follow-up. There are indications in those who were not hospitalised that a higher number of symptoms at the acute phase of the disease may be a risk factor for developping long COVID. The contribution of age (as a risk factor) is still controversial but long COVID seems to be prevalent across all age categories.**

- **The risk for being hospitalised and the risk for developing new clinical issues involving multiple organ systems requiring medical care is increased in the aftermath of COVID-19, in both groups of patients who were hospitalised or not during the acute phase of infection. Long COVID is reported regardless of the initial severity of COVID-19 and even in patients who remained initially asymptomatic.**
- **The current findings are based on studies presenting substantial limitations: (1)The absence of a homogeneous definition of long COVID with clear clinical criteria does not allow to make an accurate diagnosis. It is not always straithforward to distinguish long COVID from other overlapping conditions, especially when permanent organ damage is lacking. (2) Included populations vary widely according to demography, level of care received during the acute infection, sample sizes. (3) Study designs are heterogeneous (time of inclusion, follow-up duration). Many of them did not include a control group and present loss to follow-up. They are prone to recruitment and recall bias. (4) There is a lack of standardised and validated measures for symptom reporting. (5) Data on long COVID patients who had an asymptomatic infection are scarce.**

3 BACKGROUND

3.1 Awareness and reporting

After more than one year into the COVID-19 pandemic, evidence has surged that many symptoms can persist or appear after recovery from the acute period of illness. Those symptoms are reported after both mild or severe COVID-19. They adversely impact daily life and induce a societal burden, as the number of affected patients is increasingly growing.

Whilst many epidemiological data report that a proportion of people endure lingering symptoms after recovery from the acute disease, there is no globally accepted definition of this issue, yet. 'Long COVID' is now the most commonly used term but several terms such as 'post-COVID condition', long-haul COVID', 'post-COVID syndrome', 'post-acute COVID symptoms', 'post-acute sequelae' or 'chronic COVID' are found in the literature and encompass a wide range and variety of symptoms.

For the purpose of this review, we considered studies describing long-term symptoms following the acute phase of COVID-19 if they were observed at least 4 weeks after disease onset. We stratified by length of follow-up: early in the time-course of the disease (up to 12 weeks), between 3 and 6 months and after 6 months follow-up.

3.2 How to define long COVID?

Due to its wide heterogeneity of presentation, there is, currently, a lack of international consensus regarding the definition of long COVID. The World Health Organisation (WHO) is currently running a project aiming to result in an international consensus about a definition an clinical criteria for long COVID (a report is expected to be published in October- November 2021).[a]

In December 2020, the National Institute for Health and Care Excellence (NICE) proposed a definition of long COVID, based on the time beyond disease onset, when signs and symptoms, not explained by an alternative diagnosis are being reported: 'ongoing symptomatic COVID-19' is used for patients who have symptoms from 4 to 12 weeks beyond acute COVID-19, whereas 'post-COVID-19 syndrome' is the term used for those still experiencing symptoms after 12 weeks.[1]

Long COVID is increasingly being seen as an active and evolving medical condition bringing into play all organs. A broad spectrum of symptoms is commonly reported. People can continue to undergo single or multiple symptoms beyond the acute phase or develop new ones, or even undergo a relapsing trend.

There is substantial uncertainty about what causes long COVID and its management could vary according to related causal mechanisms. To this end, it is of utmost importance to distinguish people who have symptoms following organ damage that occurred during the hospitalisation (for example lung sequelae after prolonged mechanical ventilation) from people who undergo a mild-to-moderate disease and who were not hospitalised. For instance, the Centers for Disease Control and Prevention (CDC) proposed to make the distinction between several types of post COVID conditions and to consider the longer effects of COVID-19 hospitalisation or treatments consequences as a particular entity.[2] In this vein, some of these effects can include Post-Intensive-care-Syndrome that refers to a subset of patients who have been hospitalised in the intensive care unit[3] and must be differentiated from long COVID.

Interestingly, Amenta et al. (2020) proposed that symptoms could be classified into several groups: (1) residual symptoms that persist after recovery from acute illness, (2) organ dysfunction persisting after initial recovery, and (3) new symptoms coming up after asymptomatic or mild infection. This classification emphasises the fact that long COVID is a multi-organ condition and that further research is required to better classify the causes and types of symptoms.[4]

Definition and symptoms classification are subject to modification in the light of a new understanding of the disease. Some studies have indeed suggested a certain level of organ impairment, even in people who undergo a mild form of the disease.[5]

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[a] https://kce.fgov.be/en/needs-and-follow-up-of-long-term-covid-19-patients-ongoing-study

4 RESEARCH QUESTIONS

The following research questions are formulated for this systematic review:

- What is the prevalence of long COVID following a confirmed or suspected COVID-19 (highly suspected clinically and/or radiologically)?
- What are the symptoms of long COVID and their frequency?
- What are the risk factors for developing long COVID compared to "short" COVID-19?

This systematic review will be updated when the final report is published (October-November 2021).

5 METHODS

We followed the KCE Process Book for conducting the search. The search was conducted from 03 February to 20 May 2021 in 11 databases. Details of the search strategy are presented in Appendix 2.

5.1 Structured questions and search concepts

The research question was transformed into a PEOD (Population-Exposure-Outcome-Design) structured search question (See Appendix 1.1). Keywords and search concepts were collected through experts' opinion, existing recent publications retrieved after preliminary literature searches, and consultation of controlled vocabularies (Medical Subject headings = MeSH; Excerpta Medica = Emtree). Considering the topic specificities, only keywords related to the problem were sought.

	Inclusion criteria	Exclusion criteria
Population	People experiencing symptoms beyond 4 weeks onward (≥ 4 weeks and > 12 weeks) with appropriate denominator reported*	
Exposure	COVID-19 confirmed (PCR, antibodies) or not (but highly suspected clinically and/or radiologically)	
Outcome	• Prevalence of reported symptoms (any symptoms including biological disturbances) and daily life consequences • Risk factors for long COVID	
Design	N ≥ 250 patients included Studies conducted in Europe and the USA Systemic review, Cohort study, Cross-sectional study	Case report, Case series, Mixed method (qualitative)
Language	English, French, Dutch, Spanish	Other languages

** For prevalence assessment: denominator corresponding to the percentage of acute COVID-19 cases. For risk factors assessment, percentage of long COVID.*

5.2 Identification of studies

A set of bibliographical databases and registers to search was identified based on the search questions. Considering the topic specificities (recent topic), full text databases and pre-print registries were also sought (See Appendix 1.2). A search query was developed with the assistance of a medical information specialist and adapted to each database. Considering the topic specificities (recent topic, no clear concept, several synonyms), a pure keyword strategy was chosen. Search in those databases was supplemented by collecting additional references from different sources (external experts, exploratory searches in the bibliographical databases, identification of cited references and looking into the bibliography of key references). It was completed by a regular scan of more recent literature through PubMed, MedRXIV and international websites on COVID-19 (WHO, NICE, CDC, HAS).

All identified references were imported in Endnote X.8, the duplicate search results were detected based on title match using the build-in tool from EndNote, and supplemented by manual identification after sorting on Title.

The search strategy was challenged using the results of the initial pragmatic review of literature, published in January 2021[b]: we checked whether the current search strategy identified the studies previously included in this review.

5.3 Selection of studies

The selection of studies followed a three-stepped process conducted by the information specialist and one researcher.

The first step of studies identification was based on title and abstract screening using the research question and human context by the information specialist: irrelevant studies that were out of scope were excluded during this screening phase and potentially relevant studies were kept.

The second step was based on title and abstract screening using the PEOD and exclusion criteria by the researcher: irrelevant studies were discarded. The full text of the retained studies was then sought.

In the third phase assessing eligibility of inclusion, we selected studies according to the PEOD criteria: we selected studies that measured the prevalence of long COVID in a population of COVID patients, the distribution of symptoms in long COVID patients and/or identified risk factors for long COVID. We limited our selection to studies reporting symptoms ≥ 4 weeks after the onset of the initial disease and conducted in Europe or the US, for better inference to the Belgian population in terms of epidemiology, risk factors such as comorbidity and health-seeking behaviour. We decided to select only studies that have included at least 250 COVID-19 cases. Data on risk factors were based on studies adjusting for potential confounding factors such as age, sex and comorbidities. Languages were restricted to English, French, Dutch, and Spanish. Seeing the urgent need for identifying evidence, critical appraisal was not undertaken in this review but will be performed in the final version of this report.

6 RESULTS

6.1 Included studies

The search through databases yielded 10 445 hits. Additionally, 19 relevant articles in the references in included studies or by scanning the current literature were added. The number of articles was reduced to 6 619 after duplicates removal and 6 577 articles were discarded, based on title and abstract screening. After assessing 42 full texts of the remaining articles for eligibility, 13 were excluded. Thereby, 29 articles met our inclusion criteria and were included in the analysis. Two articles reported on the same study.[6, 7] Among the retrieved articles, 10 had already been identified among the 11 included in our preliminary pragmatic review in January 2021.[6-15] The article that we missed[16] could have been identified by a very sensitive search, but such strategy would have required to screen an unmanageable amount of references (> 35 500).

A cross-sectional survey initially included in this preliminary version was discarded because the measurement of persistent symptoms was no more in accordance with the consensus on the timing of long COVID symptoms (2-3 weeks after positive testing).[17] The selection of studies is summarised in the flow diagram (See Appendix 1.3).

Twenty-two studies were observational cohort studies[8, 10, 11, 14-16, 18-33] and 7 were cross-sectional studies[6, 7, 9, 12, 13, 34, 35] considering the frequency and the type of symptoms after COVID-19.

Eight studies included data from several countries. Five studies were from the UK, 2 studies from France, 3 from Spain, 2 from Italy, 3 from the US, 2 from Switzerland, and the remaining four studies were from Denmark, Norway, Sweden and Germany. Four studies were preprints, still under review.[9, 13, 19, 33] By stratifying by the follow-up duration, we identified 15 studies in the 1 to 3 months period, 10 in the 3 to 6 months period and 4 with a follow-up longer than 6 months (See Table 1 and Table

[b] https://kce.fgov.be/sites/default/files/atoms/files/2020-04HSR_LongCOVID_COVID%20Contributions_01022021.pdf

2). Nine studies included several points of follow-up.[9-12, 19, 25, 29, 30] Samples sizes widely varied and ranged from 256 to 236 379 included patients.

Regarding the characteristics of the infection at the initial period, 6 studies included exclusively hospitalised patients[18, 22, 28, 29, 32, 34], while five studies solely reported on ambulatory patients. [8, 11, 19, 25, 35] Other studies included a mixed population of ambulatory and hospitalised patients: three studies had a majority of hospitalised people[10, 14, 23], whereas 15 others comprised both patients who were hospitalised and nont hospitalised.[6, 7, 9, 12, 13, 15, 16, 20, 21, 24, 26, 27, 30, 31, 33]

The majority of studies included patients who experienced symptoms at the time of acute infection. Three studies included a limited proportion of patients who remained asymptomatic during acute COVID-19.[9, 12,30] Symptoms were mostly self-reported and collected through phone calls[8, 16, 22, 26, 28, 32, 34] or by electronic questionaires[6, 7, 9, 11-14, 19-21, 24, 25, 33, 35] Six studies assessed symptoms through a medical visit follow-up. [10, 23, 25, 28-30]

Among the retrieved studies, we made a distinction between studies for which COVID-19 patients were used as denominator from those in which only long COVID patients have been selected. The latter exclusively pick out patients with persisting symptoms and cannot be used to determine the prevalence of long COVID among COVID-19 cases. These studies that only assessed persisting symptoms in long COVID patients were only used to describe the frequency and duration of symptoms. Sample sizes of those studies ranged between 277 to 4 182 patients (See 6.4).[6-11, 13, 19, 26, 28, 33-35]

6.2 Prevalence estimate

6.2.1 Studies with 1 to 3 months of follow-up

We found 9 studies allowing us to assess the prevalence of long COVID between 1 to 3 months: six observational cohort studies[8, 10, 11, 19, 22, 26] and three cross-sectional surveys[9, 12, 34] (See Table 1). Among those, two were preprint articles currently under review.[9, 19] One study also assessed the effect of corticosteroids on lung function.[22]

All studies were based on self-reported symptoms by means of telemedicine through COVID app monitoring, phone or online surveys and medical visits. COVID-19 was confirmed in each study. Two studies included patients who were asymptomatic at the acute phase.[19, 30]

The number of patients ranged from 277 to 4 182 in epidemiological studies, whereas the survey from ONS included 21 622 participants. The majority of patients were middle-aged (mean ages ranging from 42 to 62 years). Three studies included non-hospitalised patients,[8, 11, 19] while 3 other studies included mostly patients who have been hospitalised.[10, 22, 34] Three studies involved ambulatory patients along with a limited proportion of hospitalised ones, below 10%.[9, 12, 26]

Globally, studies showed that among patients who were affected by COVID-19, the proportion of those who had persistent symptoms ranged from 5.2 to 71.8% (See Table 1 and Figure 1):

- Studies that included patients who were not hospitalised at the time of first infection or studies that included a minor proportion of patients hospitalised at the acute phase, reported lower prevalences ranging from 5.2 to 36%.[8, 9, 11, 12, 19, 25, 26]
- Studies that included patients predominantly hospitalised (even in ICU) reported higher prevalences that ranged between 39 and 71.8%.[10, 22, 34] The study from Myall et al. reported that 39% of the patients had symptoms 4 to 6 weeks after hospital discharge, while the study from Mandal et al. reported that up to 71.8% of patients showed at least one symptom at the same follow-up time.[22, 34] Both studies reported high proportions of patients who were hospitalised on ICU and for whom mechanical ventilation was initiated (7% in the study from Mandal et al. and 46% in the study from Myall et al.). In the study of Moreno-Perez et al., that included 66% of hospitalised patients, the reported prevalence was at a rather similar level of 36.6%, when the subgroup of patients with severe pneumonia was excluded.

