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memo

COVID-19-EPIDEMIC :

Long-Term Symptoms after COVID-19 – a rapid review

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English Summary

Background

For most COVID-19 is a mild and transient disease, although some may experience a prolonged period with symptoms before resolution. Long-term and nonspecific symptoms have been previously reported in connection with other viral infections, and it is thus not surprising that some patients experience long-term symptoms after covid-19. It is already known that people who are admitted to the intensive care unit due to severe lung failure can report long-term functional impairments such as impaired cognitive function and reduced lung function after discharge.

Prolonged symptoms have previously been observed after other viral infections, but since covid-19 has caused a pandemic, it is useful to gather knowledge about which long-term symptoms occur, how long the symptoms persist, and which patient groups have greatest risk of experiencing prolonged symptoms.

Objectives

In this rapid review, we summarize research on which long-term symptoms occur after COVID-19, how long the symptoms persist and which patient groups that have the greatest risk of experiencing long-term symptoms.

Methods

This rapid review is the 1st update in the series "*COVID-19: Long-Term Effects of COVID-19"* replacing our previous report published on March 3rd, 2021. In this review, only peer-reviewed studies with around six months follow-up or longer, and more than 100 laboratory test positive COVID-19 cases were included. We excluded studies mainly reporting on laboratory or radiological findings.

The findings are based on systematic searches in MEDLINE and WHO Global research on coronavirus disease (COVID-19) database on June 17th, 2021. One researcher screened the search results. Two researchers selected studies for inclusion and summarised study findings. Experts in the field assisted with study inclusion and provided input during the review process.

We assessed included studies in terms of quality and risk of bias using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case Series Studies.

Meta-analysis was not feasible, and the results of this rapid review are therefore presented in tables, graphics and narratively.

Results

Characteristics of included studies

We included 20 peer-reviewed studies following patients for six months or longer, analysing symptoms, quality of life or demographic and medical risk factors. Fourteen studies were conducted in Europe, thereof four in Norway. Number of participants ranged from 113 to 8 983 (19 035 in total). Participants in most studies were middle-aged, and one study only enrolled children. Sex distribution was mainly balanced. All studies used laboratory testing to diagnose COVID-19, mainly PCR. All but two studies started enrolling patients before April 2020. Follow ups were performed either at clinics or through online/phone/postal surveys, except for one study which used registry-data. Loss to follow up was generally high and ranged from six to 61%. Eleven studies followed patients who had been hospitalised with COVID-19 (>50% of participants hospitalised in intensive care unit (ICU) or other hospital department). Ten studies included both ICU and non-ICU patients, and one study included a mixed population of hospitalised and non-hospitalised patients. Nine studies followed patients with COVID-19 who did not need hospitalisation (>50% of participants non-hospitalised), including three studies with a mixed-populations with mostly non-hospitalised patients. Our quality assessment indicated that most studies were of fair quality.

Overview of symptoms around six months follow-up

The presence of any symptom six months after COVID-19 hospitalisation ranged from twelve to 81%, with dyspnoea, fatigue, anxiety and sleeping problems most reported across the studies. Five studies reported negative changes in Health-related quality of Life (HRQoL).

The presence of any one symptom at around six months after COVID-19 (non-hospitalised) ranged from eight to 61%, with fatigue, dyspnoea, loss of smell and taste being the most reported. Three studies reported negative impacts on cognitive abilities and activities of daily living.

Overview of grouped signs and symptoms

Participants reported a wide range of symptoms at and beyond six months after COVID-19. Categorisation based on ICD symptom groups revealed that *General*, *Neurological* and *Pulmonary* symptoms were the most common. Whereas hospitalised patients reported a physiologically broad spectrum of symptoms beyond the three most common groups, this pattern was less apparent among non-hospitalised patients. Across symptom groups, hospitalised patients reported more symptoms more frequently than non-hospitalised patients.

Impact on quality of Life

Across eight studies assessing quality of life after COVID-19, a reduction in overall health and quality of life was observed in 25%- 61% of hospitalised patients and 25%-46% of non-hospitalised patients. In critically ill patients, pain was the most detrimental symptom to quality of life after COVID-19. Overall, a reduction in mobility, a higher incidence of anxiety and depression, and fatigue impacted their quality of life most.

Predicting factors for long-term symptoms
Across the ten studies analysing predicting factors for length of symptoms, female sex was the most consistent variable associated with duration of symptoms, independent of hospitalisation status. In addition, severity of COVID-19, multiple symptoms at diagnosis and prior comorbidities were also correlated with length of symptoms.

Discussion

Most studies only included SARS-CoV-2 test-positive participants and no control group, a strong limitation in evaluating COVID-19 specific long-term effects. Therefore, it remains uncertain how far prevailing symptoms and impact on quality of life are specific to COVID-19 or more generally attributable to a period of illness. Equally, pandemic related infringements on personal liberty, lockdowns and changes to pre-pandemic lifestyle might also be factors underlying reporting of some symptoms. Our findings reflect participants with COVID-19 in studies that were conducted early in the pandemic, and we don't know how therapeutic advancements, new virus variants or vaccination have and will impact outcomes in the future. The heterogeneity across studies impairs direct comparison of risk estimates, and hence meta-analysis was not feasible. It should be noted that causal relationships cannot be confirmed or refuted based on the included study designs. Larger controlled studies, with participants from throughout the pandemic are needed for a more exhaustive understanding.

