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COVID 19 – KCE CONTRIBUTIONS

EPIDEMIOLOGY OF LONG COVID: A PRAGMATIC REVIEW OF THE LITERATURE

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The current work is a pragmatic review based on the available evidence at this moment (27/01/2021). KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. 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 A part of the available literature is not peer-reviewed and hence not necessarily conform with the high quality standards for scientific research. This document should be considered as a working paper that will be updated as new evidence becomes available. This implies that some findings may change over time

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1 EPIDEMIOLOGY OF LONG COVID

1.1 Disclaimer

The current work is based on the available evidence at this moment (27/01/2021). 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 A part of the available literature is not peer-reviewed and hence not necessarily conform with the high quality standards for scientific research. This document should be considered as a working paper that will be updated as new evidence becomes available. This implies that some findings may change over time.

1.2 Key points

- **A pragmatic review was conducted to get first rough estimates of the prevalence of long COVID, the most commonly reported symptoms of long COVID and the predictors (risk factors). This pragmatic review is only a first step. Next we will conduct a systematic ongoing review to regularly report on the emerging evidence.**
- **There are still many uncertainties about long COVID as there is no international consensus about the definition. High-quality long-term follow-up cohort studies of COVID-19 patients with standardized (objective) measurements of symptoms are lacking. As such, the reported results have to be interpreted with caution and are subject to change when more robust studies are published.**
- **It is estimated that in the first 12 weeks after the onset of the COVID-19 infection between 5% and 36% of patients still have symptoms. In specific patient groups (e.g. patients that have been hospitalised in the acute phase) higher rates were observed. Twelve weeks or more after onset of the disease, still about 2-15% of COVID-19 patients have symptoms.**
- **The most commonly reported long-term symptoms of long COVID are fatigue (up to 98%), dyspnoea (up to 93%) and headache (up to 91%). Yet it should be noted that a wide range of symptoms affect different body systems (e.g. neurological, cardiovascular, gastrointestinal) and fluctuate over time. For a large group of patients it seems that symptoms improve over time. Nevertheless, in a substantial number of cases symptoms persist. In addition to the symptoms, an impact on activities of daily life and (social) functioning is reported.**
- **Patients with long COVID are more likely to be older, suffer from pre-existing comorbidities, obesity or psychiatric disorders and have blood type A compared to COVID-19 patients that do not have long-term consequences. In addition, there are indications that a higher number of symptoms in the acute phase of the disease and the presence of specific symptoms such as fatigue, headache, dyspnoea, pain with deep breath, sensitive skin, hoarse voice and myalgia are also risk factors for developing long COVID.**

1.3 Definitions long COVID

Given the relatively recent nature of the outbreak of the COVID-19 pandemic, long-term follow-up after COVID-19 is still highly limited and we do not have sufficient hindsight to analyse the natural evolution of the disease. Nevertheless, chronic symptoms after COVID-19 are increasingly detected and epidemiological data reported.

In the literature different terms are used such as long COVID, long-haulers, long-term effects of COVID-19, post-COVID syndrome, chronic COVID syndrome, etc. Due to absence of an international consensus about the terminology, we have arbitrary chosen to use long COVID in the current report to refer to patients with symptoms that persist or develop after the acute phase of a confirmed or suspected COVID-19. Long COVID is reported after both a mild or severe acute phase of COVID-19. While there is still a lack of international consensus regarding its definition, different categorizations are emerging. In a recent rapid guideline from the National Institute for Health and Care Excellence (NICE), for instance, a distinction was made between three phases based on the time after disease onset when signs and symptoms, not explained by an alternative diagnosis, are being reported: acute phase (up to 4 weeks); ongoing symptomatic COVID-19 (from 4 to 12 weeks);

post-COVID-19 syndrome (> 12 weeks).[1] Nevertheless, in the currently available literature, the timing of assessment of chronic symptoms still remains heterogeneous and unstandardized. Until international consensus is reached about long COVID disease definition and classification we consider for the purpose of this review studies describing long-term symptoms following the acute phase of COVID-19 if they are observed at least 3 weeks after disease onset.

Due to uncertainties about its pathophysiology and the duration of the disease, the definition of long COVID is subject to modification, in the light of emerging evidence.

1.4 Research questions

The objective of this pragmatic review is to perform a rapid assessment of the literature on the following questions:

- What is the prevalence of long COVID following a confirmed or suspected COVID-19?
- What are the symptoms of long COVID and their frequency?
- What are the risk factors for developing long COVID compared to "short" COVID-19[a]?

