

## Summary

### Background

SBU was commissioned by the Swedish Government to evaluate the scientific evidence of care for patients with long-term symptoms or sequelae (long covid) of the disease Covid-19 (S2020/06019/FS).

### Aim

To summarize published and ongoing research regarding the following three questions.

1. Which long-term (>6 weeks) symptoms occur in people with a confirmed Covid-19 disease and how common are they?
2. Which treatment and rehabilitation are effective for long-term symptoms of Covid-19?
3. Which studies on long-term symptoms of Covid-19 are on-going or unpublished?

### Method

The project was conducted in accordance to SBU's standardized procedures. A study protocol for this project was made a priori. A systematic literature search was thereafter designed and performed by an information specialist, in order to identify all published articles and ongoing studies potentially relevant for the PICO. After the literature search was performed, two reviewers independently screened the abstracts and full text and selected the relevant studies. The risk of bias in the included published studies were assessed independently by two reviewers using RoB2 for RCT studies and an adapted assessment tool for observational studies. Any disagreement regarding relevance or risk of bias was solved by a discussion. No syntheses were made. Relevant pre-published articles (pre-prints) were identified and are reported in this report but not included in the results (Appendix 1).



### Inclusion criteria

#### Reported long-term symptoms

**Population:** Patients with a confirmed<sup>1</sup> Covid-19 disease

**Exposure:** Earlier or on-going Covid-19 disease

**Control:** No comparison

**Outcome:** Long-term symptoms, at least 6 weeks after infection

#### Treatment of long-term symptoms

**Population:** Patients with a confirmed Covid-19 disease and having long-term symptoms, at least 6 weeks after infection

**Intervention:** Treatment or rehabilitation against long-term<sup>2</sup> symptoms

**Control:** No treatment or other treatment

<sup>1</sup> In the literature, diagnostic criteria were specified according to The WHO's definition or local/regional guidelines.

<sup>2</sup> To our knowledge there is no established definition on long-term symptoms. Therefore, according to best practice we here suggested six weeks (42 days) to be the lower time limit.

**Outcome:** Change in symptoms

**Language:** English, Swedish, Norwegian, or Danish

**Search period:** From 2019 to 2020. Final search: November 2020.

**Databases searched:** Cinahl, Clinical Trials, Cochrane Covid-19 Study Register, Embase, Epistemonikos Covid-19 selection, Medline and PsycInfo

**Client/patient involvement:** No

## Results

In total, 57 relevant studies were identified. Of those 25 observational studies and one randomized control study, were assessed to have low or moderate risk of bias (Appendix 2).

The reported perceived long-term symptoms were mainly fatigue, shortness of breath, cough, palpitations and impaired sense of smell. Other symptoms were for example chest pain, muscle and joint pain, weight loss, gastrointestinal disorders, skin changes, deteriorated quality of life and a general impaired physical and mental health. The reported clinical measures were impaired lung function and lung damage, cardiovascular effects such as myocardial inflammation, cerebral changes and impaired sense of smell and taste (anosmia and hyposmia). Since the disease is new, other long-term manifestations of Covid-19 may occur.

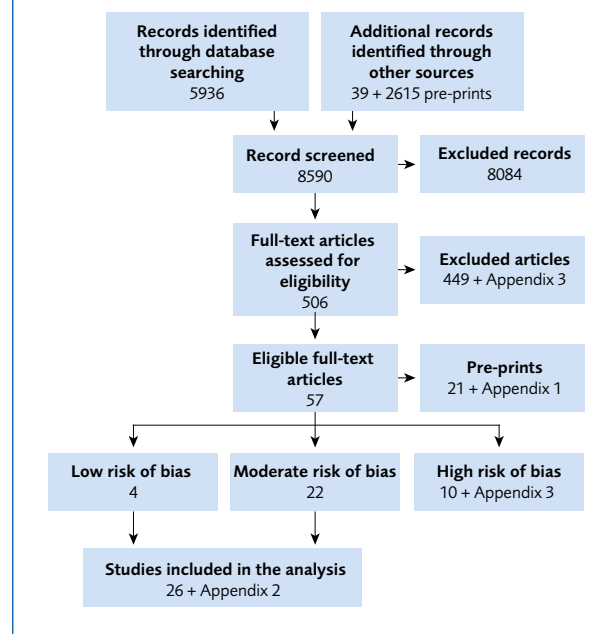
The incidence of each symptom varied from 4-78% in the included studies. The variation seems to depend on type of symptom, severity of the disease (in- or out-patient), and how the symptoms have been measured.

