Characterising long-term covid-19: a rapid living systematic review

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Section 1: What is already known on this topic?

- A significant number of people continue to describe symptoms long after the acute phase of covid-19 is over, so called ‘long covid’.
- There is no case definition for 'long covid,' which appears to be a heterogeneous condition with an uncertain prevalence.

Section 2: What this study adds

- This 'living' systematic review provides a comprehensive summary of the published evidence on persistent symptoms of covid-19 and will be regularly updated.
- The breadth of reported symptoms suggests a complex, heterogeneous condition affecting both hospitalised patients and those managed in the community.
- However, the current evidence base of the clinical spectrum of ‘long covid’ is of limited quality and is vulnerable to biases.
- Our review identifies those areas where further ‘long covid’ research is critically needed.
ABSTRACT

Objective To understand the frequency, profile, and duration of persistent symptoms of covid-19 and to update this understanding as new evidence emerges.

Design: A living systematic review produced in response to the rapidly evolving evidence base for ‘long covid’.

Data sources Medline and CINAHL (EBSCO), Global Health (Ovid), WHO Global Research Database on covid-19, LitCOVID, and Google Scholar to 28th September 2020.

Study selection Studies reporting long-term symptoms and complications among people with confirmed or suspected covid-19, both in those previously hospitalised and those never hospitalised. Only studies incorporating over 100 participants qualified for data extraction and were assessed for risk of bias. Results were analysed using descriptive statistics.

Quality assessment Risk of bias was assessed using a quality assessment checklist for prevalence studies.

Results Twenty-eight studies qualified for data extraction; 16 of these were cohort studies, ten cross-sectional, and two large case series. The analysis included 9,442 adults with covid-19 from 13 countries. The longest mean follow-up period was 111 (SD: 11) days post-hospital discharge. A wide range of systemic, cardiopulmonary, gastrointestinal, neurological, and psychosocial symptoms was reported, of which the most common were breathlessness, fatigue, smell and taste disturbance, and anxiety. Persistent symptoms were described across both previously hospitalised and non-hospitalised populations. The quality of evidence was low, with a high risk of bias and heterogeneity in prevalence. The incorporated studies demonstrated limited external validity, a lack of control subjects, and inconsistent data collection methods. Few studies were conducted in primary care, no studies focused solely on children, and no studies were set in low- and middle-income countries.
**Conclusion:** Our findings suggest that 'long covid' is a complex, heterogeneous condition; however, the limited evidence base currently precludes a precise definition of its symptoms and prevalence. There is a clear need for robust, controlled, prospective cohort studies, including different at-risk populations and settings, incorporating appropriate investigations, collected and recorded in a standardised way.

**Systematic review registration** The protocol was prospectively registered on the PROSPERO database (CRD42020211131).

**Readers’ note** This living systematic review will be updated regularly as new evidence emerges. The search terms and inclusion criteria will be updated in line with new evidence, research priorities and policy needs. This version is the original publication. Updates may occur for up to two years from the date of original publication. When citing this paper please consider adding the version number and date of access for clarity.

**Keywords:** Covid-19, long covid, prolonged, post-acute covid-19, clinical research, living systematic review

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INTRODUCTION

More than 62 million people have now been diagnosed with covid-19 following a pandemic of the novel coronavirus, SARS CoV-2. [1] Most of these people experience mild to moderate symptoms, whilst around 15% of people are estimated to progress to severe disease requiring hospitalisation and approximately 5% become critically ill. [2]

On average, it is estimated to take two to six weeks for most people to recover from covid-19. However, for an unknown number of people, symptoms may persist for weeks or even months following their initial infection, and some develop medical complications that may have longer lasting health implications. [3–5]

Such protracted illness, often referred to as 'long covid' has no widely-accepted case definition. [6] Instead, ‘long covid’ has been defined pragmatically as "not recovering [for] several weeks or months following the start of symptoms that were suggestive of covid-19, whether you were tested for covid-19 or not." [6] Others have distinguished between post-acute covid-19, referring to symptoms lasting 3-12 weeks, and chronic covid-19, referring to symptoms beyond 12 weeks. [7,8] A precise case definition is problematic because, currently, there is little consensus on the exact range, prevalence, and duration of symptoms in post-acute covid-19.