Five of the included studies extended the measure prevalence also beyond 12 weeks and indicated a higher prevalence in the first 11 weeks after disease onset compared to measurements performed after 12 weeks (See 6.2.2).[9-12, 19, 25]

6.2.2 Studies with 3 to 6 months of follow-up

Eleven studies allow to assess the prevalence of long COVID between 3 to 6 months: 9 observational cohort studies[10, 11, 19, 23, 25, 28-30, 32], and two cross-sectional studies[9, 12] (See Table 1). Among these, several studies included different time-points of follow-up: six studies were already used to determine the prevalence between 1 to 3 months[9-12, 19, 25] and two beyond 6 months.[29, 30] Two studies were reported in preprint articles.[9, 19]

All studies were based on self-reported symptoms by means of phone calls, online questionnaires, app monitoring. Six studies included patients in a multidisciplinary outpatient clinic[10, 23, 25, 28, 29, 30] and 3 of them included biological, respiratory and psychological assessments by means of various tests.[23, 28, 30] Mean ages fluctuated from 42 to 63 years. Three studies included only hospitalised patients[28, 29, 32], while three studies focused on ambulatory patients.[11, 19, 25] Five studies included a mixed population (ambulatory and hospitalised patients).[9, 10, 12, 23, 30] Among those, two studies involved a majority of hospitalised patients[10, 23], while the three others had less than 10% hospitalised patients.[9, 12, 30]

Based on those included studies, the prevalence of long COVID between 3 and 6 months was highly heterogeneous and ranged from 2.3 to 68% (See Table 1 and Figure 1):

- The three studies that reported a high prevalence mainly included hospitalised patients: Venturelli et al. have estimated the presence of ongoing symptoms at 51%, after hospital or emergency room discharge.[23] A high proportion of patients were hospitalised (88%) and followed-up at multidisciplinary outpatient clinic post-discharge. Besides, Morin et al., and Ghosn et al. reported on persistent symptoms in 51[28] and 68%, respectively.[29] They included only patients with severe or critical COVID-19 at the initial phase. In both studies, the proportions of patients who required ICU admission was 29.7 and 29%, respectively.
- Prevalence was lower in studies that predominnatly included non-hospitalised patients and ranged between 2.3 and 21.4%.[9, 11, 12, 19, 25, 30]
- Five studies reported prevalences at different time points and, we noticed a decreasing trend (Figure 1): higher prevalences were reported in the first 11 weeks after disease onset compared to measurements performed 12 or more weeks after symptom onset (ranging from 2.3 to 29%).[9-12, 19]

6.2.3 Studies with follow-up ≥ 6 months

Four observational cohort studies, allow to assess the prevalence of long COVID at more than 6 months of follow-up.[25, 29, 30, 33]

- In one study, long-term immunological response after COVID-19 in young low-risk patients was assessed. Healthcare workers from a hospital in Denmark were followed. Blood samples were performed every 4 months to assess the presence of antibodies against SARS-Cov-2 and symptoms were obtained through an app using standardised questionnaires. A decreasing trend in prevalence was observed over time in 323 seropositive participants. At 2 and 4 months, symptoms were present in 26 and 21.4%, respectively (See Figure 1). Almost 15% reported a minimum of one symptom for at least 8 months, while only 3.4% of seronegative patients did.[25]
- Another study prospectively followed patients whith predominantly mild COVID-19 in the acute phase. At 7 months, the prevalence was 12.8%. A high rate of dropouts was mentioned (only 37% of the initial number of patients were followed). Missing patients were called and 24.2% of reached dropouts reported over the phone the presence of symptoms (without medical assessment).[30]
- The third study focused on hospitalised patients only, with 29% of whom were admitted to the ICU in the acute phase. Sixty per cent presented at least one persistent symptom at 6 months and 24% of them had simultaneously three or more symptoms.[29]
- At 6 to 8 months after diagnosis, a prospective cohort study assessed patients with19 of whom hospitalisation was required (with 2.3% at ICU). Symptoms were reported by 25% of patients and 26% reported that they had not fully recovered.[33]

Figure 1 – Results of studies assessing the prevalence of long COVID according to the level of care during the acute phase

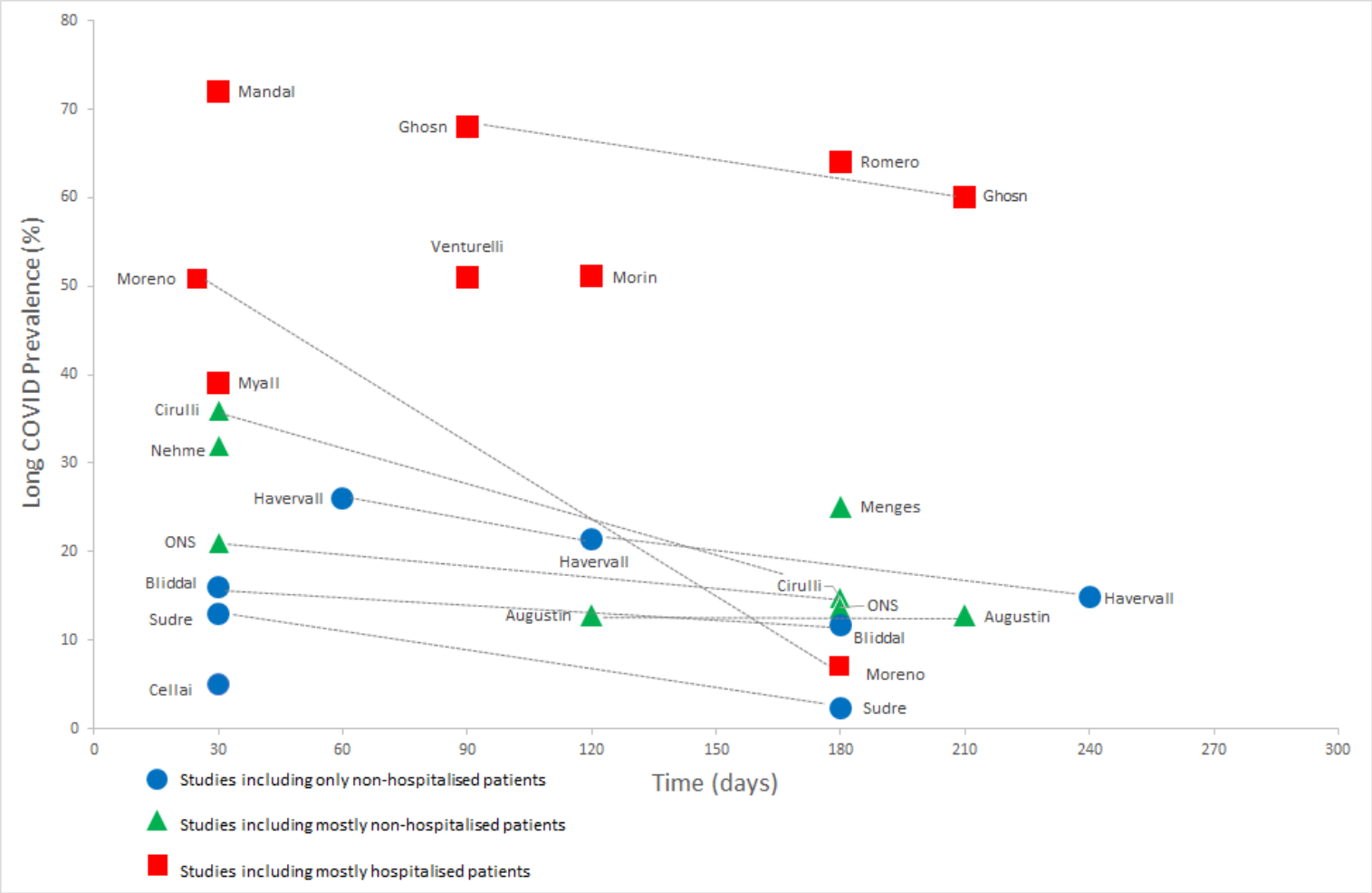

Table 1 – Results on long COVID prevalence

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
Cellai M[8], US	Telemedicine clinic program (regular phone calls) Confirmed infection (PCR)	Prospective cohort study n= 496	Persistent self-reported symptoms 6 weeks after onset of COVID-19	Ambulatory	1-3 m	5.2% (26/496)	Not reported	Published
Cirulli E[9], US	Participants to online survey in 2 projects. Confirmed infection (PCR)	Cross-sectional survey n= 357	Self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms)	Hospitalised 2.5%	1-3 m ≥ 3 m	at 30 days: 36.1% (129/357) ≥ 3 months: 14.8%	Not reported	Under review
Sudre C[11], UK, US and Sweden	Self-reporting in Covid Symptom Study App (start logging when still asymptomatic) Confirmed infection (PCR)	Prospective cohort study n= 4 182	Any self-reported symptom > 28 days after onset of COVID-19	Ambulatory	1-3 m ≥ 3 m	13.3% (558/4182) ≥ 3 months: 2.3%	Not reported	Published
Moreno-Perez O[10], Spain	Outpatient structured evaluation after hospital or emergency discharge. Confirmed infection	Prospective cohort study n= 277	Persistence of ≥ 1 symptom or abnormal spirometry or chest X-Ray at 10-14 weeks after	Hospitalised 66 % ICU 8.7%	1-3 m > 3 m	50.9% (141/277)	Not reported ≥ 3 months: 3.8% (neurological)	Published

	(PCR) or seroconverted		onset of COVID-19				6.7% (respiratory)	
Mandal S[34], UK	Phone or in-person interview of every patient after hospital discharge who had tested COVID-19 positive	Cross sectional study n= 384	Self-reported symptoms 4-6 weeks after discharge and biological, respiratory and mental assessment	Hospitalised	1-3 m	71.8% (276/384)	• Dyspnoea 53% • Cough 34% • Fatigue 69%	Published
Myall K[22], UK	Phone interview 4 weeks after hospital discharge Confirmed infection (PCR or clinically/radiologically)	Prospective cohort study n= 837	Self-reported ongoing symptom 4-6 weeks after discharge	Hospitalised ICU 54%	1-3 m	39% (325/837)	Not reported	Published
Nehme M[26], Switzerland	Phone call 30-45 days after diagnosis (remote follow-up care system) Confirmed infection (PCR)	Prospective cohort study n= 669	Self-reported ongoing symptom 30-45 days from diagnosis	Hospitalised 6%	1-3 m	32% (214/669)	Not reported	Published
Office for National Statistics (ONS)[12], UK	Positive COVID-19 patients who responded to the National Coronavirus (COVID-19) Infection Survey (CIS)	Cross sectional survey n= 21 622	Self-reported persistent symptoms at 5 weeks or ≥ 12 weeks after COVID-19 onset	Hospitalised 7.9% to 8.6%* * among those who first had infection at least 12 weeks previously	1-3 m 3-6 m	≥ 5 weeks: 21% ≥ 12 weeks: 13.7%	≥ 5 weeks: • Fatigue 11.8% • Cough 10.9% • Headache 10.1% • Myalgia 7.7% ≥ 12 weeks: • Fatigue 8.3% • Cough 7% • Headache 7.2% Myalgia 5.6%	*Not applicable*

