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Summary: What is the prevalence of the post COVID-19 syndrome (defined as having signs and symptoms 12 weeks post the acute phase of the infection)?

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Title

What is the prevalence of the post COVID-19 syndrome (defined as having signs and symptoms 12 weeks post the acute phase of the infection)?

Summary answer

In this UNCOVER rapid review we summarise and critically appraise the evidence on the prevalence of post COVID-19 syndrome, clinically defined as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis" (NICE, 2020).

We included **7 systematic reviews** (published up to 18 March 2021) and **42 primary studies** (published between 1 January 2021 and 18 March 2021) (all references are provided in a separate file). The main post COVID-19 syndrome symptoms examined in the included studies were systemic, cardiopulmonary, gastrointestinal, neurological, and psychosocial symptoms, of which the most common were breathlessness, fatigue, smell and taste disturbance, and anxiety.

Of the seven systematic reviews, four were published and three were pre-prints; there were six systematic reviews and one rapid living review. Six of the included systematic reviews focused exclusively on adults and one exclusively on children (Ludvigsson, 2021). Three focused specifically on persistent lung sequelae (Cares-Marambio et al., 2021; Fabbri et al., 2021; Torres-Castro et al., 2020). Of the 42 primary studies, 21 were published and 21 were pre-prints; 30 were prospective or retrospective cohort studies, 4 were cross-sectional and 8 were case-series.

There are severe limitations with the quality and scope of the literature, as explained below. The answer we can provide to the question at this stage is, therefore, heavily caveated: we cannot provide an estimate of prevalence with any degree of certainty. Within these limitations, if we focus only on high quality cohort studies with large sample sizes (> 1000), in European or North American populations, with outcomes reported separately for hospitalised and non-hospitalised cases, we can identify **three studies that we judge provide the best available estimates at this time**.

Hospitalised patients: Ayoubkhani et al followed-up 47,780 adult COVID-19 patients for a mean time of 140 days after discharge from NHS England hospitals and they reported a prevalence of 4.9% of new diagnoses of diabetes, 4.8% of a major adverse cardiovascular event, 1.5% of chronic kidney disease and 0.3% of chronic liver disease. 29.4% were re-admitted and 12.3% died post discharge (Ayoubkhani et al., 2021a).

Non-hospitalised patients: Sudre et al analysed data from 4,182 incident cases of COVID-19 in which adults from the UK, USA and Sweden self-reported their symptoms prospectively in the COVID Symptom Study app; 2.3% of the responders reported symptoms (including fatigue, headache, dyspnea and anosmia) lasting form more than 12 weeks (Sudre et al., 2021).

Hospitalised and non-hospitalised patients: Results from the Coronavirus (COVID-19) Infection Survey from the Office of National Statistics suggest that among a sample of over 20,000 study participants who tested positive for COVID-19 between 26 April 2020 and 6 March 2021 in the UK, 13.7% continued to experience self-reported symptoms (any of the following: abdominal pain, cough, diarrhoea, fatigue, fever, headache, loss of smell, loss of taste, myalgia, nausea/vomiting, shortness of breath, sore throat) for at least 12 weeks. This was eight times higher than in a control group of participants who are unlikely to have had COVID-19. 54.3% of people with self-reported long COVID contacted the NHS but were not hospitalised at the time of first (suspected) infection, while 8.6% were admitted to hospital. The most prevalent self-reported symptoms that persisted for at least 12 weeks post-infection were fatigue (8.3%), headache (7.2%), cough (7.0%), and myalgia (5.6%). (Ayoubkhani et al., 2021b).

Limitations of the literature

The seven systematic reviews do not provide sufficiently robust evidence to estimate the prevalence of symptoms of COVID-19 persisting beyond 3 months with any degree of certainty. This is for the following reasons:

- **Timing**: The primary studies on which these reviews were based were conducted in the early months of the pandemic, and as such, few include follow-up periods longer than 12 weeks. None of the reviews we found focused exclusively on the time period of interest, although all included at least one primary study with follow up of > 12 weeks. Future updates of the included living rapid review (Michelen et al, 2020) and a living systematic review (Ceravolo et al., 2020) that was excluded, as it did not report any studies following up patients for > 12 weeks will likely be of interest.
- **Heterogeneity**: There is considerable heterogeneity in the primary studies – some studies focus on a particular patient population (e.g. hospitalised, non-hospitalised, ICU or ventilated patients), whilst others focus on mixed populations. Review results are not stratified by disease severity or by age, sex, ethnicity or previous comorbidities, so it is not possible to say how representative or generalizable these results are.
- **Quality**: The quality of the included systematic reviews was low (2 reviews – Michelen, 2020 and Torres-Castro, 2020) to critically low (5 reviews – Cares-Marambio, 2021; Fabbri, 2021; Ludvigsson, 2021; Lopez-Leon, 2021; Willi, 2021) on the basis of AMSTAR2 criteria (Shea et al., 2017)).