Quantifying how many people develop 'long covid’ is difficult, with some cohorts suggesting only 13% of people are fully recovered from their illness at 60 days post-onset. [9] A patient-led social media survey reported that the chance of full recovery by day 50 was smaller than 20%. [10]
The symptoms of 'long covid' are equally ill-defined, with some studies characterising it as a fluctuating illness associated with cough and fever, whilst others emphasise chronic chest pain, breathlessness and neuro-cognitive difficulties. (10) Others report a wider variety of symptoms as disparate as 'brain fog’, dizziness, vertigo, diarrhoea, joint pain, chest pain and skin rashes. [11] Indeed, the NIHR has suggested that post-acute covid-19 may include any of several distinct clinical syndromes including: a post-intensive care syndrome, chronic fatigue syndrome, long-term covid-19 syndrome and disease from SARS-CoV-2 inflicted organ damage. [12]

Our current understanding of ‘long covid’ has been accumulated mainly from case reports and cross-sectional online survey studies. However, large, robust prospective cohort studies of hospitalised patients (PHOSP-COVID) [13] and non-hospitalised people (LIINC [14], SENTINEL GP [15]) have just commenced recruitment. Simultaneously, qualitative studies are ongoing to further explore the ‘long covid’ patient experience. [16]

Summarising and producing conclusions from this data will be challenging. Systematic reviews conducted early during the covid-19 pandemic soon became redundant due to the rapidity with which new research was released. In recognition of this, many reviewers have moved towards the concept of a 'living systematic review' model, which has in-built mechanisms for regular update and renewal. [17,18] Our 'living' systematic review (LSR) seeks to synthesise and continually update the evidence on the range, prevalence, and duration of persistent symptoms and long-term complications in people with covid-19.

Given the enormous number of people worldwide who have suffered from covid-19, it is essential to establish a precise categorisation of ‘long covid’. Such categorisation will not
only help people better understand their symptoms but also direct research into prevention, treatment, and support, ultimately allowing us to understand and prepare for the long-term consequences inflicted by the covid-19 pandemic.

METHODS

We conducted a ‘living’ systematic review (LSR) to provide frequently updated evidence on the symptoms and complications of ‘long covid’ during and after the pandemic. This review was developed in collaboration with infectious disease clinicians, public health professionals, information specialists, review methodologists with experience in clinical epidemic research, people living with ‘long covid’, and members of the global Long Covid Support Group.

Protocol Registration

This report was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. [19] The protocol was registered with PROSPERO (CRD42020211131).

Search Strategy

The following databases were searched: Medline and CINAHL (EBSCO), Global Health (Ovid), WHO Global Research Database on covid-19, and LitCOVID from 1st January to 28th September 2020. Additionally, we searched Google Scholar on 28th September 2020, screening the first 500 titles. A ‘backwards’ snowball search was conducted of the references in all included articles. We used broad, comprehensive search terms which will be refined as the evidence base develops. Full search terms are included in supplementary table 1.
Eligibility Criteria

Studies were considered eligible if they incorporated people with laboratory, clinically confirmed, or suspected COVID-19. We included studies which reported outcomes after 21 days post-onset of COVID-19 symptoms, or at any time post-hospital discharge. Both hospitalised and non-hospitalised people were included. There were no language restrictions. Narrative reviews and opinion pieces were excluded. Studies were excluded if they only presented acute data or if they did not specify the follow-up period.

Screening

Screening of titles, abstracts, and full text was performed independently by two reviewers. Any disagreements were resolved via consensus. Two additional reviewers checked the excluded full-text articles. Non-English articles were translated using Google translate and reviewed by a reviewer with good knowledge of the language. The data were managed using the review software Rayyan. [20]

Data Extraction

Data extraction was performed using Microsoft Excel. A data extraction template informed by a previous review [2] was reviewed, updated, and piloted before being finalised. Data extracted included study design, main outcomes, prevalence, duration of symptoms, and risk factors. Data extraction was performed by one reviewer and checked by a second reviewer. Disagreements were resolved through consensus. Studies with fewer than 100 subjects were excluded from the primary analysis due to risk of bias. To avoid duplication of data in future updates and ensure robustness, data extraction was not performed for non-peer-reviewed preprints, instead, their full bibliographies are listed (supplementary table 2).
Data Analysis

Due to heterogeneity in study design, population, setting, symptom ascertainment methods, and admission and discharge guidelines, a meta-analysis was not performed in this version. The data is presented using a mix of infographics and scientific tables to facilitate interpretation by the non-specialist. Confidence intervals for the individual studies were estimated using the exact method. [21] The analysis was performed in STATA MP 15 using the `metaprop` command. [22]

Patient and public involvement

Four members of the study team have experienced covid-19 (CH, MO, JCS, and CF). CH, MO, and JCS are members of Long Covid Support, a patient support group. Long Covid Support runs an international Facebook peer support group, with more than 30,000 members. These members actively contributed to the development of the study protocol and interpretation and presentation of the findings, including the infographics to communicate the results to lay audiences. The results of this LSR will be disseminated to ‘long covid’ patient forums for discussion and feedback.

Risk of bias assessment

The included studies were assessed for risk of bias using a modified version of the tool produced by Hoy et al. [23] This quality assessment checklist is a validated tool for assessing risk of bias in prevalence studies. The checklist has ten domains for assessing risk of bias, and a cumulative risk of bias for the whole study is then calculated.
RESULTS

We identified 1,553 studies, of which 100 met the inclusion criteria. Of these, 28 studies qualified for data synthesis and risk of bias assessment (Figure 1).