Venturelli S[23], Italy	Inclusion in an outpatient post-discharge multidisciplinary program after hospital or ED discharge Confirmed infection (PCR or seroconversion) 99%	Prospective observational study n= 767	Ongoing symptoms (psychological, biological, respiratory evaluations) at 12 weeks	Hospitalised 88% ICU 9.7%	3-6 m	51% (394/767)	• Fatigue 44% (334/758) • Dyspnea 29.7% (228/767) • Post traumatic psychological disorders 30.5% (222/727) • Functional finding: impaired lung function (DLCO) 19% (136/716)	Published
Morin L[28], France	Telephone assessment 3-4 months after hospital discharge Ambulatory visit for a subset of patients with relevant symptoms	Prospective cohort study n= 478	Symptoms at 4 months after hospital discharge	Hospitalised	3-6 m	51% (244/478)	• Fatigue 31.1% (131/431) • Memory difficulties 17.5% (73/416) • New-onset dyspnea in 16.3% (78/478) • Persistent paresthesia 12.1% (51/421)	Published
Bliddal S[19], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Prospective cohort study n= 445	Persistent symptoms > 4 weeks and > 12 weeks	Ambulatory	1-3 m 3-6 m	> 4 weeks: 16% (71/445)* > 12 weeks: 11.7% (52/445)* * Prevalence of symptoms is not reported and are based on our own calculation	Not reported	Under review
Romero-Duarte S[32], Spain	Data retrieved from follow-up consultation (primary care and hospital specialities) and	Retrospective observational study	Self-reported symptoms at any time after hospital discharge during 6	Hospitalised patients ICU 10.8%	3-6 m	≤ 6 months: Symptoms: 63.9%* (509/797) Return to emergency	• Dyspnoea 28% (223/797) • Fatigue 22.1% (176/797)	Published

	periodic telephonic reports PCR confirmed infection	n= 767	months follow-up, hospital readmission, return to the emergency services and death			department 20% (160/797) Hospitalisation 4.4% (35/767) Death 1% (8/797)	• Diarrhea 10.3% (82/797) • Mental health disorders 12.2% (97/797) • Dermatological issues 9.3% (74/797) • Superinfection 7.9% (63/797) Less frequent symptoms: ○ Smell/taste 5.3% ○ Headache 5.3% ○ Cardiovascular 5.8% ○ Ophtalmological 4.6% ○ Nephrological 4.5% ○ Haematological 4.4% ○ Urological 4.3% ○ Otorhinological 3.1% ○ Endocrine 1.5%	
Havervall S[25], Sweden	Healthcare workers participating in an online survey and regular clinical/ biological assessment	Prospective cohort study n= 1 395	Ongoing symptoms (at least one moderate to severe symptoms) at 8 months	Ambulatory	> 6 m	≥ 2 months: 26% (84/326) ≥ 4 months: 21.4% (69/323) ≥ 8 months: 14.9% (48/323)	• Anosmia 9% • Fatigue 4% • Agueusia 3.7% • Dyspnoea 1.9% • Sleeping disorders 2.2% • Headache 1.5% • Palpitations < 1% • Concentration impairment < 1% • Muscle/joint pain < 1%	Published

							Memory impairment < 1%	
Ghosn J[29] ,France	Patients who were hospitalised were assessed through physician visits 3 and 6 months after hospital admission	Prospective cohort study n= 1 137	Systematic assessment of ten persisting symptoms at 3 and 6 months	Hospitalised	3-6 m > 6 m	≥ 3 month: 68% (655/957) ≥ 6 months*: 60% (639/1068) *at 6 months, 24% with ≥ 3 symptoms	• Fatigue nearly 40% • Dyspnoea > 20% • Joint pain nearly 20% • Myalgia nearly 20% • Headache > 10% • Rhinorrhea 10% • Cough 10% • Sore throat <10% • Agueusia 7% • Anosmia 7%	Published
Augustin M[30], Germany	Invitation of each patient with confirmed infection (PCR) for follow-up medical visits at month 4 and 7, regardless of symptoms	Prospective cohort study n= 958	Assessment of long-lasting symptoms with systematic questionnaires at 4 and 7 months after symptom onset (or positive testing) Median follow-up 6.8 months	Hospitalised 2.9% ICU 0.7%	3-6 m > 6 m	At 7 months: 12.8% (123/958) At 4 months: 12.8% (123/958)	At 4 months*: • Anosmia 12.4% (55/442) • Agueusia 11.1% (49/442) • Fatigue 9.7% (43/442) • Shortness of breath 8.6% (38/442) At 7 months*: • Anosmia 14.7% (52/353) • Agueusia 14.2% (50/353) • Fatigue 13.6% (48/353) • Shortness of breath 11% (39/353)	Published

							*Due to the a high rate of dropout, we calculated the most conservative estimate at 7 months: ○ Anosmia 5.4% (52/958) ○ Agueusia 5.2% (50/958) ○ Fatigue 5.0% (48/958) ○ Shortness of breath 4.1 % (39/958)
Menges G[33], Switzerland	Inclusion through contact tracing of the Department of Health, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	Prospective cohort study n= 431	Assessment of recovery and long-lasting symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS mMRC,DASS -21)	Hospitalised 19% ICU 2.3%	> 6 m	Not fully recovered 26% (111/431) Symptoms 25% (106/431)	• Fatigue 55% (233/431) • Dyspnoea (mMRC ≥ 1) 22% (96/431) • Symptoms of depression 26% (111/431) <u>Self-reported symptoms</u>: • Fatigue 12% (52/431) • Cough 10% (41/431) • Sore throat 9% (38/431) • Headache 9% (37/431) • Smell/taste disorder 5% (21/431) • Rash 0.7% (3/431)

Legend:DASS-21: Depression Anxiety and Stress Scale 21; DLCO: Diffusing capacity for carbon dioxide; FAS: Fatigue Assessment Score; ICU: Intensive care unit; mMRC modified medical research council; PCR: Polymerase chain reaction

6.3 Prevalence of long COVID for specific organ systems or symptoms

In this section, we only describe studies reporting prevalence on specific symptoms affecting one or several particular organ systems. Results are presented in Table 1 (symptom-specific prevalence column) and Table 2. We retrieved 15 observational cohort studies[14-16, 18, 20, 21, 23-25, 27-29, 31-33] and one cross-sectional study.[12] Among these, six had a follow-up of 3 months[12, 14-16, 21, 24], while seven evaluated symptoms between 3 and 6 months.[18, 20, 23, 27, 28, 31, 32] Three studies had a follow-up beyond 6 months.[25, 29, 33] Only one article was under review. [33]

Three studies appraised mental health[14, 15, 27] and four evaluated the olfactory or taste disorders.[16, 20, 21, 24] Six other studies reported on general symptoms[12, 23, 28, 29, 31, 33], whereas two focused on mortality and hospital readmission.[18, 32]

6.3.1 Mental health symptoms

In a large retrospective observational study, Taquet et al. reported a frequency of 5.8% of new onset psychiatric illness in the aftermath of COVID-19. Anxiety or mood disorders (mainly depression) were reported up to 3 months after the onset of COVID-19 in respectively 4.7 and 2% of patients.[15] At 6 months, in a larger cohort with a hospitalisation rate of 19.6%, the same authors reported a rate of 12.84% of new-onset psychiatric or neurological illness. This rate was higher and reached 25.79% in more severe patients who had been admitted to an intensive therapy unit (ITU). Anxiety was reported in 7.11% of the total cohort and almost 10% in the more severe subgroup who needed intensive therapy. Insomnia in both groups was 2.53 and 4.24%, respectively. Psychotic disorders or brain vascular disorders, such as stroke or haemorrhage, were less frequent (below 1%).[27] Mental health problems were more often identified at a frequency rate of 55% one month after the onset of the disease among COVID-19 patients that had visited the emergency department (with 75% of them hospitalised) during the acute COVID-19 phase.[14]

6.3.2 Olfactory and smell symptoms

In three prospective cohort studies that mainly included ambulatory patients, self-reported olfactory disorders within 1 to 3 months after onset of disease varied between 26 and 42%, in those having developed anosmia or hyposmia at the acute phase of the disease.[16, 21, 24] One of these studies reported also 33.8% of taste disorder.[21] One prospective cohort study investigated the olfactory abnormalities through objective and validated tests. Authors reported a prevalence of 15.3% at 2 months and 4.7% at 6 months, in those who were anosmic/hyposmic during acute COVID-19.[20]

6.3.3 General symptoms

One cross-sectional study reported on general symptoms at different time points following acute infection[12], while three observational studies assessed the prevalence of general symptoms between 3 and 6 months[23, 28, 31]:

- In the update of the Coronavirus Infection Survey (CIS) from April 2021, the UK Office for National Statistics (ONS) reported that the most prevalent self-reported symptoms that persist at least 5 weeks after acute infection were fatigue (11.8%), cough (10.9%), headache (10.1%) and muscle pain (7.7%). The most prevalent symptoms that persisted at least 3 months were the same as those reported at 5 weeks, but prevalences were lower for all symptoms. However, ONS mentioned that those estimates must be interpreted with caution because of a low amount of participants still reporting symptoms at 12 weeks.[12]
- In the study of Venturelli et al., 767 patients discharged from hospital (88%) or emergency room underwent an assessment through a multidisciplinary follow-up clinic. About one-third of the cohort presented dyspnoea 12 weeks after discharge (See Table 1). Other symptoms were post-traumatic psychological symptoms (30.5%) and fatigue (44%).[23] Another observational study reported a prevalence of dyspnoea of 16.3% at 4 months in hospitalised patients of whom one third was admitted to ICU (See Table 1). Other reported symptoms were fatigue (31%), memory difficulties (17.5%) and paresthesia (12.1%).[28]
- One observational cohort study that estimated the prevalence of long COVID beyond 6 months reported on the prevalence of symptoms over time among a cohort of seropositive or seronegative for SARS-CoV-2 and not hospitalised people (See Table 1).[25] The most prevalent symptoms at 8 months were anosmia (9%), fatigue (4%) and ageusia (3.7%). Other less frequent

symptoms included dyspnoea, sleeping disorders, headache, palpitations, concentration/memory impairment or muscle/joint pain. The prevalence of those symptoms decreased all over time. Conversely, another study that included more severe hospitalised patients, reported fatigue by a rate of about 40%. Dyspnoea, joint/muscle pain were also common.[29]

- In a cohort comprising 19% of hospitalised patients, Menges et al. used appropriate scales (FAS, mMRC and DASS-21) to assess fatigue, dyspnoea and depression that were reported in 55, 25 and 26%, respectively. Self-reported fatigue was lower that the prevalence estimaed with the FAS. [33] (See Table 1)
- Daugherty et al. retrospectively showed, in a cohort of patients who were predominantly not hospitalised, that 14% of patients had at least one new type of clinical sequelae that required medical care 4 months after COVID-19. New symptoms were identified across a wide range of organ systems including cardiovascular, respiratory, renal, haematological and mental issues.[31]

6.3.4 Hospital readmission and mortality

Two studies focused on hospital readmission and mortality[18,32]:

- Ayoubkhani et al. conducted a large retrospective observational and matched cohort study in the UK that included 47 780 participants who were discharged from the hospital.[18] They reported on the rates of hospital readmission, mortality and new-onset diseases over a mean follow-up of 140 days and compared them to control cases matched on clinical and demographic characteristics. Twenty-nine percent of COVID-19 patients were re-admitted to the hospital whereas 9.2% of matched-control patients did. Mortality rate was 12.3% in the COVID-19 group versus 1.7% in the matched- control group. Likewise, rates of new-onset multi-organ dysfunctions (respiratory or cardiometabolic) were significantly raised in COVID-19 subjects when compared to controls (See Table 2).[18]
- Romero-Duarte et al. reported 20.3% of patients who returned to the emergency department and 12.1% were hospitalised within 6 months after COVID-19.[32]