Conclusion

Many COVID-19 patients reported prevailing symptoms after infection, with a large proportion continuing to experience one or more symptoms at six months or longer. Severe COVID-19, requiring hospitalisation or intensive care treatment correlated with longer and more severe functional limitations at follow up. Hospitalised patients had a wider range of symptoms than non-hospitalised with general, neurological and pulmonary symptoms being most common among both groups. Women had a higher risk for developing long-term symptoms.

Norsk sammendrag

Bakgrunn

For de fleste er covid-19 en mild og forbigående sykdom, men personer som gjennomgår covid-19 kan oppleve at det tar lang tid før de blir kvitt alle symptomer etter sykdommen. Denne formen for langvarige og uspesifikke symptomer er tidligere rapportert i forbindelse med andre virusinfeksjoner, og det er slik sett ikke overraskende at en del pasienter opplever langvarige symptomer etter covid-19. Fra før vet man også at personer som legges inn på intensivavdeling på grunn av alvorlig lungesvikt kan rapportere langvarige funksjonsnedsettelser som nedsatt kognitiv funksjon og redusert lungefunksjon etter utskriving.

Langvarige symptomer etter virusinfeksjoner er altså ikke noe nytt, men ettersom covid-19 er forårsaket av et nytt koronavirus som har medført en pandemi, er det nyttig å samle kunnskap om hvilke langvarige symptomer som opptrer, hvor lenge symptomene vedvarer og hvilke pasientgrupper som har størst risiko for å oppleve langvarige symptomer.

Problemstilling

I denne hurtigoversikten oppsummerer vi forskning om hvilke langvarige symptomer som opptrer etter covid-19, hvor lenge symptomene vedvarer og hvilke pasientgrupper som har størst risiko for å oppleve langvarige symptomer.

Metoder

Denne hurtigoppsummeringen er en oppdatering av "*Covid-19: Langvarige effekter av covid-19*", og den erstatter versjonen som ble publisert 3. mars 2021. I denne oppdateringen har vi inkludert fagfellevurderte studier med om lag seks måneders oppfølging som inkluderte mer enn 100 deltakere med laboratoriebekreftet covid-19. Vi ekskluderte studier som kun presenterte laboratorie- og radiologiske funn.

Vi gjennomførte systematiske litteratursøk i MEDLINE og WHO Global research on coronavirus disease (COVID-19) database 17. juni 2021. Én forsker gjennomgikk søkeresultatene, og to forskere valgte ut studier for inklusjon, ekstraherte data og sammenstilte resultater. Eksperter fra relevante fagfelt bidro i vurderingen av studier for inklusjon og bisto fortløpende med faglig innspill.

Vi vurderte inkluderte studier med tanke på kvalitet og risiko for skjevheter ved hjelp av NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case Series Studies. Sammenstilling av resultater i metaanalyser var ikke mulig, så vi presenterer hovedresultatene i denne hurtigoppsummeringen i tabeller, grafer og narrativt.

Resultater

Beskrivelse av inkluderte studier

Vi inkluderte 20 fagfellevurderte studier, som rapporterte symptomer, livskvalitet eller demografiske og medisinske risikofaktorer. Fjorten av studiene var utført i Europa, hvorav fire i Norge. Antall deltakere varierte fra 113 i den minste studien til 8 983 i den største studien (totalt 19 035 på tvers av alle studier). Deltakerne i de fleste studiene var middelaldrende, og bare én studie inkluderte barn. Studiene omfattet omtrent like mange kvinner som menn. Alle studier benyttet laboratorietester til å bekrefte smitte med covid-19, hovedsakelig PCR. Alle unntatt to studier startet å rekruttere pasienter før april 2020. Oppfølging ble gjennomført på en klinikk eller ved bruk av spørreundersøkelser på telefon/nett/post, med unntak av én studie som baserte seg på registerdata. Frafallet av pasienter i oppfølgingsperioden var generelt stort, men varierte mellom seks og 61%. Elleve studier fulgte hovedsakelig opp pasienter som hadde vært innlagt på sykehus (>50 % av deltakerne innlagt på intensiv eller annen avdeling) på grunn av covid-19, og ti av disse studiene inkluderte både intensiv- og ikke-intensivpasienter. Ni studier rapporterte i hovedsak symptomer blant pasienter med covid-19 som ikke hadde vært innlagt på sykehus (>50 % av deltakerne ikke innlagt). Vår kvalitetsvurdering av inkluderte studier tydet på at de fleste studiene hadde rimelig kvalitet.

Oversikt over symptomer rundt seks måneders oppfølging

Mellom tolv og 81% av pasientene som hadde vært innlagt på sykehus hadde minst ett symptom som vedvarte til seks måneders oppfølging og lenger. De vanligste symptomene var dyspné, tretthet/utmattelse, angst og søvnproblemer. Fem studier rapporterte negative endringer i helserelatert livskvalitet (HRQoL).