[Insert Figure 1 here]

Characteristics of included studies

Most studies were set in Europe (61%, 17/28), followed by Asia (21%, 6/28), North America (7%, 2/28), South America (4%, 1/28), and the Middle East (4%, 1/28). There was no study set in a low-middle income (LMIC) country (Figure 2). [24] Most were cohort studies (57%, 16/28), followed by cross sectional studies (36%, 10/28), and case series (7%, 2/28) (Table 1).

[Insert Figure 2 here]

| Study Design    | Cohort | Cross Sectional | Case Series | Total |
|-----------------|--------|-----------------|-------------|-------|
| BELGIUM         | 0      | 2*              | 0           | 2     |
| BRAZIL          | 1      | 0               | 0           | 1     |
| CHINA           | 3      | 2               | 1           | 6     |
| DENMARK         | 0      | 1               | 0           | 1     |
| FRANCE          | 2      | 0               | 0           | 2     |
| GERMANY         | 1      | 0               | 0           | 1     |
| IRAN            | 1      | 0               | 0           | 1     |
| ITALY           | 4      | 4               | 0           | 8     |
| SPAIN           | 1      | 0               | 0           | 1     |
| SWITZERLAND     | 1      | 0               | 0           | 1     |
| THE NETHERLANDS| 0      | 2*              | 0           | 2     |
| UNITED KINGDOM  | 0      | 1               | 0           | 1     |
| UNITED STATES   | 1      | 0               | 1           | 2     |