This pragmatic review is only a starting point. It will be followed by a more systematic ongoing review which will be published in springtime 2021 with regular updates until final publication (autumn 2021).

1.5 Methods

This pragmatic literature review focused on the primary studies included in five systematic reviews on the epidemiology of long COVID.[1-5] It was completed by a regular scan of more recent literature through PubMed, MedRXIV and international websites on COVID-19.

We selected primary studies that measured the prevalence of long COVID in a population of COVID patients (thus not in a total population), the distribution of symptoms in long COVID patients and/or identified risk factors for long COVID compared to "short" COVID-19. We limited our selection to studies on long COVID (symptoms ≥3 weeks after the onset of the initial disease) conducted in Europe or in the US for better inference to the Belgian population in terms of epidemiology, risk factors such as comorbidity and health seeking behaviour. We excluded studies with a sample size below 250 COVID-19 cases. Data on risk factors were based on studies adjusting for potential confounding factors such as age, sex and comorbidities.

1.6 Frequency of long COVID

1.6.1 Included studies

Studies reporting prevalence rates of long COVID in general

Based on the selection criteria, this pragmatic review included 12 relevant publication: 6 reporting on an observational cohort[6-11] and 6 on a cross-sectional study[12-17] investigating the frequency and the type of symptoms after COVID-19.(see Table 2) Two papers reported on the same study.[12, 14] 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 picks out patients with persisting symptoms and cannot be used to determine the prevalence of long COVID among COVID-19 cases. These studies are only used to describe the frequency and duration of symptoms in the group of long COVID patients. These studies also include self-reported long COVID and long COVID symptoms collected via social media or support groups with sample sizes ranging between 1 837 to 3 762 patients.[12, 14, 15]

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[a] We use 'short' COVID-19 to describe the group of patients with acute COVID-19 without long-term complaints or symptoms after the acute phase of the disease.

1.6.2 Prevalence estimates

We found 6 studies allowing to assess the prevalence of long COVID: three observational cohort studies[6, 8, 9] and three cross-sectional surveys.[13, 16, 17] All of them are based on self-reported symptoms by means of COVID App monitoring, medical visits and phone or online surveys.

The reported prevalence of long COVID varies between 5% and 50.9 %. Several factors contribute to this variation such as patient selection and time of measurement after initial disease onset:

- Moreno et al. (2021), for instance, reported a long COVID prevalence of 50.9% during follow-up of patients who came to the emergency department (66% of them hospitalised) during the acute phase of COVID-19 while the prevalence rates of studies including also patients without a hospital contact ranged from 5 to 36%. Furthermore, when excluding severe pneumonia, the reported prevalence of Moreno et al. was at a rather similar level of 37%, in line with the other studies. Moreover, 66% of the patients that visited the emergency department during the acute phase of COVID-19 reported having recovered to a normal health status as before the infection.[8] The higher prevalence rates of long COVID symptoms among patients that were hospitalised during the acute phase of the disease is confirmed by a Chinese study (not meeting our inclusion criteria) where only discharged patients were included. Indeed, 76% of patients (1 265 of 1 655) reported at least one symptom at 6-month follow-up.[18]
- Based on four studies we could describe the prevalence of long COVID over time. Higher prevalence rates were reported in the first 11 weeks after disease onset (prevalence ranging from 5-50.9%)[6, 9, 13, 16] compared to measurements performed 12 or more weeks after symptom onset (prevalence ranging from 2.3-14.8%)[8, 9, 16, 17] In addition, Cellai et al. reported that 92% of patients with symptoms reported symptom improvement at the time patients were discharged from a tele-monitoring follow-up program (median time from symptom onset to discharge was 47.5 days).[6]

Studies reporting prevalence rates of long COVID for specific organ systems or symptoms

In this section we only describe studies[b] reporting prevalence rates on specific symptoms affecting a particular organ system. We retrieved two observational cohort studies studying mental health disorders and one observational study reporting on olfactory or taste disorders.[7, 10, 11]

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.[10] Mental health problems were more often identified at a frequency of 55%, one month after the onset of the disease, among COVID-19 patients that had visited the emergency department (with 75% of them hospitalized) during the acute COVID-19 phase.[7]