Table 2 – Results on prevalences of long COVID for specific organ systems or symptoms

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
Taquet M, UK[15], US	Data extraction from electronic database in positive COVID-19 patients (confirmed infection PCR or antigen testings 92.2%)	Retrospective observational cohort study n= 62 354	New-onset psychiatric disorders within 14 to 90 days after COVID-19 onset	Percentage of hospitalization not mentioned	1-3 m	5.8%	• Anxiety disorder 4.7% (adjustment disorder, generalised anxiety disorder, PTSD, panic disorder) • Mood disorder 2% (depression 1.7%) • Psychotic disorder 0.1% • Insomnia 1.9% • Dementia 0.44%	Published
Taquet M[27], UK, US	Data extraction from electronic database in positive COVID-19 patients Confirmed infection (ICD-10 codes U07.1)	Retrospective observational cohort study n= 236 379	New-onset psychiatric or neurological disorders in the 6 months after COVID-19	Hospitalised 19.6% ITU 3.8%	3-6 m	Whole COVID-19 cohort: 12.84% Patients admitted in ITU: 25.79%	• Anxiety disorders 7.11 % • Psychotic disorders 0.42% • New insomnia 2.53% • Intracranial haemorrhage 0.28% • Ischaemic stroke 0.76% • Parkinsonism 0.11% • Dementia 0.67%	Published
Mazza M[14], Italy	Clinical interview and self-reported questionnaires in COVID-19 patients assessed at ED and hospitalised or not. (no information on testing)	Prospective observational cohort study n= 402	Mental health assessment at one month after COVID-19 onset	Hospitalised 75%	1-3 m	56%	• PTSD 28% • Depression 31% • Insomnia 40% • Anxiety 42% • Obsessive-compulsive symptoms 20%	Published
Makaronidis J[21], UK	Invitation of people with acute loss of smell/taste through primary care	Prospective cohort study	Smell/taste disorders at 4-6 weeks after	Ambulatory	1-3 m	Smell* 42.2% (151/357)	Not reported	Published

	centers (recruitment via online platform). Follow-up by a questionnaire that was sent. Serology positive in 82%	n= 467	COVID-19 onset	Hospitalised 2.3%		Taste* 33.8% (116/343) * of those who developed olfactory and taste disorders during the acute phase		
Chiesa-Estomba C[24], France and European	Identification of patients with total or partial loss of smell through database from 3 hospitals. Contact after 30 days for olfactory assessment via online questionnaire Confirmed infection (PCR)	Prospective cohort study n= 751	Self-reported persistent olfactory dysfunction	Ambulatory Hospitalised (no clear % mentioned)	1-3 m	Persistent loss of smell* 37% (277/751) Partial smell recovery* 14% (107/751) *of those who developed olfactory and taste disorders during the acute phase	Not reported	Published
Villarreal I[16], Spain	Phone interview in healthcare workers with PCR positive for COVID-19	Prospective cohort study n= 256	Olfactory and taste disorders at 1 month after acute infection	Hospitalised 3.5%	1-3 m	26% (43/161)* * of those who developed olfactory and taste disorders during the acute phase	Not reported	Published
Lechien J[20], **Belgium and Europe**	Online questionnaire was completed at the end of the disease or at the hospital discharge and within the 2-month post-infection (identification through hospital databases)	Prospective cohort study n= 1 363	Self-reported olfactory dysfunction at 2 and 6 months (objective testing in a subset)	Hospitalised 2%	3-6 m	24.1%* (328/1363) * of those who developed olfactory and taste disorders during the acute phase	Not reported	Published

Ayoubkhani D[18], UK	Identification through electronic health and mortality records (ICD10 codes: U07.1 and U07.2)	Retrospective matched cohort study n= 47 780	Over a mean follow-up of 140 days, assessment of: - Hospital readmission - Cause of death - Organ dysfunctions	Hospitalised	3-6 m	Not reported	• Hospital re-admission 29.4% in COVID-19 patients vs 9.2% in the control group • Death after discharge 12.3% in COVID-19 patients vs 1.7% in the control group • New-onset organ dysfunctions in COVID-19 patients versus control group: ○ Respiratory disease 21.5% vs 0.8% ○ Diabetes 1.1% vs 0.3% ○ Cardiovascular 2.6% vs 0.5%	Published
Daugherty S[31], US	Identification through electronic health from 3 data sources within the United Health Group Clinical Discovery Database (ICD10 codes: U07.1, U07.2, B34.2, B97.29) Confirmed infection (PCR)	Retrospective cohort study n= 193 113* Three comparative groups matched by propensity score * Total cohort: 266 586 and 193 113 with follow-up	Assessment of risk and relative hazards for developing clinical sequelae requiring medical care after COVID-19 in 18-65 years patients, over a follow-up of 4 months after acute infection (median 95 IQR 42-135)	Hospitalised* 8.2% ICU* 1.1% * calculated on a total of 266 586	3-6 m	14.02% with at least 1 new type of clinical sequelae that required medical care (27 074/193 113): • 10.01%: one sequela • 4.01%: > 1 new sequelae	In comparison with control groups, higher risk difference and higher hazard ratio* for several new clinical outcomes*: • Neurological disorders • Cardiovascular disorders • Hypercoagulability • Kidney disorders • Respiratory disorders • Mental health and neurocognitive issues * clinical outcomes were grouped per organ system given the high number. Results are available upon request.	Published

Legend: PCR: Polymerase chain reaction; ITU: Intensive therapy unit; PTSD: Post-traumatic stress disorder

6.4 Most common symptoms and their frequency among patients with long COVID

We report the frequency of symptoms among long COVID patients through studies assessing symptoms in this subgroup. In this case, the number of long COVID patients is used as a denominator.

We obtained data on symptom frequency in long COVID patients based on 13 articles: 7 observational cohort studies[8, 10, 11, 19, 26, 28, 33] and 6 cross-sectional surveys (See Table 3).[6, 7, 9, 13, 34, 35] Among these studies, 9 were already been used to determine long COVID prevalence.[8-11, 19, 26, 28, 33, 34]Two articles reported on the same study.[6, 7] Three other studies estimated the frequency before and after 3 months.[9, 13, 19] and three articles were preprints.[9, 13, 19] One study included patients who were hospitalised at the acute phase of infection and another one reported on a cohort of patients who were predominantly hospitalised. Four studies included patients who were not hospitalised at the acute phase[8, 11, 19, 35] and 6 articles included both hospitalised and non-hospitalised patients.[6, 7, 9, 10, 13, 26] One study reported on hospitalised patients, only.[34] Only one article reported on symptoms frequency after 6 months.[33] Not all articles reported on the exact estimation of the frequency of the symptoms and only mentioned whether they were frequently reported or not. The frequencies from the study from Moreno-Perez et al. were calculated based on the original data included in the paper such that only long COVID patients were included in the denominator.[10]

We noticed that reported frequencies highly varied across studies. Furthermore, while some symptoms were reported continuously, relapsing-remitting presentation of symptoms was also described. Other frequent symptoms are systematically described below:

- The most commonly identified long-term symptoms up to 3 months of follow-up in long COVID patients were fatigue (16%-98%; 10 studies[6-11, 13, 19, 26, 34]), dyspnoea (10-93%; 9 studies[6, 8-11, 13, 19, 26, 34]) and headache (9-91%; 8 studies[6, 8-11, 13, 19, 26]).
- The most commonly identified symptoms at 3 to 6 months follow up were fatigue (16-78%; 3 studies[13, 19, 35]), cognitive disorders (13-55%, 3 studies [13, 19, 28]), dyspnea or dysfunctional breathing (16-20.9%, 2 studies[28, 35]) and post-exertional malaise (72%, one study[13]).
- The study from Menges et al. identified fatigue as the most frequent symptom after 6 months.[33]

We did not notice substantial differences between the types of symptoms among studies with ambulatory patients and studies with hospitalised patients. However, it should be noted that a clear distinction between both groups is not easy since many studies mixed hospitalised and non-hospitalised patients.

General health

General symptoms regularly reported include fatigue, muscle weakness, headache, pain (muscular, joint or bone pain), sleep disorders and less frequently low-grade fever or skin disorders (See Table 3). Fatigue and headache were both reported in the first 3 months and beyond. Exercise tolerance (post-exertional malaise) is also part of the reported complaints, reported by the international survey of Davis et al.-preprint. This symptom was frequently reported (89%) up to 6 months after the acute phase.[13]

Respiratory

- Respiratory symptoms like dyspnoea are frequent but highly variable in the aftermath of COVID-19 (from 10 to 93% in the first three months). Frequencies were high in both cohort studies and surveys. Nevertheless, beyond 3 months, they seem less commonly reported.
- Importantly, the frequency of dyspnoea in patients with long COVID has to be distinguished from its prevalence as an organ-specific symptom following acute COVID-19 frequently associated with lung damages. For the latter, we have already reported prevalence ranging between 16 to 30% (See 6.2). [8, 10, 11, 9-6]
- Cough is also frequently reported in the first three months after acute infection. Frequencies ranged from 10.9 to 34% in 6 studies.[6, 9, 10, 19, 26, 34] One study reported a frequence of 39% after 6 months. [33]
- Chest pain (or chest tightness) ranged from less than 10 to 88.5% in 4 studies conducted in the first 3 months.[6, 8, 9, 19] One study reported a low prevalence of chest pain beyond 12 weeks.[19]

- Functional measurements of lung damage were also performed. Alteration of lung diffusion capacity was described in two studies[23, 28] including patients who were initially hospitalised and one study reported functional alterations, mainly marked by obstructive patterns at spirometry assessment[10] (See Table 2 and Table 3).

Cardiovascular

Cardiovascular symptoms such as heart palpitations or tachycardia were mainly reported in the first 3 months after COVID-19. The reported frequency among long COVID patients varied widely from 6 to 86% in 5 studies.[6, 8, 9, 11, 13]

Gastroenterological

Gastroenterological conditions were reported in 7 studies performed in the first 3 months.[8-11, 13, 19, 26] The reported? symptomatology largely varied: diarrhoea, acid reflux, loss of appetite or nausea. Some studies did not elaborate on the type of symptoms[11, 26] or did not mention the frequency.[11]

Gastrointestinal symptoms varied between 5 and 85%. Moreno et al. reported diarrhoea in 5.3% of cases.[10] Nehme et al. reported a low frequency beyond one month and did not go into detail of symptoms.[26] In the survey of Davis et al.-preprint that included 50% of people < 60 years, a frequency of 85% was reported with diarrhoea as the most prevalent symptom in the first three months after acute infection.[13]

Neurological

- Cognitive disorders are some of the most common neurological symptoms (often referred to as 'brain fog'). They were reported in 5 studies in the first 3 months (3 cohort studies[10, 11, 19], 2 cross-sectional studies[9, 13]) and 3 studies with follow-up beyond 3 months (2 cohort studies[19, 28] and 1 cross-sectional one[13]). Symptoms are disabling and vary widely (memory disorders, concentration, executive functioning difficulties).[9-11, 13]

  In the first 3 months, reported frequencies were particularly heterogeneous ranging from 4 to 85%. The highest value came from the international survey of Davis et al.-preprint.[13]

  Beyond 3 months, frequencies ranged from 13 to 55%. Such cognitive problems were part of the three most frequent symptoms at 6 months in the survey of Davis et al.-preprint.[13]

- Olfactory and/or taste dysfunction are also very often identified among long COVID patients. Six studies (4 cohort studies[10, 11, 26, 34], 2 cross-sectional studies[9, 13]) reported the in 10.8% to 57.6% of patients in the first three months, whereas one cross-sectional study identified them in 10% (smell dysfunction) and 12% (taste dysfunction) of the cases.[35] Not all studies provide the crude values. A study reported a frequency at 20% between 6 and 8 months.[33]

- Other neurological symptoms include dizziness, tinnitus, visual disorders or peripheral neuropathy (See Table 3).