Furthermore key limitations of the evidence from primary studies (either those included in the systematic reviews or newly identified) are:

- Studies are based on a variety of **different populations** (hospitalised, non-hospitalised, ICU and mixed cohorts), where it is expected that hospital survivors will have greater symptom burden than community cases.
- The **representativeness** of the populations may be limited given that there is over-representation of patients with severe illness that will increase the prevalence of persisting symptoms.
- Most of the primary studies are case series and the **lack of control groups** severely limits the conclusions which can be drawn.
- **Few primary studies presented data on baseline symptoms** and therefore further research needed to establish whether the reported symptoms are new, related to COVID-19, or associated with COVID-19 measures (e.g. lockdown) rather than COVID-19 itself.

Recommendations

As new research emerges, high quality, living systematic review evidence is required, which will:

- Extract data from high quality cohort studies with control groups;
- Stratify results by initial disease severity, pre-existing comorbidities, age, sex and ethnicity.

Extended abstract

To identify relevant studies reporting on the post COVID-19 syndrome (defined by NICE as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis (NICE, 2020), we used a combination of literature database searches, screening the UNCOVER reviews register, and screening websites of key organisations, and consultation with experts to identify relevant literature. The literature databases Medline, WHO Covid-19 literature database, and ZBMed's preVIEW database of COVID-related preprints were searched (MD, LG, PK). Search histories for each database are available in the full report. PK screened the UNCOVER reviews register. XZ screened the websites of Office for National Statistics, COVID Symptom Study, BMJ, MSD, Harvard Health Publishing, NIHR, CDC, Mayo Clinic, Houston Methodist leading medicine, NICE, British lung foundation, BMA, gov.uk, WHO, Beat

heartbreak forever, Don't forget the bubbles. Database search results, UNCOVER register results, and papers identified by experts were added to an EndNote library and de-duplicated. The remaining records were uploaded to Covidence for title and abstract, and full text screening stages. This search covers the period up to 18 March 2021.

A total of 820 publications were retrieved and 786 were screened after 34 duplicates were removed (**Figure 1**). The literature screening was shared between 13 reviewers (WX, ET, RM, LG, JR, YD, PK, MN, GC, EMcS, DI, EG, AK) using predefined inclusion and exclusion criteria (see full report). Each new title, abstract and full text was screened by two reviewers using Covidence. After parallel review, a total of 49 unique studies were included: 7 systematic reviews and 42 primary studies conducted after 1 January 2021. Data were extracted using two data extraction forms and included studies were critically appraised using the following tools: NICE guidelines for case series (NICE, 2003), JBI appraisal tools for primary studies (JBI, n.d.) and AMSTAR 2 for systematic reviews (Shea et al., 2017). Data extraction and critically appraisal was conducted by 1 reviewer (WX, ET, RM, LG, JR, YD, PK, MN, GC, EMcS, DI, EG, AK) and the details are presented in **Tables 1-3** in the accompanied excel file.

Key results from systematic review evidence

Key symptoms in adults where it was possible to extract prevalence estimates were fatigue (three reviews, prevalence range 1.5 to 73%), neurological/cognitive symptoms (2 reviews, prevalence range 27 – 55%), dyspnoea (2 reviews, prevalence range 24-74%), headache (one review, prevalence estimate 44% (95% CI 13, 78)), reduced lung function (3 studies, prevalence range 5 to 83%) and mental health (anxiety and depression – two reviews, prevalence range 5 to 13%). The systematic review focusing on "long COVID" in children analysed 19 publications but found none with any relevant information. Details and references of all seven systematic reviews are presented in the full report.