Andelen pasienter som rapporterte minst ett symptom omtrent seks måneder etter covid-19 (ikke-innlagt) varierte mellom åtte og 61%, og tretthet/utmattelse, dyspné og nedsatt lukte- og smaksans forekom hyppigst. Tre studier rapporterte nedsatt kognitiv funksjon og redusert nivå av aktiviteter i dagliglivet blant noen deltakere.

Gruppering av kliniske tegn og symptomer

De inkluderte studiene viste at noen pasienter rapporterte et bredt spekter av symptomer seks måneder og mer etter gjennomgått covid-19. Kategorisering basert på ICD symptomgrupper viste at allmennsymptomer, nevrologiske og lungesymptomer var de vanligste vedvarende symptomene. Mens sykehusinnlagte pasienter rapporterte et bredt spekter av fysiske symptomer utover de tre vanligste gruppene, var dette mindre tydelig hos pasienter som ikke hadde vært innlagt. Uavhengig av symptomgruppe, rapporterte sykehusinnlagte pasienter oftere og flere symptomer, enn ikke-innlagte pasienter.

Livskvalitet
Åtte studier vurderte livskvalitet og rapporterte en reduksjon i generell helsetilstand og livskvalitet blant 25% - 61% av covid-19 pasientene som hadde vært innlagt på sykehus, sammenlignet med 25% -46% av pasientene som ikke hadde vært innlagt på sykehus. Hos pasienter som hadde vært kritisk syke, var generelle smerter det mest plagsomme symptomet med tanke på deres livskvalitet etter covid-19. Samlet sett var det reduksjon i mobilitet, høyere forekomst av angst, depresjon og utmattelse som påvirket livskvalitet mest.

Risikofaktorer for langvarige symptomer etter covid-19
Ti studier analyserte risikofaktorer for langvarige symptomer. Kvinner ser ut til å være mer utsatt for vedvarende symptomer enn menn, et funn som ser ut til å gjelde uavhengig av om de har vært innlagt på sykehus eller ikke. I tillegg var alvorlighetsgraden av covid-19, flere symptomer ved diagnosetidspunktet og samsykelighet også assosiert med økt risiko for å rapportere vedvarende symptomer etter seks måneder.

Diskusjon

Få studier inkluderte kontrollgrupper, noe som er en sterk begrensning for å kunne evaluere spesifikke langvarige symptomer etter gjennomgått covid-19. Derfor er det fortsatt usikkert i hvor stor grad gjennomgått covid-19 fører til langtidssymptomer og redusert livskvalitet, eller om dette kan skyldes andre forhold. De pandemirelaterte begrensningene i personlig frihet, nedstenging, sosial isolasjon og livsstilsendringer kan også tenkes å påvirke rapportering av symptomer. Våre funn er relatert til studier som ble gjennomført tidlig i pandemien, og det er usikkert hvordan forbedrede behandlingsmetoder, nye virusvarianter eller vaksinasjon vil kunne påvirke utfall av covid-19 i fremtiden. På grunn av heterogenitet på tvers av studier var det ikke mulig å sammenstille resultater i metaanalyser. Det skal bemerkes at vi ikke kan bekrefte eller avkrefte årsakssammenhenger mellom gjennomgått covid-19 og langvarige symptomer basert på de inkluderte studiene. Det er behov for større kontrollerte studier med deltakere fra hele pandemien for å få sikrere kunnskap om langtidseffekter etter covid-19.

Konklusjon

Mange pasienter rapporterte om vedvarende symptomer seks måneder eller mer etter gjennomgått covid-19. Allmennsymptomer, nevrologiske symptomer og symptomer fra lungene var vanligst både blant innlagte og ikke-innlagte pasienter, men pasienter som hadde vært innlagt på sykehus rapporterte gjennomgående et bredere symptomspekter, flere symptomer og flere alvorlige funksjonelle begrensninger. Kvinner hadde høyere risiko for å utvikle langvarige symptomer enn menn.

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Problem statement

COVID-19 has been associated with long-lasting symptoms. Aiming to offer customized treatment, policy makers, health care professionals and patients need access to up-to-date evidence about long-termed symptoms after COVID-19. In this rapid review we search evidence aiming to explore:

1. Which proportion of patients experience long-term symptoms after COVID-19?
2. Which symptoms occur, and how long they last.
3. Which factors predict long-term effects of COVID-19.

The outbreak team at the Norwegian Institute of Public Health has commissioned this update of previous version of this rapid review published on 3rd March 2021 (1). Additionally, this update addresses research needs of the assignment 479 from the Norwegian Ministry of Health and Care Services.

Methods

Literature search

We applied an open search strategy to identify all relevant studies on prevalence of lasting COVID-19 symptoms, demographic and medical risk factors associated with symptoms on follow-up, and studies analysing the impact of long presenting COVID-19 on the healthcare system. We searched for studies with more than 100 participants where a majority of the COVID-19 cases were laboratory confirmed cases of infection, that reported on symptoms, quality of life, and predicting factors for long-lasting symptoms. One researcher (JH) conducted a search on June 17th, 2021 in the MEDLINE database for studies published in the period 20.01.2021 -16.06.2021. This search was expanded with a search in the WHO Global research on coronavirus disease (COVID-19) database on June 17th, 2021 (2). In combination with the previous reports' search period, the timeframe since 01.01.2020 was covered.