Mental health

Anxiety and mood disorders (depression) are the most commonly reported mental health symptoms (3 studies[13, 28, 34]). As mentioned previously, they were longitudinally studied in two retrospective cohorts (See 6.3). Post-traumatic stress disorder (PTSD) is also part of the reported problems and was reported in two studies, in which patients required intensive care or emergency services.[10, 28]

Table 3 – Frequency of symptoms among long COVID patients

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Symptoms frequency	Duration of follow-up (months)	Publication status
Cellai M[8], US	Telemedicine clinic program (regular phone calls) Confirmed infection (PCR)	Prospective cohort study n= 496	Persistent self-reported symptoms 6 weeks after onset of COVID-19	Ambulatory	• Respiratory symptoms (dyspnea, chest tightness) 88.5% • Fatigue 65% (17/26) • Headache 50% (13/26) • Gastrointestinal symptoms 34% (9/26) • Palpitations 23% (6/26) • Low grade fever 11% (3/26) • 69.2% (18/26) reported at least 4 concurrent symptoms	1-3 m	Published
Cirulli E[9], US	Participants to online survey in 2 projects Confirmed infection (PCR)	Cross-sectional survey n= 357	Self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms)	Hospitalised 2.5%	Most frequent: • Anosmia, ageusia, • Dyspnea, chest pain • Memory loss, confusion, difficulty concentrating Others: • Decreased alertness, dizziness • Headache, insomnia • Muscle weakness • Dry cough • Tachycardia • Bone or joint pain • Fatigue • Tingling, sensitive skin, back pain • Acid reflux, diarrhoea	1-3 m	Under review
Sudre C[11], UK, US and Sweden	Self-reporting in Covid Symptom Study App (start logging when still asymptomatic) Confirmed infection (PCR)	Prospective cohort study n= 4 182	Any self-reported symptom > 28 days after onset of COVID-19	Ambulatory	• Fatigue 97.7% • Headache 91.2% • Dyspnoea (?) • Anosmia (?) • Cardiac symptoms 6.1% • Lower respiratory symptoms (?) • Memory 4.1% • Tinnitus/earache 3.6% • Neuropathy 2%	1-3 m	Published

					• Fever (?) • Gastroenterological symptoms (?)		
Moreno-Perez O[10], Spain	Outpatient structured evaluation after hospital or emergency discharge Confirmed infection (PCR) or seroconverted	Prospective cohort study n= 277	Persistence of ≥ 1 symptom or abnormal spirometry or chest X-Ray at 10-14 weeks after onset of COVID-19	Hospitalised 66 % ICU 8.7%	• Dyspnea 17.2% • Cough 10.6% • Fatigue 17.6% • Anosmia-Dysgeusia 10.8% • Cognitive disorders 7.6% • Headache 8.9% • Myalgia, arthralgia 9.8% • Functinal finding: spirometry alterations 4.7%	1-3 m	Published
Goertz Y[6] and **Vaes A[7], The Netherlands and Belgium**	Persistent symptoms reported in social media in patients who experienced COVID-19 Confirmed: 16%[1] - 27%[2] [1] Goertz Y et al. [2] Vaes A et al.	Cross-sectional survey n=2 113[1] n=1 837[2]	Any symptoms > 3 weeks to 3 months after infection onset	Hospitalised 5%	Goertz et al.: • Fatigue 87% • Dyspnoea 71% • Chest tightness 44% • Headache 38% • Muscle pain 36% • Heart palpitation 32% • Cough 29% Vaes et al.: • Fatigue: 98% • Sleeping disorders 88% • Pain 87% • Increased need for care: - Care-dependent: 31% - Limitation in daily activities: 41.1% in the independent group	1-3 m	Published
Davis H[13], Europe and US	Persistent symptoms in people who experienced symptoms consistent with COVID-19, reported on a survey through social media and support groups	Cross-sectional survey n= 3 762	Persistent symptoms >28 days	Hospitalised 8.4%	**1-3 months (most frequent):** • Fatigue 98% • Post extertional malaise 89% • Cognitive dysfunction 85.1% • Headache 77% • Cardiovascular symptoms 86 % • Musculoskeletal symptoms 93.6% • Sore throat 59% • Respiratory symptoms 93% • Gastrointestinal symptoms (diarrhea, loss of appetite, abdominal pain) 85% • Anxiety 57.9% • Depression 47.3%	1-3 m 3-6 m	Under review

	Confirmed infection: 27%				• Taste and smell disorders 57.6% **At 6 months (most frequent):** • Fatigue 77.7% • Post extertional malaise 72.2% • Cognitive dysfunction 55.4% • Sensorimotor symptoms 55.7% • Headache 53.6% • Relapses of symptoms 85.9%		
Nehme M[26], Switzerland	Phone call 30-45 days after diagnosis (remote follow-up care system) Confirmed infection (PCR)	Prospective cohort study n= 669	Self-reported ongoing symptom 30-45 days from diagnosis	Hospitalised 6%	• Fatigue • Dyspnea • Taste/smell disorders • Cough • Headache Digestive symptoms	1-3 m	Published
Bliddal S[19], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Prospective cohort study n= 445	Persistent symptoms > 4 weeks and > 12 weeks	Ambulatory	<u>> 4 weeks</u>: • Fatigue 16% • Concentration or memory difficulties 13% • Reduced sense of smell 10% • Shortness of breath 10% • Headache < 10% • Muscle/joint pain <10% • Cough/chest pain <10% • Digestive symptoms <10% <u>> 12 weeks</u>: • Fatigue 16% • Concentration difficulties 13% • Headache < 10% • Muscle/joint pain <10% • Cough/chest pain <10% Digestive symptoms <10%	1-3 m 3-6 m	Under review
Stavem K[35], Norway	Population-based cross-sectional cohort survey n= 451 PCR confirmed infection	Identification of patients through PCR positivity and invitation to a postal survey or electronically	Persistent symptoms from 1.5 to 6 months after symptom onset	Ambulatory	• Dyspnea 16% • Smell disorders 12% • Taste disorders 10%	3-6 m	Published

Morin L[28], France	Telephone assessment 3-4 months after hospital discharge Ambulatory visit for a subset of patients with relevant symptoms	Prospective uncontrolled cohort study n= 478	Symptoms at 4 months after hospital discharge	Hospitalised	<u>Ambulatory assessment (n=177)</u>: • Cognitive disorders 38.4% (61/159) • Dysfunctional breathing 20.9% (37/177) • Chest CT scan: ○ 63% (108/171) lung abnormalities (ground glass opacities) ○ 19% (33/171) with fibrotic lesions • DLCO 87% of predicted values (n=152) • Altered heart left ventricular contractility 9.6% (8/83) • In ICU patients (n=94): anxiety (23.4%), depression (18.1%), PTSD (7.4%)	3-6 m	Published
Mandal S[34], UK	Phone or in-person interview of every patient after hospital discharge who had tested COVID-19 positive	Cross sectional study n= 384	Self-reported symptoms 4-6 weeks after discharge and biological, respiratory and mental assessment	Hospitalised	• Breathlessness: 74% (204/276) • Cough: 47.5% (131/276) • Fatigue: 96% (265/276)	1-3 m	Published
Menges G[33], Switzerland	Inclusion through contact tracing of the Department of Health, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	Prospective cohort study n= 431	Assessment of recovery and long-lasting symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS mMRC,DASS-21)	Hospitalised 19% ICU 2.3%	• Fatigue 49% (52/106) • Cough 39% (41/106) • Sore throat 36% (38/106) • Headache 35% (37/106) • Taste/smell disorders 20% (21/106)	> 6 m	Under review

Legend: DLCO: Diffusing capacity for carbon dioxide; ICU: Intensive care unit; PCR: Polymerase chain reaction; PTSD: post-traumatic stress disorder

6.5 Consequences on daily-life

Among the studies included in the review, seven studies showed that the burden of persisting symptoms has an impact on the quality of life, daily life activities or the return to work.[6, 7, 10, 12, 13, 28, 29]

- In the large national survey conducted by ONS, an evaluation of the impact of long COVID on daily-life activities has newly been added. It is estimated that 61% of patients with long COVID experienced at least some limitation to their daily-life activities and 17.9% reported important limitations.[12]
- Moreno-Perez et al. observed that the impact of COVID-19 on quality of life was significantly more frequent in patients with chronic symptoms compared to those without chronic symptoms (66.9% versus 43.2%).[10]
- In the cohort study of Morin et al. conducted in hospital discharged patients, authors found an alteration of the quality of life, evaluated through the 36-Item Short-Form Health Survey questionnaire. Many patients scored lower on several domains of quality of health.[28]
- In another large prospective cohort study that included patients who had been hospitalised, about one-third of those who had a professional occupation had not resumed work after 6 months.[29]
- Davis et al. reported that 45.2% of patients who experienced long COVID reduced their work schedule compared to pre-illness and 22.3% were not working at the time of the survey due to a bad health state (being on sickness- or disability leave, being fired, quitting or being unable to find a job). They showed that cognitive problems including memory disorders negatively impacted their daily life (making decisions, following conversations, remembering medications, driving, cooking, watching children,…).[13]
- In a survey conducted in Belgium and The Netherlands, authors reported limitations in daily activities or care-dependency in th ambulatory setting. The level of care dependency was assessed with the Care Dependency Scale tool. The need for assistance significantly increased after the infection (7.7% vs 52.4%) when compared with life before. Of importance, 41.1% of the patients who were not dependent after infection reported to be at least to a limited extent dependent on others in the performance of daily activities.[6, 7]

6.6 Risk factors for long COVID

6.6.1 Included studies

Among the studies included in the review, eleven cohort studies[9, 10, 11 , 14, 18, 19, 21, 29-32] aimed at measuring the association between potential risk factor and long COVID (or specific symptoms of long COVID) and are presented inTable 4.

Six cohort studies assessed the risk factors for long COVID per se[9-11, 19, 29, 30], while one cohort study was limited to the psychiatric symptoms of long COVID[14] and another cohort study focused on olfactory disorders.[21] Three cohort studies reported on the mortality, hospital/emergency admission or organ dysfunction following COVID-19.[18, 31, 32]

Eight studies reported adjusted odds ratio[9-11, 14, 19, 21, 30, 32] and two studies provided risk ratio or risk difference.[18] Symptoms were self-reported and collected either through a COVID app to monitor patients [11], an online survey [9, 21] or through a search in electronic medical records.[18, 31, 32] Two studies were based on medical visit follow-up.[10, 14] Two studies were still under review.[9, 19]

6.6.2 Risk factors

- Evidence regarding risk factors for long COVID is very sparse and studies that aimed at determining them are limited and considerably heterogeneous. Results are presented in Table 4. Moreover, there is no study with large follow-up, yet.
    - In the update of April 2021, the survey from UK ONS found that a higher percentage of female (23.0%) than male (18.7%) participants reported symptoms that persisted for at least 5 weeks.[12] However, there was a degree of uncertainty over this finding (wide confidence

intervals). Two studies showed that males were less likely to experience long-term symptoms[30, 33] and, similarly, two others found that the female gender was associated with long COVID.[19, 29] The female gender is also associated with the likelihood of mental health issues and persistent smell/taste disorders (See below).[14, 21] Finally, regarding the risk for new clinical conditions 4 months after acute infection, a large retrospective study in the US showed that excess of risk rarely differed according to gender (anosmia, fatigue were commonly diagnosed in women whereas myocarditis, hypercoagulability, deep vein thrombosis, kidney injury, sleep apnea were more commonly diagnosed in men).[31]

- Obesity may be associated with the likelihood of long COVID according to one study under review.[19] Another study showed an association between BMI and dyspnoea still present at 6-8 months.[33]
- Another pre-print article identified that patients with long COVID were more likely to have blood type A.[9]
- Long COVID patients are also more likely to have experienced a higher number of symptoms in the acute phase of the COVID, according to three studies.[9, 11, 30] The presence of symptoms such as fatigue, headache, dyspnoea, pain with a deep breath, sensitive skin, hoarse voice and myalgia (viral symptoms) in the acute phase of the disease were recognised as risk factors for developing long COVID, in two studies.[9, 11] One of those found that three variables - number of symptoms in the first week, age and sex - allowed to distinguish individuals with long COVID from those with short duration in a sample of patients from three countries (AUC 77%).[11] One study showed an association between long COVID and the severity of symptoms during infection.[33] Conversely, Moreno-Perez et al. found, in the adjusted analysis, that baseline characteristics (age, sex, comorbidities) and severity of initial infection did not behave as predictor factors. In their analysis, clinical signs of severity (based on chest X-ray and heart rate) at the initial visit to the emergency department were predictive of long COVID, in those presenting with severe pneumonia.[10] Another study showed that patients who presented symptoms such as thoracic pain, persistent fever or pneumonia were more likely to undergo hospital or emergency service admission.[32]
- A lower baseline level of SARS-CoV-2 immunoglobulins (several months after acute infection) was associated with persistent symptoms in one study.[30]
- One study showed that patients who developed long COVID tended to be older.[11] However, age remains somewhat controversial regarding long-term symptoms. Ayoubkhani et al. compared a large cohort of individuals discharged from hospital after COVID-19 with matched control subjects (electronic health records from the general population). The rate ratio for mortality, hospital readmission and organ dysfunctions were greater in patients less than 70 compared to those 70 or older.[18] Daugherty et al. showed that the risk for new-onset clinical issues increased with age and pre-existing comorbidities but younger patients and those without comorbidities had also an increased risk of developing new clinical sequelae, in comparison to control groups.[31] The April Update from UK ONS showed that people aged 35 to 49 years have the greatest prevalence of symptoms at 5 weeks followed by those aged 50 to 69 years and 25 to 34 years.