*These studies were conducted with participants from Belgium and The Netherlands

Table 1. Study design by country
These studies present data on 9,442 (range: 100-2,113) people from 13 countries. Ages varied from a mean of 37.7 (SD: 10.4) to 73.9 (SD: 12.9) years old. Most studies (57%, 16/28) were cohort studies of hospitalised patients post-discharge, 25% (7/28) were set in the community whilst 18% (5/28) included both. Ten studies included people requiring ICU admission during the acute phase. [9,25–32] The longest follow-up period in any study was a mean of 111 (SD: 11) days post-discharge (Table 2). Most studies did not specify covid-19 severity nor treatment received during the acute phase. Pre-existing comorbidities were reported in half of the studies (54%, 15/28), [9,25,27–31,33–38] with hypertension and diabetes most commonly documented.
| Study | Study Design | Country | Size (n) | Age (Years) | Sex (% Female) | COVID-19 Confirmation | Follow Up | Follow Up Time (days) |
|-------|--------------|---------|----------|-------------|----------------|-----------------------|-----------|-----------------------|
| **Non-Hospitalised Population** | | | | | | | | |
| Boscolo-Rizzo et al. [39] | Cross Sectional | Italy | 187 | Median (range): 56 (20-89) | 55.1 | Lab | Post Diagnosis | 28 |
| Brandao Neto et al. [27] | Cohort (P) | Brazil | 143 | Mean (SD): 37.7 (10.4) | 64.7 | Lab | Post Onset | Median (IQR): 76 (66-88) |
| Chiesa-Estomba et al. [33] | Cohort (P) | - | 751 | Mean (range): 41 (18-60) | 63.5 | Lab | Post Diagnosis | Mean (range): 47 (30-71) |
| Lovato et al. [34] | Cross Sectional | Italy | 121 | Mean: 46.7 | 59.5 | Lab | Post Diagnosis | Mean (SD): 38 (3) |
| Villarreal et al. [40] | Cohort (P) | Spain | 230 | Median (range): 43 (18-62) | 85 | Lab or Suspected* | Post Onset | 28 |
| Fjaeldstad et al. [41] | Cross Sectional | Denmark | 109 | Mean: 39.4 | 79 | Lab | Post Onset | 30 |
| Vaes et al. [42] | Cross Sectional | The Netherlands and Belgium | 1837 | Median (IQR): 47.0 (38-54) | 86.1 | Lab | Post Onset | Mean (SD): 79 (17) |
| **Previously Hospitalised Population** | | | | | | | | |
| Bai et al. [43] | Cross Sectional | China | 126 | Mean (SD): 45.7 (14) | 52.4 | Lab | Post Discharge | 14 |
| Carfi et al. [9] | Cross Sectional | Italy | 143 | Mean (SD): 56.5 (14.6) | 37 | Lab | Post Onset | Mean (SD): 60 (14) |
| Liu, Baumeister et al. [44] | Cross Sectional | China | 675 | Median (IQR): 55 (41-66) | 53 | Lab | Post Discharge | Mean: 37 |
| Garrigues et al. [28] | Cohort (P) | France | 120 | Mean (SD): 63.2 (15.7) | 37.5 | Lab/CT | Post Discharge | Mean (SD): 111 (11) |
| Halpin et al. [29] | Cross Sectional | UK | Ward: 68 | Median (range): Ward: 70.5 (20-93) | 48.5 | Lab | Post Discharge | Mean (SD): 48 (10) |
| Liu, Zhang et al. [45] | Cohort (P) | China | 149 | Median (IQR): 43 (36-56) | 55 | Lab | Post Discharge | 21 |
| Belli et al. [46] | Cross Sectional | Italy | 103 | Mean (SD): 73.9 (12.9) | 48.5 | Lab | Post Discharge | Mean (SD): 16 (7) |
| Somani et al. [30] | Cohort (P) | US | 103 | Median (IQR): 66.1 (53.7-75) | 36.9 | Lab | Post Discharge | 14 |
| Tomasoni et al. [47] | Cohort (P) | Italy | 105 | Median (IQR): 55 (43-65) | 27 | Lab/CT | Post Discharge | Mean (IQR): 46 (43-48) |
| Rahmani et al. [31] | Cohort (P) | Iran | 176 | Mean (SD): 60 (14) | 46.9 | Lab/CT | Post Discharge | Mean (SD): 56 |
| Wang et al. [48] | Cohort (R/S) | China | 131 | Median (IQR): 49 (36-62) | 54.96 | Lab | Post Discharge | Mean (SD): 28 |
| Yan et al. [49] | Cohort (R/S) | China | 337 | Median (IQR): 44 (35-55) | 54.3 | Lab | Post Discharge | Mean (SD): 14 |
| Bougiovanni et al. [50] | Cohort (R/S) | Italy | 125 | Mean (95% CI): 65.7 (26-95) | - | Lab | Post Discharge | Mean (95% CI): 19.9 (3-43) |
| Wu et al. [38] | Case Series | China | 370 | Mean (SD): 50.5 (13.1) | 45.1 | Lab/CT | Post Discharge | Median (IQR): 22 (20-30) |
| McCarthy et al. [51] | Case Series | US | 213 | Median (IQR): 61 (50-76) | 42 | Lab | Post Discharge | Median (IQR): 80 (68-84) |
| Pellaud et al. [52] | Cohort (R/S) | Switzerland | 196 | Median (IQR): 70 (60-80) | 39 | Lab | Post Onset | 30 |
| **Hospitalised and non-hospitalised** | | | | | | | | |
| Mazza et al. [52] | Cohort (P) | Italy | 402 | Mean (SD): 57.80 (13.33) | 34.3 | Lab | Post Discharge | Mean (SD): 31 (16) |
| Vaira et al. [25] | Cohort (P) | Italy | 138 | Mean (SD): 51.2 (8.8) | 50.7 | Lab | Post Onset | Mean (SD): 60 |
| Poncet-Megemont et al. [26] | Cohort (R/S) | France | 139 | Mean (SD): 48.5 (15.3) | 62.6 | Lab/CT | Post Diagnosis | Mean (SD): 30 - 35 |
| Puntmann et al. [37] | Cohort (P) | Germany | 100 | Mean (SD): 49 (14) | 47 | Lab | Post Diagnosis | Median (range): 71 (64-92) |
| Goertz et al. [53] | Cross Sectional | The Netherlands and Belgium | 2113 | Median (IQR): 47 (39-54) | 85.3 | Lab | Post Onset | Mean (SD): 79 (17) |

*Suspected: No test or symptom based diagnosis by doctor
**Clinically: symptom based diagnosis by doctor

Table 2. Study characteristics
Risk of bias

Fourteen studies were assessed as possessing a high risk of bias, ten moderate, and four low risk of bias. Most studies had a high risk of bias with regards to the generalisability of their results to the wider population with covid-19 (supplementary table 3). Further, the recruitment process and response rates were often not well-described and several studies applied different data collection methods. Although most studies applied validated measurement methods to assess participants, most were not designed to detect symptoms arising from covid-19. Furthermore, only one cohort study included a control group for comparison. [37]

Symptoms

A wide range of new or persistent symptoms were documented in both the hospitalised and non-hospitalised cohorts. Symptoms were organised into physiological clusters for this review (Figure 3).