No study on treatment of long-term symptoms was identified. One study was identified on respiratory rehabilitation among the elderly (Appendix 2).

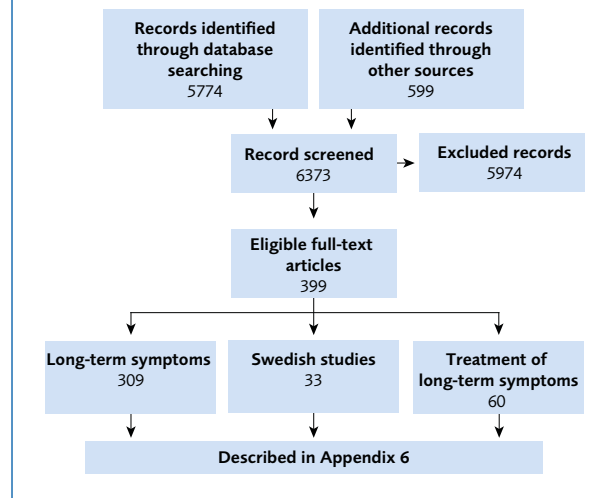
Some studies reported results by gender and age, but these studies are too few and too different in order to give an overall picture of possible differences between groups. No study reported long-term symptoms for people with earlier disabilities.

Almost 400 ongoing studies have been identified, which may provide information about the long-term symptoms of Covid-19. Among these were 60 studies on treatment. The majority of the ongoing studies concern adults in hospital care (Appendix 6). Even if there are significant research activities regarding

**Figure 1** Flowchart over the literature review for question 1 and 2.



**Figure 2** Flowchart of the literature review for question 3.



Covid-19, there are uncertainties regarding the actual number of ongoing studies. In this systematic review we have included studies that might give information regarding the three different questions. However, especially regarding treatment studies it is hard to know if these studies will focus on long-term symptoms, due to the limited information given. It is also uncertain if all studies will be finished and published. No treatment studies were identified that included children and none of the identified treatment studies specified that they focused on out-patients only.

## Discussion

The descriptions of long-term symptoms illustrate the diverse manifestations of the disease Covid-19. The results show that there is some knowledge on different long-term symptoms, but less on treatment and rehabilitation of those symptoms. Thus, the results indicate that despite many ongoing studies, more studies may be needed on treatment and rehabilitation of long-term symptoms, as well as on out-patients and children.

Given the high level of scientific activity on Covid-19, it is likely that a later review of the scientific literature may provide more evidence about the potential long-term consequences of Covid-19.

In order to enable patient and clinician input regarding important research questions, the SBU have initiated a priority setting partnership with a focus on long-term symptoms of the Covid-19 disease. This includes an identification of research questions using online surveys and a priority setting engaging patients, clinicians, researchers and other relevant stakeholders. This work will be published during spring 2021.

## Appendices ([www.sbu.se/319e](http://www.sbu.se/319e))

- Appendix 1. List of pre-prints (pdf)
- Appendix 2. Characteristics of included studies (pdf)
- Appendix 3. Excluded articles (pdf)
- Appendix 4. Search strategies (pdf)
- Appendix 5. Reference list (pdf)
- Appendix 6. Ongoing studies (xlsx)

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