In a prospective cohort study on PCR positive healthcare workers, Villarreal et al. reported a prevalence of 26% of olfactory or taste disorder one month after onset of disease, in those having developped such symptoms at the acute phase of the disease.[11]

1.6.3 Most common symptoms and their frequency among long COVID patients

We obtained data on symptom frequency in long COVID patients based on 8 papers: three observational cohort studies[6, 8, 9], four cross-sectional surveys (5 publications).[12-16] (Table 3) For the Moreno-Perez et al. study, frequencies were calculated based on the original data included in the paper such that only long COVID patients were included in the denominator.[8]

Based on the reported frequencies across the included studies, the most commonly identified long-term symptoms in long COVID patients are fatigue (17%-98%; 8 studies[6,8, 9, 12-16], dyspnoea (17-93%; 7 studies)[6, 8, 9, 13-16]and headache (38-91%; 4 studies).[6, 9, 14, 15] Other frequent symptoms are systematically described below.

Based on the reported duration of follow-up it appears that, in general, symptoms improve over time but they remain substantial in the long run. Furthermore, while some symptoms are reported continuously, relapsing-remitting presentation of symptoms is also described.[9, 15]

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[b] Please note that prevalence rates for a wider range of symptoms (e.g. based on data included in papers that report general prevalence rates) will be included in an update of the current report.

General health

General symptoms commonly reported include: fatigue, headache, pain (back pain, bone or joint or muscle pain), sleep disorders and less frequently low-grade fever.

Exercise tolerance (post-exertional malaise) is also part of the reported complaints, reported by the international survey of Davis *et al*. This symptom was frequently reported (89%), up to 6 months after the acute phase.[15]

Respiratory

Respiratory symptoms like dyspnoea are frequently reported in the aftermath of COVID-19 (from 17 to 93%).[6, 8, 9, 13-16] Frequencies are high in both cohort studies and surveys. Cough is also a frequently reported respiratory symptoms and ranged from 29 to 43% in 4 studies.[8, 13-16] Chest pain (or chest tightness) ranged from 44 to 88.5% in 3 studies. [6, 14, 16] Moreno-Perez et al. reported functional alterations in 4.7%, mainly marked by obstructive patterns at spirometry assessment. Alterations at chest X-ray were present in 9.4% but half of them were free of symptoms. However, patients with dyspnoea and cough showed relevant findings on chest imaging by 20.7% or pulmonary function test by 14.3%.[8]

Cardiovascular

The most frequent cardiovascular symptom included heart palpitations or tachycardia. The reported frequency among long COVID patients varied widely from 6 to 86% in 5 studies.[6, 9, 14-16]

Gastroenterological

Gastroenterological conditions seem less frequent and symptoms may largely vary: diarrhea, acid reflux, loss of appetite or nausea. Two cohort studies reported gastroenterological symptoms. Sudre et al. did not mention the frequency and Cellai et al. reported 34%.[6, 9] In the survey of Davis et al., a frequency of 85% was reported with diarrhoea as the most prevalent symptom.[15]

Neurological

Olfactory dysfunction is part of commonly reported symptoms and was identified in six studies.[8, 9, 13, 15, 16] Frequency was not systematically reported in all studies. Davis et al. found 57% of smell and taste disorders in a survey including patients with persistent disease.[15]

Cognitive problems are reported and vary widely (memory disorders, concentration, executive functioning difficulties).[8, 9, 15, 16]

Other symptoms include tinnitus, earache, visual disorders or peripheral neuropathy.

Mental health

Anxiety and mood disorders (depression) are the most commonly reported symptoms. Post-traumatic stress disorder (PTSD) is also part of the reported problems.[7, 10, 15]

1.6.4 Other consequences on daily life

Some studies showed that the burden of chronic symptoms has an impact on the quality of life, daily life activities or the return to work.