Key results from primary studies published in 2021

Seven studies included more than 1,000 COVID-19 patients, 5 of which were pre-prints. Huang et al found that at 6 months after acute infection, 76% of 1,655 adult COVID-19 survivors (discharged from Jin Yin-tan Hospital (Wuhan, China)) had at least one symptom with the main ones being fatigue or muscle weakness, sleep difficulties, and anxiety or depression (Huang et al., 2021). Ayoubkhani et al followed-up 47,780 adult COVID-19 patients for a mean time of 140 days after discharge from NHS England hospitals and they reported a prevalence of 4.9% of new diagnoses of diabetes, 4.8% of a major adverse cardiovascular event, 1.5% of chronic kidney disease and 0.3% of chronic liver disease. 29.4% were re-admitted and 12.3% died post discharge (Ayoubkhani et al., 2021a). Perlis et al did ten waves of a fifty USA state survey and included 6,211 adult survey respondents reporting COVID-19 illness. Of those 3.4% were symptomatic for 4 months or more and 2.2% for 6 months or more (Perlis et al., 2021). Taquet et al used a retrospective cohort study design of 236,379 USA patients (age >=10 years old) with a confirmed COVID-19 diagnosis to estimate the incidence of ICD-10 diagnoses in the 6 months after a confirmed diagnosis of COVID-19. They found that 12.8% of the included patients received a first diagnosis of a neurological or psychiatric sequelae at 6 months (Taquet, John, Masud, Sierra, & Paul, 2021). Sudre et al analysed data from 4,182 incident cases of COVID-19 in which adults from the UK, USA and Sweden self-reported their symptoms prospectively in the COVID Symptom Study app; 2.3% of the responders reported symptoms (including fatigue, headache, dyspnea and anosmia) lasting form more than 12 weeks (Sudre et al., 2021). The PHOSP-COVID is a multi-centre, UK, observational study of adults discharged from hospital with a clinical diagnosis of COVID-19 and they reported that of 1,077 patients discharged in 2020 92.8 % had at least one persistent symptom (median (IQR) number of 9 (4 to 16) symptoms) at 5 months (IQR 4-6 months) after discharge (Evans et al., 2021). Munblit et al followed-up 2,649 adults COVID-19 patients discharged from the Sechenov University Hospital Network in Moscow, Russia. After a median follow-up time of 217.5 days (IQR 200.4-235.5), 47.1% participants reported persistent symptoms with fatigue, shortness of breath and forgetfulness being the most commonly reported (Munblit et al., 2021). Details and references of the remaining 38 primary studies are presented in the full report.

Additional identified research items

In addition to published studies and pre-print articles, we identified the following grey literature items. A policy brief by WHO Europe (Rajan, Khunti, Alwan, Steves, & Greenhalgh, 2021) concluded that one in ten people that were infected with SARS-COV-2 are still unwell after 12 weeks. In this brief the prevalence, main symptoms, main risk factors and policy responses in Europe are also highlighted. In addition, the NIHR has published two themed reviews on Long COVID (NIHR, 2020) (NIHR, 2021b), with the most recent one having considered more than 300 papers and academic opinion pieces and concluding that for those admitted to hospital, between 50-89% had at least one enduring symptom after two months and of those not admitted to hospital at least 10% experience one or more enduring symptoms three months later. Both the WHO and NIHR reports conclude that persisting symptoms appear to be more prevalent in women, health workers and children. Finally, the Office for National Statistics, plans to estimate the prevalence and risk factors of "long COVID" and they have released initial results, where they estimate that the prevalence of post COVID-19 syndrome in the UK is 9.9% (95% Confidence Interval 6.7%-14.7%) (ONS, 2020). In addition, ONS released data on 01/04/2020, suggesting that of people with self-reported long COVID, 697,000 first had (or suspected they had) COVID-19 at least 12 weeks previously, and 70,000 first had (or suspected they had) COVID-19 at least one year previously. In addition, among a sample of over 20,000 study participants who tested positive for COVID-19 between 26 April 2020 and 6 March 2021, 13.7% continued to experience symptoms for at least 12 weeks. This was eight times higher than in a control group of participants who are unlikely to have had COVID-19 (Ayoubkhani, 2021b).

Future research is urgently needed to understand the prevalence, symptoms and risk factors of post COVID-19 syndrome both in adults and children. The UK and Scottish governments have funded a number of studies already (Chief Scientist Office, n.d.; DHSC, 2021) and a new £20M NIHR call was launched in March 2021 (NIHR, 2021a).

Disclaimer

This rapid review has not been peer-reviewed. Many of the included studies are pre-print publications or reports and therefore not peer-reviewed either. This review should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent those of the authors and are not a substitute for professional medical advice.