[Insert Figure 3 here]

Across both hospitalised and non-hospitalised populations, the most frequently reported symptoms were breathlessness, found in 13 studies (46%), [9,28–31,35–39,47,48,53] followed by persisting smell and taste disturbance documented in 12 studies (43%) [25–28,33–35,39–41,47,53] and fatigue in 11 studies (39%). [9,28,29,34,37,39,42,44,49,50,53] Psychological symptoms were also frequently reported, of which anxiety was most common (25%), [29,38,43,44,47,49,52] followed by depression, [38,43,44,47,52] sleep disorders, [28,38,42,52] and post-traumatic stress disorder (PTSD). [43,44,52] Increased dependency in activities of daily living (ADLs), comprising personal care and social activities, was reported by almost half of participants in one study (47.5%, 49/103), [46] as well as reduced quality of
Musculoskeletal symptoms were also frequently reported, especially myalgia. Upper respiratory tract symptoms including sore throat and nasal congestion, and gastrointestinal (GI) symptoms were reported less frequently, with nausea being the most commonly documented. Less frequently documented symptoms were dizziness, incontinence, skin related, and hair loss. Further, three studies reported memory impairment and two concentration impairment, in previously hospitalised populations.

Symptom prevalence across the studies varied (Figures 4-6). Some symptoms were only reported in studies deemed to be at medium or high risk of bias. Even the prevalence of the more commonly reported symptoms (e.g. breathlessness, fatigue and anxiety) varied markedly. As such a meta-analysis was not appropriate.

Imaging

Imaging results were reported in 11% (3/28) of the studies. One of these, found that 78% (78/100) of people assessed at a median of 71 (IQR, 64-92) days post-diagnosis using cardiovascular magnetic resonance imaging (MRI) presented cardiac involvement (raised myocardial native T1 and T2, late gadolinium enhancement, or pericardial involvement) and 60% (60/100) had myocardial inflammation, independent of risk factors. In another study, chest computed tomography scans showed interstitial lung changes in 47% (70/149) of subjects at three weeks post-discharge. In addition, one study reported pulmonary embolism in 9.1% (2/22) of patients returning to hospital at a median of 19 (IQR, 8–32) days post-discharge.
Risk factors

Some studies presented data on risk factors such as age, sex, pre-existing comorbidities, and severity of the acute phase. However, it is not possible to confidently identifying risk factors for ‘long covid’ given the limitations of the existing data.

Severity

Some studies have attempted to compare ‘long covid’ symptoms in hospitalised patients admitted to ICU to those managed at ward level. Within those studies, psychosocial and respiratory symptoms are the most commonly cited long-term sequelae, but their findings are inconsistent. [28,29]

Pre-morbid conditions

One study reported that patients with COPD or hypertension were more likely to be readmitted to hospital post initial discharge, but did not find this association for other comorbidities or demographic factors. [30] A patient survey suggested that pre-morbid health status and self-reported symptoms at disease onset were associated with the risk of continuing symptoms three months later.[53] However, this type of studies were associated with high levels of recall bias.

Psychosocial illness

Five cohort studies evaluated the association between psychosocial illness, including PTSD, depression, and anxiety and risk factors such as age, sex, hospitalisation, pre-existing comorbidities, [38,43,44,52] covid-19 severity, and treatment.[44,47]
One study concluded that a cohort treated with corticosteroids was at a lower risk of developing PTSD, but at a higher risk of anxiety compared to controls. The same study found no link between covid-19 severity and depression, anxiety, or PTSD.[44] The very persistence of covid-19 symptoms has been associated with anxiety and depression post-discharge. [47] The links between chronic illness and psychosocial health are well known but establishing causality is fraught with difficulty.

Taste and smell disturbances

Six studies evaluated risk factors for prolonged smell and/or taste disturbance.[25,27,33,34,39,41] Most found no association between age, [25,27,39,41] sex, [25,27,39] pre-existing comorbidities [25,27,33] or initial covid-19 severity (invasive ventilation and ICU admission) [27] and persistent smell or taste disturbances. One study reported that absence of fever at disease onset was an independent prognostic factor for disturbed smell and taste at follow up.[34]

DISCUSSION

This living systematic review captures the breadth of persistent symptoms associated with covid-19. Diverse symptoms have been reported in both hospitalised and non-hospitalised people with ‘long covid’. It is currently unclear whether that heterogeneity is a true effect or generated by the varied methods by which it has been studied.

Our study is not without limitations. The literature on ‘long covid’ is still immature, and most of the incorporated studies were not designed as prevalence studies. Symptoms were mostly reported by a small number of studies and participants, without control subjects, limiting our ability to establish causality. For example, anxiety, depression, and fatigue could have a
multifactorial aetiology and be direct results of the viral infection or may be influenced by other factors, including lockdown and media reporting.

Furthermore, the studies have considerable heterogeneities due to study designs, settings, populations, follow-up time, and symptom ascertainment methods. In addition, the inconsistent terminology describing symptoms and limited details on pre-existing comorbidities, the severity of covid-19, and treatment methods prevented reliable meta-analysis. This inconsistency and limited reporting partly explain the high degree of variability observed and prevents us from drawing clear estimates of symptom prevalence. Smaller studies were not included in the analysis in order to avoid bias; this together with the limited reporting in the included studies may mean that new, emerging evidence was not detected in this version.