- One cohort study on the psychiatric symptoms of long COVID found that female patients or those with a previous psychiatric history were more likely to present psychiatric symptoms one month after hospitalisation or an emergency department visit for COVID-19.[14]
- The cohort study on the olfactory dysfunction evidenced, after adjustment for confounding factors, that female sex and presence of parosmia were associated with unresolved smell loss at 4 weeks of follow-up.[21]

Table 4 – Results on risk factors for long COVID in the selected studies

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
Sudre C[11], UK, US, Sweden	Inclusion by prospective self-reporting of symptoms in the COVID Symptom Study App (start logging when still asymptomatic)	Any symptom >28 days after onset, self-reported	Adjusted analysis (age and sex), compared to "short" (<10 days) COVID, symptoms during first week of COVID (aOR ratio; 95CI): • Fatigue 2.83 (2.09-3.83) • Headache 2.62 (2.04-3.37) • Dyspnoea 2.36 (1.91-2.91) • Hoarse voice 2.33 (1.88-2.90) • Myalgia 2.22 (1.8-2.73)	Main predictors: age, sex, symptoms in 1st week (AUC 76.8%). In 70+ years (aOR ratio; 95CI): Fever 5.51 (1.75-17.36) Loss of smell 7.35 (1.58-34.22) Hoarse voice 4.03 (1.21-13.42) and comorbidities
Cirulli E[9], US	Participants to online survey in 2 projects, with positive COVID test	Any self-reported short and long-term symptom at 30, 60, 90 days from onset (list of 32 symptoms)	Adjusted analysis at day 30 (aOR ratio; 95CI): • Number of initial symptoms • Dyspnoea • Pain with deep breath • Sensitive skin • Blood type A No risk factor at 60 and 90 days (in multivariate)	Comorbidities and sex were risk factors in the unadjusted analysis, not in the multivariate analysis, probably due to low sample size

Moreno-Perez O[10], Spain	Outpatients structured evaluation after hospital or ED discharge in patients with confirmed infection	Persistence of ≥1 symptom or abnormal spirometry or chest X-ray at 10-14 weeks after onset	Adjusted analysis, (aOR ratio; 95CI):
			• For long COVID (overall): no significant risk factor
			• For those with initial severe pneumonia:
			  ○ opacities of lung surface on X-rays >50% 2.87 (1.13-7.32)
			  ○ higher heart rate at admission 1.03 (1.01-1.06)
				Predictors of spirometry abnormalities in overall cohort: estimated glomerular filtrate, male sex, comorbidities (high Charlson index associated with lower incidence)
				
				Higher imaging score at acute disease was associated with persistence of X-ray signs in overall cohort aOR (95CI): 1.66 (1.30-2.11) and severe

				pneumonia patients 1.68 (1.28,2.19)
Mazza M[14], Italy	COVID-19 patients assessed at ED and hospitalised or not; no information on testing	Mental health assessment at one month after hospital or ED discharge	Adjusted analysis (sex, previous status and hospitalisation): • Female sex • Previous psychiatric history	Older age and long duration of hospitalisation were risk factors in the unadjusted analysis Hospitalisation was not a risk factor
Bliddal S[19], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Persistent symptoms > 4 weeks and > 12 weeks	Adjusted analysis (sex, age, smoking, BMI, comorbidity and time from symptom start to follow-up) for the risk of symptoms after 4 weeks (aOR ratio; 95CI): • Female sex 2.91 (1.32-6.39) • BMI 1.13 (1.05-1.22)	In a subgroup of 117 women with follow-up > 4 weeks, BMI is a risk factor aOR 1.10 (1.0-1.20) Being healthcare worker was not a risk factor 1.50 (0.60-3.8)
Ayoubkhani D[18], UK	Identification through electronic health and mortality records (ICD10 codes: U07.1 and U07.2)	Assessment of mortality, hospital readmission, organ dysfunctions > 3 months after hospital discharge	• In COVID-19 patients, rates of all outcomes were greater in 70+ patients than in those aged less than 70. • In COVID-19 patients, rates of all outcomes other than diabetes were greater in the white ethnic group than in the non-white group. • After matching for baseline personal characteristics (age, sex, ethnicity, region, IMD category, and smoking status) and comorbidities, rate ratio were greater in patients less than 70 than those 70+ and in non-white ethnicity, for all outcomes.	Greater rates of death and hospital readmission in patients admitted to ICU
Daugherty S[31], US	Identification through electronic health from three data sources within the UnitedHealth Group Clinical Discovery Database (ICD10 codes: U07.1, U07.2, B34.2, B97.29)	Assessment of risk and relative hazards for developing clinical sequelae requiring medical care after COVID-19 in 18-65 years patients, at 4 months after acute infection	• Risk differences were increased in older individuals, had pre-existing conditions, and were admitted to hospital because of Covid-19. • Younger patients (aged ≤50), those with no pre-existing conditions, or not admitted to hospital for covid-19 also had an increased	Risk for new clinical sequelae after acute covid-19 rarely differed between men and women, apart from fatigue and anosmia (more commonly diagnosed in women)

			risk of developing new clinical sequelae, in comparison to control groups-	
Makaronidis J[21], UK	Invitation of people with acute loss of smell/taste through primary care centers (recruitment via online platform). Serology assessment.	Smell/taste disorders at 4-6 weeks after onset	Adjusted analysis (age, ethnicity, patterns of smell loss and smoking) for the risk of persistent smell loss (aOR; 95CI): • Female sex 2.46 (1.47-4.13) • Presence of parosmia 2.47 (1.54-4.00)	Age was not recognised as a risk factor 0.99 (1.01-1.03)
Ghosn J[29], France	Patients who were hospitalised were assessed through physician visits 3 and 6 months after hospital admission.	Ongoing self-reported symptoms within a list of 10 symptoms at 3 and 6 months after hospital admission	Adjusted analysis for the risk of having 3 or more symptoms at 6 months follow-up (aOR; 95CI): • Female sex 2.40 (1.75-3.30) • ≥ 3 symptoms at admission 2.04 (1.45-2.89) • ICU admission at the acute phase 1.55 (1.09-2.18)	Comorbidities and age were not associated with the presence of symptoms at 6 months in univariate analysis
Romero-Duarte A[32], Spain	Data retrieved from follow-up consultation (primary care and hospital specialities) and periodic telephonic reports	Self-reported symptoms at any time after hospital discharge at any time during 6 months follow-up, hospital readmission, return to the emergency services and death	Adjusted analysis for return to emergency services (aOR, 95CI): • Persistent fever 2.23 (1.18-4.19) • Thoracic pain 2.55 (1.33-4.90) • Anosmia/dysgueusia 0.28 (0.10-0.74) • Arrhythmia or palpitations 3.08 (1.21-7.79) • Superinfection 1.90 (1.05-3.42) • Pneumonia 7.65 (1.27-45.97) • Dermatological symptoms 1.75 (1.01-3.03) Adjusted analysis for hospital readmission: • Persistent fever 8.31 (2.31-29.89) • Nephrological disorders 6.49 (1.50-21.14) • Superinfection 3.14 (1.05-9.40) • Pneumonia 11.81 (1.40-99.39)	
Augustin M[30], Germany	Follow-up medical visits at month 4 and 7 months after acute infection (PCR confirmed), regardless of symptoms	Assessment of long-lasting symptoms with systematic questionnaires	Adjusted analysis for the risk to develop long-term symptoms (aOR, 95CI)*: • Lower baseline level of SARS-CoV-2 IgG 1.90 (1.13-3.18) • Number of symptoms 1.29 (1.08-1.55) • Male gender 0.59 (0.36-0.98)	

			*We observed a difference between odds ratio mentioned in the text and the tables. We are awaiting author's reply.	
Menges G[33], Switzerland	Inclusion through contact tracing of the Department of Health, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	Assessment of recovery and long-lasting symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS mMRC,DASS-21)	<u>Adjusted analysis for not having recovered at 6 to 8 months (aOR, 95CI)</u>: • Severe symptoms during acute illness 2.05 (1.27-3.34) • Comorbidities 2.08 (1.24-3.50) • Male gender 0.53 (0.33-0.85) <u>Adjusted analysis for fatigue at 6 to 8 months (aOR, 95CI)</u>: • Age group: 18-35 ref; 40-64 0.59 (0.39-0.91); ≥ 65 0.41 (0.21-0.78) <u>Adjusted analysis for dyspnea at 6 to 8 months (aOR, 95CI)</u>: • Male gender 0.45 (0.26-0.76) • Hospitalisation 4.17 (2.23-7.91) • BMI 1.14 (1.08-1.20) • Comorbidities 2.71 (1.38-5.36)	No evidence for an association of depression with age, sex, initial hospitalisation, severity of symptoms at diagnosis, or the presence of comorbidities

Legend: aOR: adjusted odds ratio; AUC: area under the curve; BMI: Body mass index; 95CI: 95% confidence interval; DASS-21: Depression Anxiety and Stress Scale 21;ED: emergency department; FAS: Fatigue Assessment Score; ICU: Intensive care unit; mMRC modified medical research Council; OR: odds ratio

7 DISCUSSION

7.1 Main findings

The current body of evidence about the epidemiology of long COVID is still limited. There is a huge variation of the reported prevalence and no data robust enough is available to determine patients at risk for developing long COVID. The largest and more robust study up to now is the survey from UK ONS that allows to conclude that at least 13.7% continue to report symptoms after 12 weeks.

Our results are in line with a recent review from the UK National Institute for Health Research (NIHR) that outlined the high variability in reported prevalence and the absence of reliable evidence for risk factors.[36]

Since our previous preliminary report published in January 2021, results have changed in the light of newly published evidence. For patients who were not hospitalised during acute COVID-19, long COVID prevalences slightly increased for both periods ranging from 1 to 3 months and beyond. In the first prelimlinary report, the range of long COVID prevalence up to 3 months was 5 to 36% and remained at the level. Similarly, prevalences rates beyond 3 months ranged from 2 to 15% and ranges now from 2 to 21%. Likewise, we noticed that prevalences are higher in patients who were initially hospitalised and could still reach 68% beyond 3 months. New studies with longer follow-up durations are now available and report that prevalence is still above 10% and up to 25%.The most frequently reported symptoms did not substantially change. Finally, new studies on the potential risk factors have been published.

7.2 Limitations of available evidence

The included studies suffer from several shortcomings:

- First, the definition of long COVID is still heterogeneous and this can give rise to difficulties when trying to synthesise information:
    - There is currently emerging evidence that long COVID encompasses distinct phenotypes (or clusters of symptoms) that can overlap and evolve over time.[11, 12] For instance, people can experience exclusively cognitive disorders, while others will present only respiratory symptoms. However, it should be noted that studies widely report on symptoms that are considered regardless of their phenotype or whether they are related to distinct causes and permanent organ damage.
    - People may indeed experience symptoms possibly related to organ damage (cf: preliminary report on pathophysiology-May 2021). For instance, pulmonary sequelae can arise after prolonged mechanical ventilation in critically-ill patients. This gives rise to many difficulties in accurate diagnosis. Current evidence does not clearly allow to distinguish between the symptoms following organ damage from those unrelated to organ damage. Both types of symptoms are included in studies regardless if this distinction.

      Moreover, determining the extent to which symptoms are specifically related to COVID-19 remains challenging. According to the available evidence, the distinction between patients who suffered from organ damage because of interventions at the hospital (or a worsening of prexisting comorbidities) and another causes cannot be made. This overlap contributes to the observed heterogeneity and illustrates that long COVID relates to several conditions.