Inclusion criteria:

Population:	More than 100 participants, majority laboratory confirmed COVID-19
Outcome:	Any long-term symptoms, consequences associated with COVID-19 (excluding studies only/mainly reporting on laboratory or radiological findings)
Follow-up:	Included participants followed up for six months
Study types:	Cohort studies (prospective and retrospective), case-series, surveys
Exclusion criteria:	Non-peer-reviewed studies, studies limited to participants with one main underlying disease

Some of the inclusion criteria listed above are narrowed down as compared to the previous version of the review, leading to some publications previously included no longer being relevant for this update. The most important changes are that studies with observation times below six months and studies that are not peer-reviewed (pre-prints) were not included in this update. The narrowing of the inclusion criteria was based on the assumption that more studies had been published since the first version, and our inclusion criteria were defined prior to the search.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (JH, MGC) reviewed the studies in full text, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. A group of experts in the field provided feedback for the study inclusion process, methodological approach, and results presentation (AM, HLG, KG, HNE).

Quality assessment

We performed quality assessment of the included studies using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case Series Studies (3). The NIH assessment tool focuses on the key concepts for evaluating the internal validity of studies, quality rating can be good, fair or poor methodological quality, based on level of fulfilment of 14 aspects (maximum score is 14 points). Two researchers independently performed quality assessment, followed by discussion to reach consensus on study quality. We set no cut-off for included studies by total quality score. We have not graded the certainty of the evidence. Therefore, the results should generally be interpreted with caution.

Data extraction

Two researchers (JH, MGC) extracted relevant information from included studies to Excel. Information on study country, participants, follow-up period, symptom prevalence and statistics (e.g. odds ratio, rate ratio, hazard ratio) were extracted. For prevalence of symptoms, we calculated percentages based on provided fractions. We grouped collected data by hospitalisation status. In case of mixed populations (hospitalised and non-hospitalised groups), we defined status by the majority (>50%) of respective participants. Reported symptoms were matched to ICD-10 based symptom groups (4) (Appendix 2). Studies with participants mainly below 18 years of age were described separately.

Data analysis

Analysis of extracted endpoints was performed by hospitalisation status. Data tables were exported to *plotly,* an online tool for data analysis and visualisation (5). We plotted prevalence of symptoms against individual studies and symptom groups in scatterplots. We used colours to differentiate authors and symptom groups. Not-to-scale bubble-sizes were used to visualise study size. The heterogeneity of included studies prevented us from compiling data quantitively. The included scatterplots are simple graphical presentations of extracted endpoints across included studies. Studies with participants mainly below 18 years of age were not included in the scatterplots but reported descriptively in text.

Peer review

Signe Flottorp (research director, NIPH), Ernst Kristian Rødland, (senior medical officers, NIPH) critically reviewed the draft before publication.

Acknowledgements

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Results

Description of studies

Results of the literature search

We identified 2167 unique references through the systematic literature searches in MEDLINE and WHO Global research on coronavirus disease (COVID-19) database. JH screened all potentially relevant titles and abstracts in EPPI reviewer (6). After all MEDLINE references were screened, we built a Machine Learning Model in EPPI reviewer 4 based on articles that were