‘Long covid’ is an emerging area of study and we anticipate future updates of this review will address these challenges, provided more robust and consistent methods are used to study ‘long covid’ in the future. Such is the strength of a living systematic review approach.

**Future research directions**

Our findings have identified several research gaps which should help inform future research priorities. The available data do not allow a direct attribution of multifactorial symptoms solely to covid-19. Larger prospective studies with matched control groups are needed to clearly establish causal links but may be challenging in community settings.

Our study confirms the need for standardised, validated covid-19 research tools to harmonise data collection and reduce reporting variability. The International Severe Acute Respiratory
and emerging Infection Consortium has developed open access research tools available to sites globally to facilitate standardisation of data collection.[56]

Our findings also reflect a lack of evidence among certain populations and settings. For example, there is limited data for non-hospitalised patients, suggesting a need for more studies to be conducted in the community. Similarly, our review did not identify studies focusing on children, yet anecdotal evidence shows there are also long-term symptoms among paediatric populations.[57] Additionally, no study was set in a LMIC.

As this is a living systematic review, emerging themes from this first version will inform future updates. Search terms will be adjusted in light of new evidence. The LSR will be updated periodically, as new research is published internationally, in order to provide relevant up to date information for clinicians, patients, researchers, policymakers, and health-service commissioners. Version changes will be identified, and previous reports will be archived.

**CONCLUSION**

The evidence presented in this living systematic review summarises findings on the spectrum of long term covid-19 associated symptoms and sequelae up to 28th September 2020. Currently the strength of the available evidence is limited and prone to bias. The long-term effects of covid-19, in both hospitalised and non-hospitalised individuals, should be a priority for future research using robust study designs. Robust research is needed to inform a long covid-19 clinical case definition, prevention, rehabilitation, clinical and public health management to improve long term covid-19 outcomes and recovery.
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Authors contributions:
MM and CS led on the drafting of the manuscript with contributions from AD, VC, NE, CS, LM, LS, CH, MOH, JS, GC, PO. MM, NE, LM, VC, CS critically appraised the studies. VC led on the presentation of the results. CS, MM, VC, LS conceptualised the study, all authors contributed to the final protocol, the interpretation and analysis of the results. All co-authors reviewed and approved the manuscript (MM, VC, NE, LM, LS, CS, DD, JS, MO’H, CH, AB, CF, GC, PO).

Competing interest statement:
All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. JCS declares he is an individual living with long-term symptoms of probably covid-19. All other authors declare no other relationships or activities that could appear to have influenced the submitted work.
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Identification
- Records identified from literature search (n = 1541)
- Additional records from other sources and researcher input (n = 12)

Screening
- Records identified from literature search (n = 1541)
- Records after duplicates removed, screened by title and abstract (n = 1335)
- Records excluded after title and abstract screening (n = 1085)

Eligibility
- Full-text articles assessed for eligibility (n = 250)
- Full-text articles excluded (n = 150)
  - Ineligible population (n = 62)
  - Ineligible follow up time (n = 33)
  - No persisting symptoms described (n = 29)
  - Ineligible study design or publication type (n = 26)

Included
- Studies identified (n = 100)
- Pre-prints, case reports and small case series not extracted but listed with bibliography (n = 72)

Studies that met the criteria for data extraction (n = 28)
Long Covid symptoms

People non-hospitalised during acute phase of COVID-19
Based on 7 studies with 3378 people aged 18 or over

- Neurological
  - Taste disturbance
  - Smell disturbance
  - Headache
  - Visual disturbance*
  - Ear pain*

- Musculoskeletal
  - Muscle pain
  - Joint pain*

- Gastrointestinal
  - Nausea
  - Abdominal pain
  - Diarrhoea
  - Loss of appetite

- Systemic
  - Fever
  - Weakness

- Fatigue

- Other
  - Dizziness
  - Skin rash*

- Upper respiratory
  - Sore throat
  - Sinonasal pain
  - Nasal congestion

- Cardiopulmonary
  - Breathlessness*
  - Chest pain
  - Cough
  - Palpitations*

- Psychosocial
  - Post-traumatic stress disorder*
  - Depression*
  - Anxiety*
  - Sleep disorder
  - Psychological symptoms*
  - Care dependency

People hospitalised during acute phase of COVID-19
Based on 16 studies with 3172 people aged 18 or over

- Neurological
  - Taste disturbance
  - Smell disturbance
  - Headache
  - Visual disturbance*
  - Ear pain*

- Musculoskeletal
  - Muscle pain
  - Joint pain

- Gastrointestinal
  - Difficulty swallowing
  - Nausea
  - Diarrhoea
  - Loss of appetite

- Bowel continence problems

- Systemic
  - Fever
  - Weakness

- Fatigue

- Other
  - Dizziness
  - Urinary continence problems
  - Hair loss
  - Skin rash*