- 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,…).[15]
- In a study conducted in Belgium and The Netherlands, authors reported limitations in daily activities or care-dependency although patients had not been hospitalized. 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.[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%).[8]

1.7 Risk factors for long COVID

1.7.1 Included studies

The five studies that reported adjusted analyses on risk factors for long COVID are described in Table 4. Four of five analyses included only test positive COVID-19 cases.[8, 9, 13, 16] Three of them are cohort studies,[7-9] and two are based on cross-sectional surveys.[13, 16] Three of them are based on self-reported symptoms, collected either through a COVID app to monitor patents,[9] an on-line survey[16], or a phone survey,[13] and two cohort studies are based on medical follow-up after visit to emergency department.[7, 8] One cohort study is limited to the psychiatric symptoms of long COVID, and results are presented separately.[7]

1.7.2 Risk factors

Studies indicate that patients with long COVID are more likely to be older, suffer from pre-existing comorbidities, obesity, psychiatric disorder and have blood type A compared to those with short COVID-19 (Table 1).[13, 16] Long COVID is more frequent in female patients but this is not corrected for confounding factors. Long COVID patients are also more likely to have experienced a higher number of symptoms in the acute phase of the COVID.[9] The presence of symptoms such as fatigue, headache, dyspnoea, pain with deep breath, sensitive skin, hoarse voice and myalgia in the acute phase of the disease are also risk factors for developing long COVID.[9, 16] One study found that 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.[8] One study 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%,Table 4).[9]

Table 1 – Summary of risk factors for (self-reported) long COVID in adjusted analyses

Symptoms during the acute phase of COVID	Pre-existing risk factors
High number of symptoms	Older age
Fatigue	Co-morbidities (≥3 chronic conditions)
Headache	Obesity
Dyspnoea	Pre-existing psychiatric disorder
Pain with deep breath	Blood type A
Sensitive skin	
Hoarse voice	
Myalgia	
Signs of severe pneumonia	

The 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 emergency department visit for COVID-19.[7]

No study focusing on hospitalized COVID cases, or comparing hospitalised to non-hospitalised cases, met our selection criteria.

Nevertheless, a large study from China published in The Lancet, not meeting our selection criteria, evaluated long-term consequences of COVID-19 in patients discharged from the hospital. It also found that age and disease severity during the acute phase were, after correcting for confounding factors, associated with long COVID respiratory symptoms and signs, as well as fatigue and muscle weakness at a median follow-up of 6 months.[18]

1.8 Limitations of retrieved studies

The current body of evidence about the epidemiology of long-COVID is limited and the published studies suffer from several other shortcomings:

- There is no standard definition - or even standard term - for long-term consequences of COVID-19, and the timing of assessment is heterogeneous across studies. However, we stratified results by timing of assessment when data were available. It should be noted that the COVID status is often based on laboratory tests while in the section on reported symptoms also studies with self-reported long-COVID are included.
- Most studies are based on self-reported symptoms of long COVID and this may lead to recall biases and case misclassification.
- The use of a COVID app and an on-line survey to recruit patients may result in a selection bias. One study, for instance, reported an under-representation of male and elderly patients.[9] Other studies stated that those with more severe illness might have been less likely to respond to telephone calls or to enter data in the app, and this may result in an underestimation of the prevalence.[9, 13] However it is also likely that those experiencing persistent symptoms will be more likely to participate to studies, but this has not been assessed in the studies.
- There are also variations across the studies in the COVID-19 patient population examined. The two studies based on cross sectional survey data include an hospitalization rate of <10% during the acute COVID-19 illness, while one study based on the follow-up of COVID-19 patients presenting at the emergency department reports a 66% hospitalization rate in the acute phase. However, the prevalence of self-reported symptoms and risk factors do not differ markedly.
- Although we only selected studies with a sample size of at least 250 COVID-19 cases, the four studies on 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.[8, 9, 13, 16] As for any study on risk factors, only factors that were included in the multivariate analysis could be identified. The fact that three studies were survey-based could explain that risk factors such as hospitalisation for acute COVID or medical markers were not assessed.
- There are limitations to the potential transferability of the results of some studies to the Belgian population. For instance one study from the US included a higher proportion of Hispanic and African-American cases (54%) than likely found in Belgium,[13] and it has been hypothesized that COVID-19 was more severe in those population groups.[19]
- Due to our strict selection criteria for primary studies, our conclusions may differ from published systematic reviews that include studies from any setting, with any sample size, and that report risk factors identified in non-adjusted analyses as well, or studies not comparing long COVID to short COVID.[1, 3]