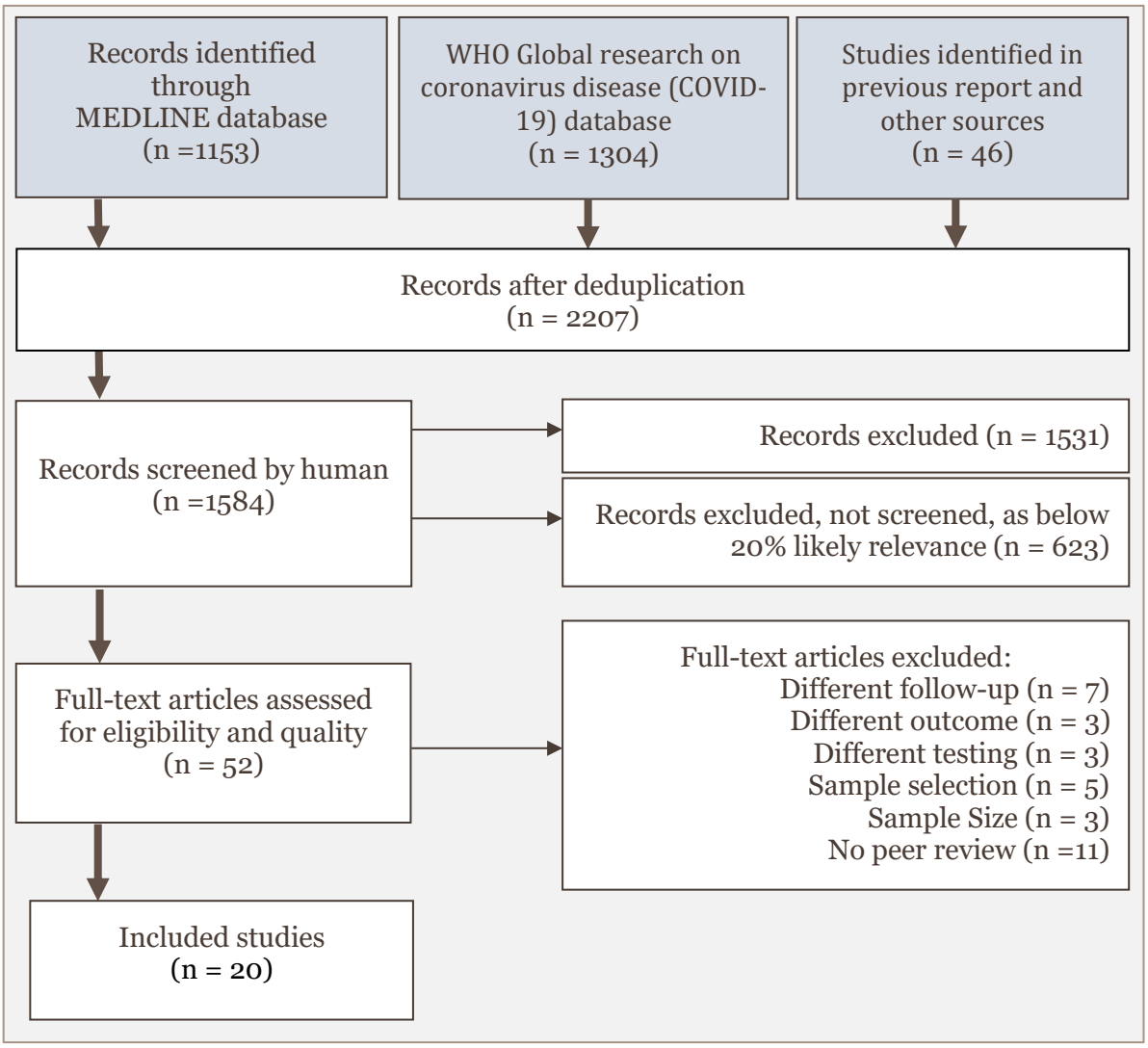

Figure 1. Flow diagram of search strategy and study inclusion

included and excluded during the title and abstract screening. The model was applied to the references of WHO Global research on coronavirus disease (COVID-19) database. The model considered 623 references as having less than 20% chance of being relevant, and we excluded these references without human screening. In total, we read 52 references in full text, of which 20 articles matched our inclusion criteria, including two studies from our previous report (7, 8). Most studies from our previous report (n=43) were excluded from this update because they were not peer-reviewed (n=8) or due to short follow-up (n=32). Figure 1 shows a graphical representation of our search and screening methodology, and Table 1 lists the included studies.

Included studies

After full text screening we included 20 studies, including two out of 43 studies from the preceding report (table 1). We excluded 32 studies not matching our inclusion criteria (Appendix 3). The studies were conducted in Australia n=1 (21), China n=2 (8, 23), Denmark n=1 (18), France n=1 (16), Germany n=1 (9), Italy n=4 (10, 12, 20, 25), Iran n=1 (24), Norway n=4 (7, 11, 13, 26), UK n=1 (15), USA n=1 (17), Singapore n=1 (19), Spain n=1(14) and Sweden n=1 (22). The median length of follow-up was six months with some variation (range from two weeks to twelve months). Follow-up time was measured from hospital discharge, initial symptoms or mixed. Number of participants ranged from 113 to 8 983 (19 035 in total). The participants in most studies were middle-aged, one study only enrolled children. The sex distribution was mainly balanced. All studies used laboratory testing to diagnose COVID-19 (mainly PCR). Follow ups were performed either at clinics or through online/phone/ postal surveys, except for the Danish study which used national registry-data. Loss to follow up was generally high, ranging between six to 61%.

Table 1. Overview of included studies

First author	Country	Participants (n)	Sex (% male)	Study type (as reported)	Study population*	Length of follow up (days/months)
Augustin et al. (9)	Germany	958	47	Prospective cohort	Non-hospitalised	6.8m (med. 207d (IQR 187-234)
Baricich et al. (10)	Italy	204	60	Cross-sectional	Hospitalised	124.7d (SD 17.5d)
Blomberg et al. (11)	Norway	312	49	Prospective cohort	Non-Hospitalised	6 months
Boscolo-Rizzo et al. (12)	Italy	304	39	Prospective cohort	Non- hospitalised	12 months
Einvik et al. (13)	Norway	583	58 / 44	Cross-sectional	Non-hospitalised	116d (range 41-200d)
Fernandez-de-las-Penas et al. (14)	Spain	1142	52	Cross-sectional	Hospitalised	7 months (SD 0.6)
Gautam et al. (15)	UK	200	63	Retrospective case series	Hospitalised	143.4 (SD 42.4d)
Ghosn et al. (16)	France	1137	63	Prospective cohort	Hospitalised	6 months
Huang et al. (8)	China	1733	52	Prospective cohort	Hospitalised	6 months
Logue et al. (17)	USA	177	43	Prospective cohort	Non-hospitalised	169d (range 31- 300)
Lund et al. (18)	Denmark	8983	39	Prospective controlled cohort	Non-hospitalised	14-180d
Ong et al. (19)	Singapore	183	75	Prospective cohort	Hospitalised	181d (IQR 103-191; range 31-295)
Pehgin et al. (20)	Italy	599	47	Prospective cohort	Non-hospitalised	187d (SD 22)
Say et al. (21)	Australia	152	53	Prospective cohort	Non-hospitalised (children)	3-6 months
Schandl et al. (22)	Sweden	113	83	Prospective cohort	Hospitalised	5 months (2-7 months)
Shang et al. (23)	China	1174	51	Prospective cohort	Hospitalised	6 months
Simani et al. (24)	Iran	120	67	Prospective cohort	Hospitalised	6 months
Stavem et al. (7)	Norway	451	44	Cross-sectional	Non-hospitalised	6 months
Trunfio et al. (25)	Italy	200	58	Retrospective cross-sectional	Hospitalised	194d (181–198)
Walle-Hansen et al. (26)	Norway	216	57	Prospective cohort	Hospitalised	186d