      Hence, the higher prevalence of symptoms observed in patients who were hospitalised could potentially be related to higher likelihood to develop organ impairment when the disease is severe. This emphasises the fact that this particular subset of patients with long-lasting symptoms may represent a different phenotype of the long COVID entity. In this way, the entity of long COVID can partially overlap with other issues such as post-intensive care syndrome, for instance.

      Other studies that were not selected in our systematic review observed a similar trend. For instance, a short survey conducted in the UK by the NIHR reported this difference according to the hospitalisation status (it was not included in the review because results were not decscribed in detail).[36] Nearly a third of those who were not hospitalised experienced at least one enduring symptoms at one month and still 10% after three months. For those who were admitted to the hospital, between 50 and 89% had at least one remaining symptom after two

months.[36] Similarly, a study conducted in China, that was excluded from our analysis for country exclusion, showed that 76% of discharged patients reported at least one symptom at 6-month follow-up.[37] Another study, also excluded from our analysis for limited sample size, identified a high proportion (51.6%) of respiratory damages (diffusion capacity) after hospital discharge.[38]

- The severity of persistent symptoms following COVID-19 may also differ. The study from Ayoukhani et al., for example, emphasised that hospital discharged patients had an increased risk of multi-organ dysfunctions.[18] Daugherty et al. retrospectively showed in a cohort of patients who were predominantly not hospitalised that the risk for new clinical problems requiring medical care was also high in this group.[31]

  Conversely, another recent nationwide cohort study in Denmark estimated that the risk of severe complications was low in COVID-19 who did not require hospital admission. By comparing with non-COVID-19 matched subjects, the authors showed that the risk of receiving one of 25 selected new hospital diagnoses within 6 months after infection, or the risk of initiating a new drug therapy was low. Only the risk of venous thromboembolism, receiving a hospital diagnosis of dyspnoea, initiating new drugs (bronchodilator therapy or triptans) were slightly increased. It may be noted that this study mainly focused on patients who did not experience severe COVID-19 and that the prevalence could be underestimated since they reported on symptoms that led to hospital encounter.[39]

- The question of knowing whether and to what extent all reported symptoms are excess symptoms in comparison with other infectious diseases, could also be addressed. Similar multi-organ long-term consequences have been reported after other types of coronaviruses or other viral or bacterial infections.[40, 41] Nevertheless, those symptoms were not so precisely and longitudinally assessed as for long COVID, and no clear conclusion can be drawn, up to now.

- In the same line, it is vey difficult to ascertain that symptoms are typical for long COVID or if they would have occurred anyway. Similarly, for health conditions already existing before COVID-19 (e.g.mental health disorders), there is no possibility to distinguish a relapse that would have occurred independently of the infection or really a specific long COVID symptom. In the same vein, symptoms pre-existing before COVID-19 are not mentioned in studies. The However, the UK-ONS survey included a control group of people with the same age and sex profile as those tested positive for SARS-Cov-2, but who were unlikely to have been infected. Reported symptoms were significantly height fold lower in the control group (prevalence of symptoms at 5 weeks at 2.8% and 1.7% at 12 weeks).

- Second, there are also variations across the studies regarding the targeted patient populations:
  - Study populations were markedly differed in terms of severity of the level of care at the acute phase and hospitalisation. Our analyse retrieved studies with a high proportion of hospitalisation (including ICU admission) along with studies with less than 10% hospitalisation or exclusively ambulatory patients. Moreover study populations included COVID-19 confirmed (PCR, antibodies) cases as well as non-confirmed cases (highly suspected clinically and/or radiologically; self-reported). Reporting a general prevalence is not reliable enough with such a high heterogeneity.
  - Moreover, demographic variables, health conditions and risk factors for long COVID also vary among studies. The ONS-update of April 2021 identified that prevalence was greatest among people aged 35 to 69 years, females, and those with a pre-existing activity-limiting health condition.[12] We noticed, in this review, that people who were hospitalised were likely to be older probably because older patients were more severely ill. Evidence on the female gender as a risk factor seems still limited and the impact of chronic comorbidities is poorly considered across studies.
  - Sample sizes, time of inclusion and follow-up duration of studies vary widely. Although we only selected studies with a sample size of at least 250 COVID-19 cases, the studies included for risk factors report a lack of power for multivariate analysis and state that the lack of significance should not be taken for a lack of association. It should also be noted that follow-up is more precise for hospital discharged patients since some studies proposed multidisciplinary follow-up clinics.

- Variability of time of inclusion (after infection confirmation, after onset of symptoms, after hospital discharge), follow-up duration and important loss to follow-up are hurdles to correctly estimate long COVID prevalence.
- Studies are prone to several bias. Most studies are based on self-reported symptoms and this may lead to recall biases and cause misclassification. The use of a COVID app and an online survey to recruit patients may also result in a selection bias. One study, for instance, reported an under-representation of male and elderly patients.[11] Besides, those with more severe illness might have been less likely to enter data in the app, and this may result in an underestimation of the prevalence.[11] However, it is also likely that those experiencing persistent symptoms will be more likely to participate in studies. Conversely, some studies organised a structured assessement through medical visits and through the use of appropriate and objective measurements tools. Overall, those studies mainly included emergency or hospital-discharged patients.[10, 23, 28]

  Recruitment bias was observed in studies that assessed the olfactory disorders in which only those who reported smell or taste disorders were followed-up. It is likely that prevalence was overrated.

  Furthermore, the lack of control group in many studies can lead to an overestimation of prevalence.
- Due to the nascent nature of COVID-19, physicians might have underestimated and overlooked the long COVID symptoms early in the pandemic. Moreover, testing was not available at the beginning of the pandemic making difficult to associate the complaint of non-tested patients with COVID-19. Besides, since testing is often required in studies and was initially limited to hospitalised people, this can account for a selection bias for the patients infected during the first wave of the pandemic.
- Few studies report on patients who remained without symptom at the acute phase. This is a limitation and may also bias the estimation of prevalence.

7.3 Limitations of this review

This review has several limitations:

- First, due to our strict selection criteria and our distinction between prevalence of long COVID (or symptom) and symptom frequency, our conclusions may differ from other reviews that include studies from any setting, with a lower sample size, and which report risk factors identified in non-adjusted analyses as well, or studies not comparing long COVID to short COVID.
- Second, seeing the urgent need for identifying evidence, critical appraisal was not undertaken in this review and articles still under reviewing were included. The appraisal of the quality of evidence will be performed in the final version.
- Third, interpretation of results is limited by our inclusion criteria since we include only studies from Europe and US. Risk factors and comorbidities can considerably vary also within the countries that we selected.
- Data on unemployment, sick-leave or disability leave (See Consequences on daily-life) may considerably be influenced by the laws of each country and will have to be interpreted with great caution.
- We did not analyse whether our conclusion varied from the conclusions of studies with smaller sample sizes.

Limitations for the assessment of long COVID prevalence and risk factors

- **Variability in the definition of long COVID across studies:**
  - **Symptom pattern variability**
  - **Permanent organ damage as sequelae of the acute phase, or not**
  - **Severity of persistent symptoms and requirement for hospital admission**
  - **Difficulty in knowing to what extent long COVID symptoms are excess symptoms**
  - **Difficulty in accurate diagnosis (prexisting symptoms and role of comorbidities)**
- **Heterogeneity of targeted populations:**
  - **Severity and level of care of acute infection (ambulatory, hospitalisation, need for ICU admission)**
  - **Characteristics and risk factors of studied populations**
  - **Sample sizes variability**
- **Variability of study design: time of inclusion and follow-up duration and large loss to follow-up**
- **High risk of recall bias (self-reporting; no objective measurement) and lack of control group in most studies**
- **Underestimation in people who were infected during the first wave of pandemic and were not tested**
- **Few data on long COVID is available in patients who had asymptomatic infection**

7.4 Perspectives

- More research is needed on the characterisation and classification of long COVID symptoms. To this end, a distinction would have to be made between long COVID symptoms and post-COVID conditions that refers for the most part to symptoms related to organ damage (and post-intensive care syndrome) and not necessarily specific to COVID-19. This would allow a better definition and characterization of subgroups. Adequately defining long COVID would guide more efficiently the future research on treatments and the management.
- Since there is now evidence that long COVID symptoms fluctuate over time, further studies should always promote assessments at different time points.
- In order to minimise recall bias, newly conducted studies should assess symptoms during medical visits and by using appropriate and validated tools such as spirometry, cardiac echography or validated measurement scales. This approach could probably reduce the hetereogeneity of reported prevalences. Since long COVID symptoms might overlap with other issues and seeing that it is not uncommon to present long-lasting symptoms after some infections, a control population should be included in the experimental design.
- Determining long COVID prevalences within each level of severity would harmonise the results.
- Research on the underlying causes of long COVID would certainly help to better classify complaints and provide new insights on how to prevent and manage it.
- Looking ahead, more research is needed on the effect of vaccination on long COVID evolution.

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APPENDICES

APPENDIX 1. SEARCH STRATEGY

Appendix 1.1. Research question and PEO

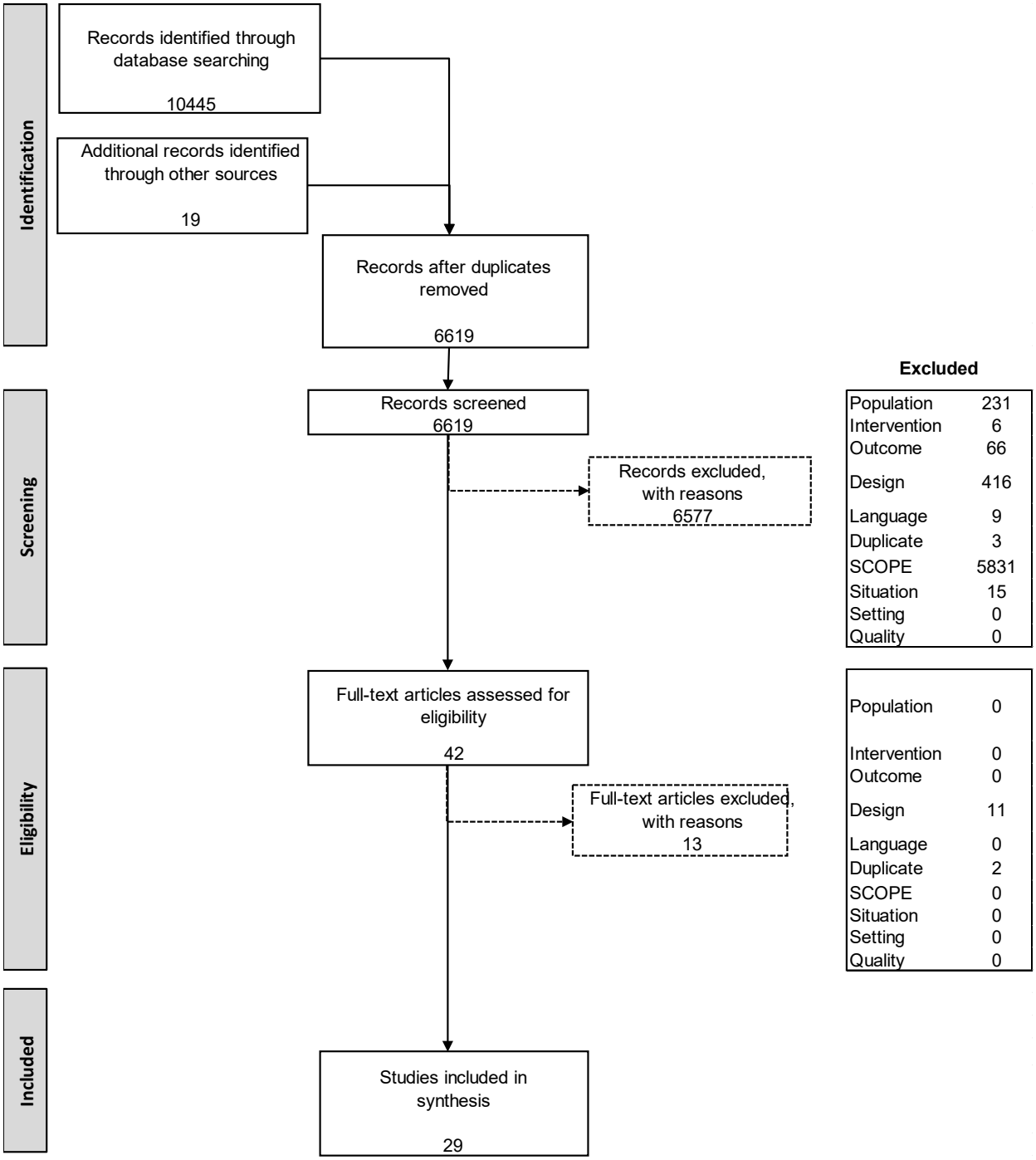
Project number	2020-04 HSR
Project name	Long COVID
Research question	Which putative pathophysiological mechanisms are likely to be involved in long COVID symptoms? Which pathophysiological mechanisms have been demonstrated in patients?
Structured search question(s)	
P (population)	chronic covid syndrome (CCS) chronic post-COVID-19 symptoms Chronicity AND COVID continuing complication COVID-19 survivors linger Long term cardiopulmonary Long term complications of COVID-19 long term effects of COVID-19 Long term glucometabolic long term neuropsychiatric long term symptoms of COVID-19 long-COVID long coronavirus long-haulers in COVID-19 long-lasting COVID symptoms long-SARS long-term consequences of COVID-19 long-term health consequences of COVID-19 Long-Term Sequelae of COVID-19 long tail COVID persistant COVID Post-COVID-19 syndrome post- corona post corono post-viral fatigue post discharge prolonged inflammatory status recurring COVID Coronavirus Infections* / complications
E (exposure)	COVID-19 confirmed (PCR, antibodies),or not
O (outcome)	Pathophysiological mechanisms likely to explain long COVID symptoms