Date completed

1 April 2021

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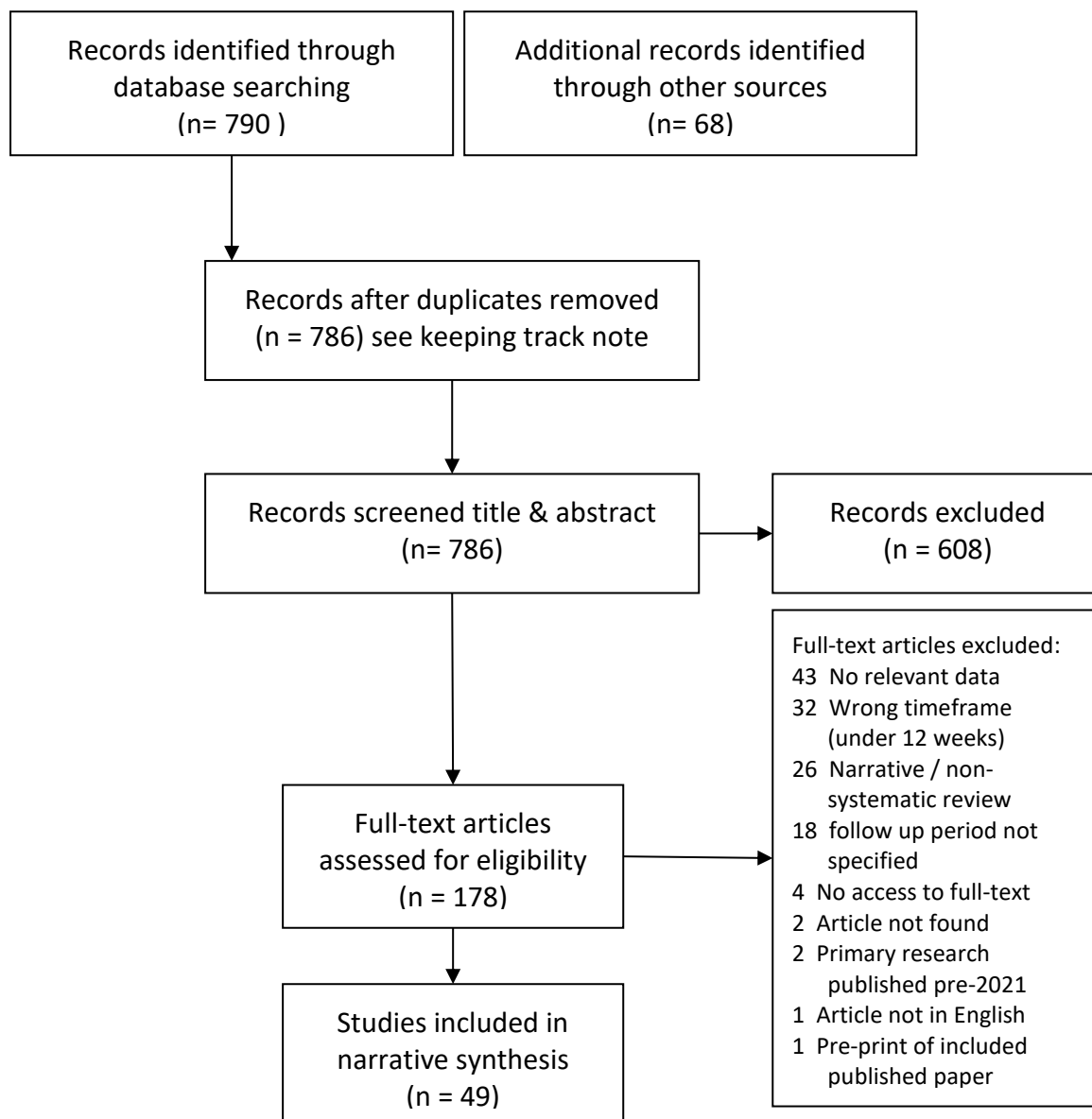Expert advice was given by Nazir Lone, Gerry Fowkes and Harry Campbell

Records identified through
database searching
(n= 790)

Additional records identified
through other sources
(n= 68)

Records after duplicates removed
(n = 786) see keeping track note

Records screened title & abstract
(n= 786)

Records excluded
(n = 608)

Full-text articles
assessed for eligibility
(n = 178)

Full-text articles excluded:
43 No relevant data
32 Wrong timeframe
    (under 12 weeks)
26 Narrative / non-
    systematic review
18 follow up period not
    specified
4 No access to full-text
2 Article not found
2 Primary research
    published pre-2021
1 Article not in English
1 Pre-print of included
    published paper

Studies included in
narrative synthesis
(n = 49)

Figure 1: PRISMA flow chart

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