*Categories reflect the hospital status of >50% of participants. Some studies (9,11,16,25) included both hospitalised and non-hospitalised participants

Eleven studies included mainly hospitalised patients (>50%, ICU and non-ICU patients) and nine studies mainly non-hospitalised patients (>50%). More in detail, nine studies only included hospitalised patients, six studies only non-hospitalised participants, four mixed populations and one study only ICU patients. All but two studies started enrolling patients before April 2020 (Figure 2).

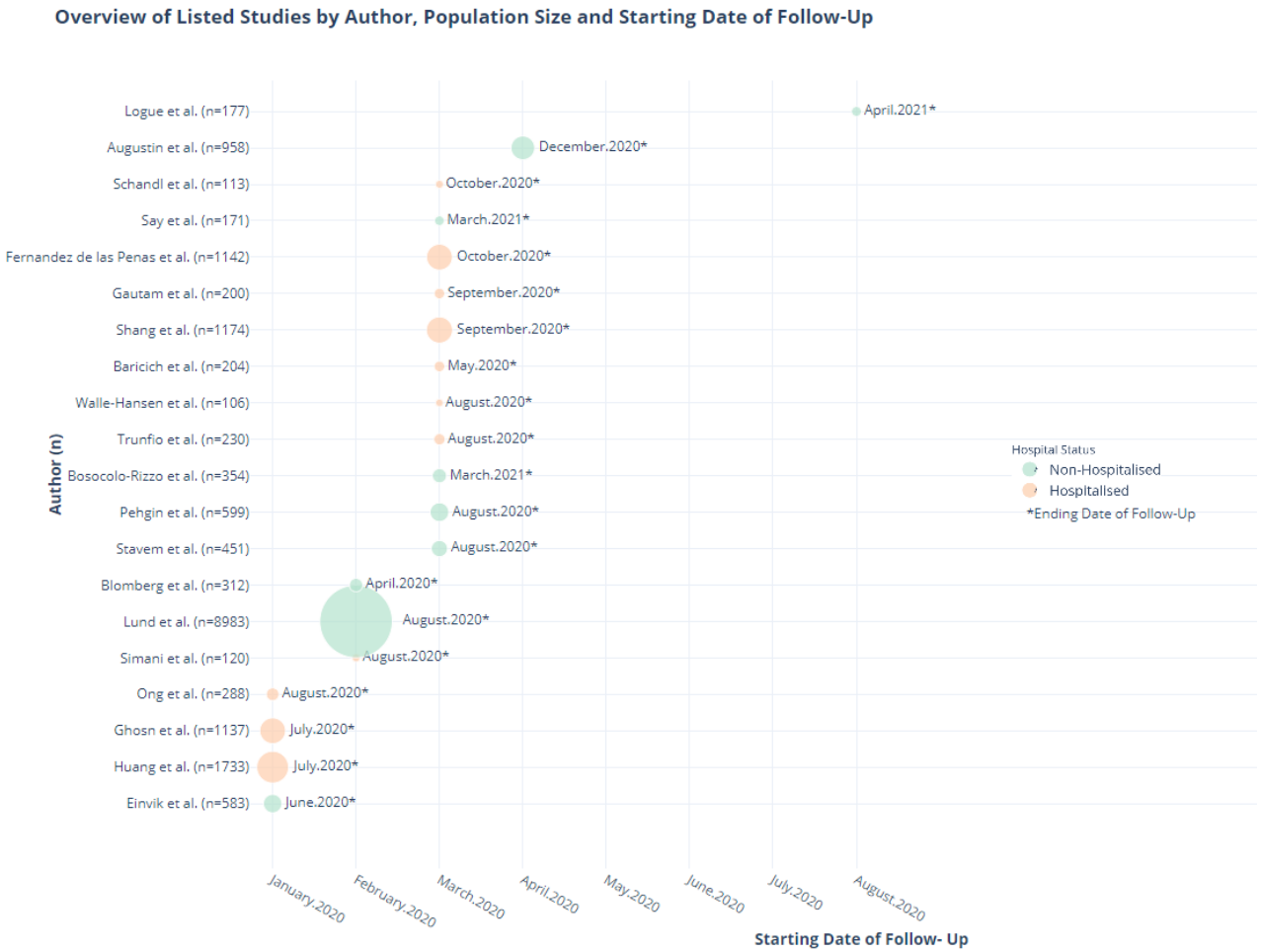

Figure 2. Start and end date of studies, bubble-size indicating number of study participants, red bubble indicates mainly hospitalised participants, and green bubble mainly non-hospitalised.