Table 2 – Results on long COVID prevalence

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Prevalence	Prevalence at < and ≥ 12 weeks**	Symptom-specific prevalence
Cellai, US[6]	Confirmed infection (PCR)	Prospective cohort study n=496	Persistent symptoms 6 weeks after onset of COVID-19	5.2% (26/496)	Not reported	Not reported
Cirulli, US[16]	Participants to online survey in 2 projects, with positive COVID-19 test	Cross sectional survey n=357	≥1 self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms), self-reported	36.1% (129/357)	<12 weeks 25.3% ≥12 weeks 14.8%	Not reported
Moreno-Perez, Spain[8]	Adults attending the emergency department for COVID-19, PCR positive 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	50.9% (141/277)	≥12 weeks: neurological 3.8% respiratory 6.7%	Not reported
Sudre, UK, US and Sweden[9]	App users, adults, PCR positive, no physical problem before COVID-19	Prospective cohort study n=4182	Any symptom, >28 days after onset of COVID-19, self-reported	13.3% (558/4182)	< 12 weeks 4.5% ≥12 weeks: 2.3%	Not reported
Tenforde, US[13]	COVID-19 cases reporting at phone interview, PCR-positive, non-hospitalised at testing	Cross sectional survey n=292	Return to baseline health after COVID-19 (interview at 14-21 days after PCR), self-reported	35% not having recovered previous health status (95/270)	Not reported	Not reported
Office for National Statistics (ONS), UK[17]	Positive COVID-19 patients who responded to the National Coronavirus (COVID-19) Infection Survey (CIS)	Cross sectional survey n=not reported	Persistent symptoms at 5 weeks or longer and 12 weeks or longer, after COVID-19 onset.	At 5 weeks or longer: 21% At 12 weeks or longer: 9.9%	< 12 weeks 21% ≥12 weeks: 9.9%	Not reported

Taquet , US[10]	Positive COVID-19 patients (confirmed infection PCR or antigen testings 92.2%)	Retrospective observational cohort study n=62354	Psychiatric disorders (or dementia or insomnia) within 14 to 90 days after COVID-19 onset	5.8%	Not reported	• 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%
Mazza , Italy[7]	Adult COVID-19 patients assessed at emergency department 75% hospitalised	Prospective observational cohort study n=402	Mental health assessment at one month after COVID-19 onset	56%	Not reported	• PTSD 28% • Depression 31% • Insomnia 40% • Anxiety 42% • Obsessive-compulsive symptoms 20%
Villarreal, Spain[11]	Healthworker with PCR positive for COVID-19. (phone interview)	Prospective observational cohort n=256; 230 after exclusions	Olfactory and taste disorders assessed at acute phase and at one month	26%* * **of those who developed olfactory and taste disorders during the acute phase (43/161)**	Not reported	

***we used < and ≥ 12 weeks as arbitrary cut-off to report prevalence of long COVID based on duration after disease onset. Yet the exact time of measurement used to measure symptoms after disease onset can differ from study to study*

Table 3 – Frequency of symptoms among long COVID patients

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Symptom frequency
Cellai, US[6]	Confirmed infection (PCR)	Prospective cohort study n=496	Persistent symptoms 6 weeks after onset of COVID-19	• Respiratory symptoms (dyspnea, chest tightness) (88.5%) • Fatigue 17/26 (65%) • Headache 13/26 (50%) • Gastrointestinal symptoms 9/26 (34%) • Palpitations 6/26 (23%) • Low grade fever 3/26 (11%) • 18/26 (69.2%) reported at least 4 concurrent symptoms.
Cirulli, US[16]	Participants to online survey in 2 projects, with positive COVID-19 test	Cross sectional survey n=357	≥1 self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms), self-reported	Most frequent: • Anosmia, ageusia, • Dyspnea, chest pain • Memory loss, confusion, difficulty concentrating Other: • Decreased alertness,dizziness • Headache, insomnia • Muscle weakness • Dry cough • Tachycardia • Bone or joint pain • Fatigue • Tingling, sensitive skin, back pain, • Acid reflux, diarrhea