- Upper respiratory
  - Sore throat
  - Voice change
  - Nasal congestion*

- Cardiopulmonary
  - Breathlessness
  - Chest pain
  - Cough
  - Palpitations*

- Neurocognitive
  - Memory impairments
  - Concentration impairments

- Psychosocial
  - Post-traumatic stress disorder
  - Depression
  - Anxiety
  - Sleep disorder
  - Impaired mobility
  - Care dependency
  - Falls
  - Reduced quality of life
  - Unspecified psychological symptoms

* Identified in studies including both hospitalised and non-hospitalised people (5 studies including 2892 people)

Last updated 28 Sep 2020
| Study                  | n/N    | RoB | Study                  | n/N    | RoB | Study                  | n/N    | RoB |
|-----------------------|--------|-----|-----------------------|--------|-----|-----------------------|--------|-----|
| Fatigue               | 9/125  |     | Anxiety               | 28/126 |     | Breathlessness         | 62/143 |     |
| Borgioanni et al.     |        |     | Cai et al.            |        |     | Carfi et al.           |        |     |
| Carfi et al.          | 76/143 |     | Halpin et al.         | 11/68  |     | Garrigues et al.       | 50/120 |     |
| Garrigues et al.      | 66/120 |     | Halpin et al. (ICU)   | 12/32  |     | Halpin et al.          | 26/68  |     |
| Halpin et al.         | 41/68  |     | Liu et al.            | 219/675|     | Halpin et al. (ICU)    | 21/32  |     |
| Halpin et al. (ICU)   | 23/32  |     | Tomasoni et al.       | 29/100 |     | Pellau et al.          | 41/73  |     |
| Liu et al.            | 88/675 |     | Wu et al.             | 50/370 |     | Rahmani et al.         | 6/176  |     |
| Yan et al.            | 5/337  |     | Yan et al.            | 17/337 |     | Somani et al.          | 52/103 |     |
| Fever                 | 18/125 |     | Sleep Disorder        | 48/126 |     | Tomasoni et al.        | 7/106  |     |
| Borgioanni et al.     |        |     | Garrigues et al.      |        |     | Wang et al.            | 2/131  |     |
| Carfi et al.          |        |     | Wu et al.             |        |     | Wu et al.              | 45/370 |     |
| Garrigues et al.      |        |     | Yan et al.            |        |     | 28/337                |       |     |
| Weakness              |        |     | Nausea                | 1/131  |     | Chest Pain            | 31/143 |     |
| Wang et al.           | 4/337  |     | Yan et al.            | 1/337  |     | Carfi et al.           | 13/120 |     |
| Diarrhoea             |        |     | Sleep Disorder        | 37/120 |     | Garrigues et al.       | 96/875 |     |
| Yan et al.            |        |     | Wu et al.             | 109/370|     | Liu et al.             | 6/103  |     |
| Loss of Appetite      | 6/68   |     | Psychological Symptoms | 39/126 |     | Somani et al.          | 1/113  |     |
| Halpin et al.         | 2/32   |     | Cai et al.            |        |     | Cough                 | 20/120 |     |
| Halpin et al. (ICU)   | 22/103 |     | Halpin et al.         | 10/68  |     | Garrigues et al.       | 9/372  |     |
| Bowel Contiencence    | 28/68  |     | Halpin et al. (ICU)   | 15/32  |     | Liu et al.             | 12/131 |     |
| Bell et al.           | 1/32   |     | Somani et al.         | 5/103  |     | Wang et al.            | 60/370 |     |
| Halpin et al.         | 4/68   |     | Reduced GoL©          | 6/143  |     | Wu et al.              | 31/370 |     |
| Halpin et al. (ICU)   | 4/32   |     | Carfi et al.          |        |     | Yan et al.             | 3/137  |     |
| Difficulty swallowing | 4/68   |     | Halpin et al.         | 10/68  |     | Sore Throat            |        |     |
| Halpin et al.         | 4/32   |     | Halpin et al. (ICU)   | 5/103  |     | Halpin et al.          | 8/88   |     |
| GI Symptoms           | 1/106  |     | Falls                 | 5/103  |     | Halpin et al. (ICU)    | 8/32   |     |
| Tomasoni et al.       |        |     | Somani et al.         |        |     | Wang et al.            | 2/131  |     |
| Taste Disturbance     | 13/120 |     | Impaired Mobility     | 5/53   |     | Voice Change           |        |     |
| Garrigues et al.      | 7/73   |     | Bell et al.           | 5/103  |     | Halpin et al.          | 10/98  |     |
| Pellau et al.         | 6/105  |     | Care Dependency       | 49/103 |     | Muscle pain            | 10/88  |     |
| Tomasoni et al.       |        |     | Bell et al.           |        |     | Halpin et al.          | 9/32   |     |
| Smell Disturbance     | 18/120 |     | Memory Impairments    | 41/120 |     | Somani et al.          | 6/103  |     |
| Garrigues et al.      | 7/73   |     | Garrigues et al.      |        |     | Yan et al.             | 1/337  |     |
| Pellau et al.         | 6/105  |     | Halpin et al. (ICU)   |        |     | Joint pain             |        |     |
| Tomasoni et al.       |        |     | Halpin et al. (ICU)   |        |     | Carfi et al.           | 39/143 |     |
| Dizziness             | 4/176  |     | Tomasoni et al.       |        |     |                     |        |     |
| Rahmani et al.        |        |     |                      |        |     |                     |        |     |
| Urinary Incontinence  | 28/103 |     |                      |        |     |                     |        |     |
| Bell et al.           | 28/103 |     |                      |        |     |                     |        |     |
| Halpin et al.         | 6/68   |     |                      |        |     |                     |        |     |
| Halpin et al. (ICU)   | 4/32   |     |                      |        |     |                     |        |     |
| Skin Rash             | 5/103  |     |                      |        |     |                     |        |     |
| Somani et al.         |        |     |                      |        |     |                     |        |     |
| Hair Loss             | 24/120 |     |                      |        |     |                     |        |     |
| Garrigues et al.      | 3/176  |     |                      |        |     |                     |        |     |
| Rahmani et al.        |        |     |                      |        |     |                     |        |     |