Quality assessment

Our quality assessment found study quality to be overall fair, ranging from 8-11 points for observational cohort and cross-sectional studies. The only case-series scored 7 points out of a total 9 points. Table 2 provides an overview of the evaluations by question order. Most studies did not include matched control groups, limiting the ability to analyse causal factors.

Table 2. Results of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case-Series

First author	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***Total***
Augustin et al. (9)	x	x	x	x	-	x	x	x	x	-	x	-	-	x	**10**
Baricich et al. (10)	x	x	-	x	-	x	-	x	x	-	x	-	NA	x	**8**
Blomberg et al. (11)	x	x	x	-	-	x	x	x	x	-	x	-	x	x	**10**
Boscolo-Rizzo et al (12)	x	x	x	x	-	x	x	-	x	-	x	-	x	-	**9**
Einvik et al. (13)	x	x	x	x	-	x	x	x	x	-	x	-	-	x	**10**
Fernandez-de-las-Penas et al. (14)	x	x	x	x	-	x	x	x	x	-	x	-	x	-	**10**
Gautam et al. (15)*	x	x	-	x	NA	x	x	x	x	NA	NA	NA	NA	NA	**7 /9**
Ghosn et al (16)	x	x	-	x	-	x	x	x	x	-	x	-	-	x	**9**
Huang et al. (8)	x	x	x	x	-	x	x	x	x	-	x	-	x	x	**11**
Logue et al (17)	x	x	x	x	-	x	x	x	x	-	x	-	-	-	**9**
Lund et al. (18)	x	x	x	x	-	x	x	x	x	-	x	-	x	x	**11**
Ong et al. (19)	x	x	x	x	-	x	x	x	x	-	x	-	-	x	**10**
Pehgin et al. (20)	x	x	x	x	-	x	x	x	x	-	x	-	x	x	**11**
Say et al. (21)	x	x	x	x	-	x	x	-	x	-	x	-	x	-	**9**
Schandl et al. (22)	x	x	x	x	-	x	x	x	x	-	x	-	-	-	**9**
Shang et al. (23)	x	x	x	x	-	x	x	x	x	-	x	-	-	-	**9**
Simani et al. (24)	x	x	x	x	-	x	x	-	x	-	x	-	x	x	**10**
Stavem et al. (7)	x	x	x	x	-	x	x	-	x	-	x	-	-	x	**9**
Trunfio et al. (25)	x	x	x	x	x	x	-	x	x	-	x	-	x	x	**11**
Walle-Hansen et al. (26)	x	x	x	x	-	x	x	-	x	-	x	-	x	-	**9**

1. Research question, 2 and 3. Study population, 4. Groups recruited from the same population and uniform eligibility criteria, 5. Sample size justification, 6. Exposure assessed prior to outcome measurement, 7. Sufficient timeframe to see an effect, 8. Different levels of the exposure of interest, 9. Exposure measures and assessment, 10. Repeated exposure assessment, 11. Outcome measures, 12. Blinding of outcome assessors, 13. Follow-up rate, 14. Statistical analyses.

* Case-series assessment tool used

Results from studies with hospitalised patients

Eleven studies followed up patients after COVID-19 hospitalisation (8, 10, 14-16, 19, 22-26), ten of these studies included both ICU and non-ICU patients. One of the studies included a mixed population of hospitalised and non-hospitalised patients (25). Study population size ranged from 113 –1 733 participants. The presence of any one symptom six months after COVID-19 hospitalisation ranged from twelve to 81%, with dyspnoea, fatigue, anxiety and sleeping problems most reported across the studies. Five studies reported negative changes in Health-related quality of Life (HRQoL) (8, 10, 15, 22, 26). Despite generally heterogenous findings, both female sex and ICU admission during acute phase stood out as predicting factors for symptoms on follow-up.

Baricich et al. assessed the physical performance of COVID-19 survivors at three to six months (mean 125 days) from hospital discharge at the University Hospital of Novara, Italy (10). The authors conducted a cross-sectional study focused on mid-term functional outcomes measured by the short physical performance tests, the 2-minute walking test and the 1-minute sit-to-stand test. In total, 204 volunteer patients were included (mean age 58 years, 40% female) from which 66 patients (32%) showed impaired physical performance at three to six months after hospital discharge, measured by a reduced score in the short physical performance battery or 1-minute sit-to-stand test. The authors found a correlation between ICU hospitalisation or mechanical ventilation and physical impairment, and between number of comorbidities and reduced walking ability.