Moreno-Perez, Spain[8]	Adults attending the emergency department for COVID-19, PCR positive 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	- Symptoms: • Dyspnea 17.2% • Cough 10.6% • Fatigue 17.6% • Anosmia-Dysgeusia 10.8% • Cognitive disorders • 7.6% • Headache 8.9% • Myalgia, arthralgia 9.8% • Diarrhea 5.3% • Skin disorders 4.2% • Visual loss 2.7% - Spirometry alterations 4.7% - Chest X-ray alterations 9.4% - Quality of life more frequently impacted 66.9% vs 43.2%
Sudre, UK, US and Sweden[9]	PCR positive tested app users and feeling physically normal before COVID-19	Prospective cohort study n=4182	Any symptom, >28 days after onset of COVID-19, self-reported	• Fatigue (97.7%) • Headache (91.2%) • Dyspnoea (?) • Anosmia (?) • Cardiac symptoms (6.1%) • Lower respiratory symptoms (?) • Memory (4.1%) • Tinnitus/earache (3.6%) • Neuropathy (2%) • Fever (?) • Gastroenterological symptoms (?)
Tenforde, US[13]	COVID-19 cases reporting at phone interview, PCR-positive, non-hospitalised at testing	Cross sectional survey n=292	Return to baseline health after COVID-19 (interview at 14-21 days after PCR), self-reported	• Fatigue 35% • Cough 43% • Shortness of breath 29% • Anosmia, dysgueusia (?)

Davis, Europe and US[15]	Persistent symptoms in people who experienced symptoms consistent with COVID-19, reported on a survey through social media and support groups Confirmed 27%	Cross-sectional survey n=3762	Symptoms > 28 days	• 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: 85% • Anxiety 57.9% • Depression 47.3% • Taste and smell disorders 57.6%
Goertz[a] and **Vaes[b], The Netherlands and Belgium[12, 14]**	Persistent symptoms reported in social media in patients who experienced COVID-19 Confirmed: 16%[a] -27%[b]	Cross sectional suvey n=2113[a] n=1837[b]	Any symptoms > 3 weeks after infection onset Follow-up 79 (±17) days after acute infection	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

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

First author, country	Inclusion criteria	Outcome and timing	Risk factors (adjusted OR and 95%CI)	Other results
Sudre, UK, US and Sweden[9]	App users, adults, PCR positive, no physical problem before COVID-19	Any symptom, >28 days after onset of COVID-19, self-reported	Adjusted analysis (age and sex), compared to "short" (<10 days) COVID, symptoms during first week of COVID: - fatigue (2.83; 2.1-3.8) - headache (2.62; 2.0-3.4) - dyspnoea (2.36; 1.9-2.9) - hoarse voice (2.33; 1.9-2.9) - myalgia (2.22; 1.8-2.7)	Main predictors: age, sex, symptoms in 1st week (AUC 77%). In 70+ years: fever, loss of smell and comorbidities.
Cirulli, US[16]	Participants to online survey in 2 projects, with positive COVID-19 test (for risk factor analysis)	In positive COVID-19 test: symptoms lasting longer than 30 days after onset (from a list of 32 symptoms), self-reported	Adjusted analysis at day 30, p<0.05: - 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
Tenforde, US[13]	COVID-19 cases reporting at phone interview, PCR-positive, non-hospitalised at testing	No return to usual state of health at 2-3 weeks after testing, self-reported	Adjusted analysis (age, sex, ethnicity), compared to return to baseline health at 2-3 weeks: - age ≥50 years (2.29; 1.1-4.6 vs 18-34) - ≥3 chronic conditions (2.29; 1.1-4.9) - obesity defined as BMI>30 (2.31; 1.2-4.4) - reporting a psychiatric condition (2.32; 1.2-4.6)	54% included COVID cases were non-Hispanic/black
Moreno-Perez, Spain[8]	Adults attending the emergency department for COVID-19, PCR positive or seroconverted	Persistence of ≥1 symptom or abnormal spirometry or chest X-Ray at 10-14 weeks after onset	Adjusted analysis: - for long COVID (overall): no significant risk factor - for those with initial severe pneumonia: opacities of lung surface on X-rays >50% (2.87; 1.1-7.3) and higher heart rate at admission (1.03; 1.0-1.1)	Higher imaging score at acute disease was associated with persistence of XRay signs
Mazza, Italy[7]	Adults attending the emergency department (ED) for COVID-19, no information on testing	Presence of psychiatric symptoms at one month after ED discharge	Adjusted analysis (sex, previous status and hospitalisation): - female sex - previous psychiatric history Hospitalisation was not a risk factor	Older age and long duration of hospitalisation were risk factors in the unadjusted analysis

Note that a more detailed version of the tables is available upon request.

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Colophon

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Disclaimer: The current work is a pragmatic review based on the available evidence at this moment (27/01/2021). KCE synthesised the evidence in short time frames to respond to urgent questions and could therefore not follow its regular methodological procedures. 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 conform with the high quality standards for scientific research. This document should be considered as a working paper that will be updated as new evidence becomes available. This implies that some findings may change over time

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