**Symptom cluster**
- Fatigue
- Musculoskeletal
- Upper Respiratory
- Systemic
- Neurocognitive
- Neurological
- Gastrointestinal
- Psychosocial

**Risk of bias**
- Low
- Medium
- High
| Symptom                | Study                                      | n/N         | RoB |
|------------------------|--------------------------------------------|-------------|-----|
| Fatigue                | Boscolo-Rizzo et al.                       | 20/121      | Red |
|                        | Lovato et al.                              | 1800/1837   | Red |
|                        | Vaes et al.                                |             |     |
| Fever                  | Boscolo-Rizzo et al.                       | 5/104       | Green |
|                        | Lovato et al.                              | 11/121      | Red |
| Weakness               | Vaes et al.                                | 1653/1837   | Red |
| Breathlessness         | Boscolo-Rizzo et al.                       | 30/77       | Green |
| Chest Pain             | Boscolo-Rizzo et al.                       | 2/29        | Green |
| Cough                  | Boscolo-Rizzo et al.                       | 46/116      | Green |
|                        | Lovato et al.                              | 18/121      | Red |
| Sore Throat            | Boscolo-Rizzo et al.                       | 8/59        | Green |
| Nasal Congestion       | Boscolo-Rizzo et al.                       | 16/70       | Green |
|                        | Lovato et al.                              | 7/121       | Red |
| Sinonasal Pain         | Boscolo-Rizzo et al.                       | 3/31        | Green |
| Nausea                 | Boscolo-Rizzo et al.                       | 1/38        | Green |
| Diarrhoea              | Boscolo-Rizzo et al.                       | 10/84       | Green |
| Loss of Appetite       | Boscolo-Rizzo et al.                       | 14/101      | Green |
| Abdominal Pain         | Boscolo-Rizzo et al.                       | 2/23        | Green |
| Sleep Disorder         | Vaes et al.                                | 1617/1837   | Red |
| Care Dependency        | Vaes et al.                                | 65/210      | Red |
| Taste Disturbance      | Boscolo-Rizzo et al.                       | 58/113      | Green |
|                        | Brandao et al.                             | 39/143      | Red |
|                        | Fjaeldstad et al.                          | 54/104      | Red |
|                        | Lovato et al.                              | 26/121      | Red |
| Smell Disturbance      | Boscolo-Rizzo et al.                       | 58/113      | Green |
|                        | Brandao et al.                             | 64/143      | Red |
|                        | Chiesa-Estomba et al.                      | 275/751     | Yellow |
|                        | Fjaeldstad et al.                          | 56/100      | Red |
|                        | Lovato et al.                              | 26/121      | Red |
|                        | Villarreal et al.                          | 43/165      | Red |
| Headache               | Boscolo-Rizzo et al.                       | 19/80       | Green |
| Muscle pain            | Boscolo-Rizzo et al.                       | 17/85       | Green |
|                        | Lovato et al.                              | 14/121      | Red |
|                        | Vaes et al.                                | 1598/1837   | Red |
| Dizziness              | Boscolo-Rizzo et al.                       | 3/25        | Green |

**Risk of bias**

- **Low**
- **Medium**
- **High**

**Symptom cluster**

- Fatigue
- Systemic
- Cardiopulmonary
- Gastrointestinal
- Musculoskeletal
- Neurological
- Psychosocial
- Upper Respiratory
- Other