Appendix 1.2. List of sources searched for studies

Source (Interface)	Set	Date of the search	Limits
Cochrane Database of Systematic Reviews		2021-02-03	none
JBI EBP Database	Current to January 13, 2021*	2021-02-03	none
MEDLINE (OVID)	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 01, 2021>	2021-02-03	none
Embase (Embase.com)		2021-02-04	none
PsycInfo (OVID)	2002 to January Week 4 2021	2021-02-03	none
Econlit (OVID)	1886 to January 21,2021	2021-02-03	none
Ovid Nursing	1946 to January Week 4 2021	2021-02-03	none
scilit.net/		2021-02-04	none
europepmc.org/		2021-02-04	none
Journals@Ovid Full Text	February 01, 2021	2021-02-03	none
coronacentral.ai/	longhaul	2021-02-24	none

* *Edition Jan 13, 2021*

Appendix 1.3. Flow diagram



APPENDIX 2. DETAILS OF SEARCH STRATEGY IN EACH SOURCE

Appendix 2.1. Cochrane Database of Systematic Reviews

Date	03/02/2021
Database	Cochrane Database of Systematic Reviews Issue 2 of 12, February 2021
Strategy	388 Cochrane Reviews matching covid* in All Text OR sars-cov* in All Text OR ncov* in All Text OR "coronavirus disease 2019" in All Text OR "severe acute respiratory syndrome coronavirus 2" in All Text - (Word variations have been searched)

Appendix 2.2. JBI EBP Database

Date	03/02/2021
Database	JBI EBP Database - <Current to January 13, 2021> (OVID)
Strategy	1 covid*.mp. (71) 2 sars-cov*.mp. (5) 3 ncov*.mp. (2) 4 "coronavirus disease 2019".mp. (4) 5 "severe acute respiratory syndrome coronavirus 2".mp. (3) 6 1 or 2 or 3 or 4 or 5 (72) 7 chronic*.mp. (2569) 8 complicat*.mp. (1824) 9 continu*.mp. (2616) 10 linger*.mp. (15) 11 long*.mp. (3160) 12 ongoing.mp. (745) 13 persist*.mp. (738) 14 post*.mp. (3172) 15 prolong*.mp. (687) 16 recurr*.mp. (619) 17 sequel*.mp. (146) 18 surviv*.mp. (942) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (6057) 20 6 and 19 (66)

Appendix 2.3. Medline

Date	03/02/2021
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 01, 2021>
Strategy	1 covid*.mp. (97304) 2 sars-cov*.mp. (41886) 3 ncov*.mp. (1693) 4 "coronavirus disease 2019".mp. (18515) 5 "severe acute respiratory syndrome coronavirus 2".mp. (39642) 6 1 or 2 or 3 or 4 or 5 (103558) 7 chronic*.mp. (1444607) 8 complicat*.mp. (3277182) 9 continu*.mp. (1141060) 10 linger*.mp. (2809) 11 long*.mp. (2360519) 12 ongoing.mp. (169115) 13 persist*.mp. (496696) 14 post*.mp. (2967850)

	15 prolong*.mp. (391871) 16 recurr*.mp. (730089) 17 sequel*.mp. (79502) 18 surviv*.mp. (1492823) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (10257634) 20 6 and 19 (35486) 23 ((covid* or sars-cov* or ncov* or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2") adj2 (chronic* or complicat* or continu* or linger* or long* or ongoing or persist* or post* or prolong* or recurr* or sequel* or surviv*)).mp. (4008)

Appendix 2.4. Embase

Date	04/02/2021
Database	Embase (Embase.com)
Strategy	#23. (covid* OR 'sars cov*' OR ncov* OR 'coronavirus disease 2019' OR 'severe acute respiratory syndrome coronavirus 2') NEAR/2 (chronic* OR complicat* OR continu* OR linger* OR long* OR ongoing OR persist* OR post* OR prolong* OR recurr* OR sequel* OR surviv*) 3,610 5 Feb 2021 #19. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 13,426,644 5 Feb 2021 #18. surviv* 2,044,038 5 Feb 2021 #17. sequel* 105,703 5 Feb 2021 #16. recurr* 1,094,799 5 Feb 2021 #15. prolong* 546,789 5 Feb 2021 #14. post* 4,472,700 5 Feb 2021 #13. persist* 678,567 5 Feb 2021 #12. ongoing 310,519 5 Feb 2021 #11. long* 3,382,297 5 Feb 2021 #10. linger* 3,759 5 Feb 2021 #9. continu* 1,544,748 5 Feb 2021 #8. complicat* 3,406,441 5 Feb 2021 #7. chronic* 2,111,426 5 Feb 2021 #6. #1 OR #2 OR #3 OR #4 OR #5 108,451 5 Feb 2021 #5. 'severe acute respiratory syndrome coronavirus 2' 26,313 5 Feb 2021 #4. 'coronavirus disease 2019' 84,404 5 Feb 2021 #3. ncov* 1,746 5 Feb 2021 #2. 'sars cov*' 33,477 5 Feb 2021 #1. covid*

Appendix 2.5. PsycInfo

Date	03/02/2021
Database	APA PsycInfo (OVID) <2002 to January Week 4 2021>
Strategy	1 covid*.mp. (3448) 2 sars-cov*.mp. (424) 3 ncov*.mp. (30) 4 "coronavirus disease 2019".mp. (375) 5 "severe acute respiratory syndrome coronavirus 2".mp. (80) 6 1 or 2 or 3 or 4 or 5 (3493) 7 chronic*.mp. (122042) 8 complicat*.mp. (39731) 9 continu*.mp. (200140) 10 linger*.mp. (1566)

	11 long*.mp. (362201) 12 ongoing.mp. (46047) 13 persist*.mp. (66335) 14 post*.mp. (331214) 15 prolong*.mp. (23205) 16 recurr*.mp. (29631) 17 sequel*.mp. (8593) 18 surviv*.mp. (70040) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (1006943) 20 6 and 19 (1487) 22 ((covid* or sars-cov* or ncov* or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2") adj3 (chronic* or complicat* or continu* or linger* or long* or ongoing or persist* or post* or prolong* or recurr* or sequel* or surviv*)).mp. (216)

Appendix 2.6. EconLit

Date	03/02/2021
Database	Econlit <1886 to January 21,2021> (OVID)
Strategy	1 covid*.mp. (1190) 2 sars-cov*.mp. (35) 3 ncov*.mp. (7) 4 "coronavirus disease 2019".mp. (13) 5 "severe acute respiratory syndrome coronavirus 2".mp. (2) 6 1 or 2 or 3 or 4 or 5 (1208) 7 chronic*.mp. (3250) 8 complicat*.mp. (5581) 9 continu*.mp. (46703) 10 linger*.mp. (311) 11 long*.mp. (137530) 12 ongoing.mp. (7085) 13 persist*.mp. (26176) 14 post*.mp. (64415) 15 prolong*.mp. (1966) 16 recurr*.mp. (2551) 17 sequel*.mp. (203) 18 surviv*.mp. (13009) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (271942) 20 6 and 19 (388) 21 ((covid* or sars-cov* or ncov* or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2") adj5 (chronic* or complicat* or continu* or linger* or long* or ongoing or persist* or post* or prolong* or recurr* or sequel* or surviv*)).mp. (79)

Appendix 2.7. Ovid Nursing Database

Date	03/02/2021
Database	Ovid Nursing Database <1946 to January Week 4 2021>
Strategy	1 covid*.mp. (3574) 2 sars-cov*.mp. (1683) 3 ncov*.mp. (18) 4 "coronavirus disease 2019".mp. (490) 5 "severe acute respiratory syndrome coronavirus 2".mp. (192) 6 1 or 2 or 3 or 4 or 5 (3702) 7 chronic*.mp. (61219) 8 complicat*.mp. (106625) 9 continu*.mp. (80457)

	10 linger*.mp. (208) 11 long*.mp. (77301) 12 ongoing.mp. (10190) 13 persist*.mp. (12631) 14 post*.mp. (117838) 15 prolong*.mp. (10585) 16 recurr*.mp. (14127) 17 sequel*.mp. (3144) 18 surviv*.mp. (27822) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (386772) 20 6 and 19 (995) 22 ((covid* or sars-cov* or ncov* or "coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2") adj3 (chronic* or complicat* or continu* or linger* or long* or ongoing or persist* or post* or prolong* or recurr* or sequel* or surviv*)).mp. (176)

Appendix 2.8. SciLit

Date	04/02/2021
Database	https://www.scilit.net/
Strategy	Long covid (all fields, lim preprint) (2416)

Appendix 2.9. EuropePMC

Date	04/02/2021
Database	europepmc.org/
Strategy	1 ("long covid") AND (SRC:"PPR") (91) 2 ("long-term covid") AND (SRC:"PPR") (41) 3 ("post covid") AND (SRC:"PPR") (750)

Appendix 2.10. Journals@OVID

Date	03/02/2021
Database	Journals@Ovid Full Text <February 01, 2021>
Strategy	1 covid*.mp. (42367) 2 sars-cov*.mp. (14758) 3 ncov*.mp. (1329) 4 "coronavirus disease 2019".mp. (10761) 5 "severe acute respiratory syndrome coronavirus 2".mp. (6991) 6 1 or 2 or 3 or 4 or 5 (45309) 7 chronic*.mp. (1597003) 8 complicat*.mp. (1559894) 9 continu*.mp. (2717400) 10 linger*.mp. (17981) 11 long*.mp. (3398881) 12 ongoing.mp. (637263) 13 persist*.mp. (1008457) 14 post*.mp. (3285408) 15 prolong*.mp. (785079) 16 recurr*.mp. (846402) 17 sequel*.mp. (159911) 18 surviv*.mp. (1431049) 19 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (6330977) 20 6 and 19 (36718) 25 (long adj2 covid*).mp. (314)

Appendix 2.11. CoronaCentral

Date	24/02/2021
Database	https://coronacentral.ai/longhaul
Strategy	“Filter” Long Haul (201)

Colophon

Title:	Epidemiology of Long COVID: a preliminary report
Authors:	Diego Castanares-Zapatero, Patrice Chalon, Koen Van den Heede
Reviewers:	Brecht Devleesschauwer (Sciensano), Jean Yombi (UCLouvain), Nathalie Lorent (UZ Leuven), Karin Rondia (KCE), Rik Gosselink (UZ Leuven) Sarah Wolf (Austrian Institute for Health Technology Assessment)
At the request of:	LUSS (Ligue des Usagers des services de santé)
Disclaimer:	This document is a rapid review of scientific literature retrieved from several publicly funded COVID-19 resource collections. The literature included in these repositories is not always peer-reviewed or externally validated. KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. This work is used to inform guidance of other governmental agencies (like Sciensano, CSS/HGR, AFMPS/FAGG and SPF/FOD).
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