Fernandez-de-las-Penas et al. reported a multi-centre observational study assessing post-COVID symptoms and associated risk factors seven months after hospital discharge (14). SARS-CoV-2 PCR confirmed patients discharged from four Spanish hospitals between March 10th to May 31st, 2020 were included. Trained researchers interviewed patients by telephone. In total, 1142 (48% women, mean age 61 years, SD 17 years) were included. At seven months, 19% (212) of patients were completely free of any post-COVID symptom, 21% (238) had one symptom, 23% (267) had two symptoms, and 37% (425) had three or more symptoms. The most prevalent symptoms were fatigue, hair loss, and dyspnoea. Female gender, number of days at hospital, previous comorbidities, and number of symptoms at hospital admission were found to be associated with more long-term symptoms. The authors performed an additional analysis in a subgroup of the study population to investigate the association between COVID-19 related myalgia at hospital admission and the presence of post-COVID symptoms (27). Of 369 patients with myalgia at hospital admission 20% showed >3 post-COVID-19 symptoms. The prevalence of musculoskeletal post-COVID-19 pain in this subgroup was 38%, and 50% of patients with pre-existing musculoskeletal pain experienced a worsening of their symptoms after COVID-19.

Gautam et al. conducted a retrospective case series to assess the medium-term effects of severe COVID-19 in patients with underlying co-morbidities from three hospitals in the UK (15). A total of 200 hospitalised patients were included and assessed at 4-7 months from disease onset. Among the 144 patients assessed for symptoms at follow-up, 63% experienced persistent breathlessness, 54% exhibited significant fatigue, 38% reduced mobility and 37% pain. All patients reported an important reduction in quality of life across all domains of the EuroQoL 5L - health-related quality of life (EQ-5D-5L) measures.

Ghosn et al. conducted a longitudinal prospective cohort study to assess symptoms that persisted six months after hospital admission in France (16). Patients' follow-up was planned with a physician's visit at month three and six after admission. In total, data was available for 1137 patients (median age 61 years, IQR 51-71). Six hundred and fifty-five (68%, 95% CI 65-71%) and 639 (60%, 95% CI 57-63%) participants had at least one symptom at three months and six months visit, respectively. At month six, 24% (255) of patients had three or more persistent symptoms. One hundred and twenty-five (29%, 95% CI 25-34%) of those who initially had a professional occupation were not back to work. The authors found that the presence of three or more symptoms at month six was independently associated with female gender, having three or more symptoms at admission and ICU admission during the acute phase.

Huang et al. conducted a cohort study of 1733 hospitalised patients in Wuhan, China (8). The authors found that six months after acute infection, COVID-19 survivors most frequently reported fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655)(8). Anxiety or depression was reported among 23% (367 of 1617) of the patients. The authors performed a 6-min walking distance test, finding that many patients lay below the lower limit of the normal range, most impacted were patients with more severe initial presentation. In 107 of 822 participants without acute kidney injury a reduced estimated glomerular filtration rate was found at follow-up. Patients who were more severely ill during their hospital stay had more severely impaired pulmonary diffusion capacities and more abnormal chest imaging manifestations.

Ong et al. conducted a prospective longitudinal multicentre cohort study at four hospitals in Singapore to assess the complications and sequelae of COVID-19 and their effect on long-term health (19). Patients were offered follow-up post discharge at 30, 90, 180, 270, and 320 days post symptom onset. Two hundred eighty-eight patients were recruited from which 120 had available data at 180 days post symptom onset. Symptoms related to COVID-19 were present in 11.7% (14) of patients six months after COVID-19. Among those with long lasting symptoms, respiratory symptoms were the most common.

Schandl et al. conducted a single-centre prospective follow-up study of COVID-19 patients admitted to the ICU for respiratory organ support in Sweden between March and July 2020 (22). Patients with invasive ventilation were compared to those with high-flow nasal oxygen or non-invasive ventilation regarding functional outcome and health-related qualify of life. The mean follow-up time was five months after ICU discharge and included clinical history, three well-validated questionnaires about health-related quality of life and psychological health, pulmonary function test, 6-minute walk test and work ability. Data were analysed with multivariable general linear and logistic regression models with 95% confidence intervals. Among 248 ICU patients, 200 patients survived. Of these, 113 patients came for follow up. Seventy patients (62%) had received invasive ventilation. Most patients reported impaired health-related quality of life. Approximately one third suffered from posttraumatic stress, anxiety and depression. Thirty-four percent had reduced walking ability and 50% worked fulltime. The outcomes were similar regardless of ventilatory support, but invasive ventilation was associated with more bodily pain (MSD – 19; 95% CI: -32 to -5).

Shang et al. followed up 1174 hospital discharged patients with severe COVID-19 for six months in Wuhan, China (23). The authors found that 441 of the 796 participants who provided data (55.4%) had sequelae. The most common symptoms were fatigue (25%), sleep disorder (23%) and shortness of breath (20%). In those who had sequelae, 262 (59%) had more than one symptom. Critical cases were more likely to have cough (21% vs. 12%) and hypomnesia (poor memory) (15% vs 8%), than severe cases. Univariate and multivariate logistic regression analyses revealed that women were more likely to have multiple symptoms, fatigue, and sleep disorder, whereas critical illness was found as an independent risk factor for hypomnesia.

Simani et al. investigated psychological morbidities such as chronic fatigue syndrome (CFS) and post-traumatic stress disorder (PTSD) among survivors of COVID-19 (24). A total of 120 COVID-19 survivors from a Tehran hospital, Iran, were assessed at six months after infection onset by a previously validated questionnaire based on the Fukuda criteria for CFS/ME and DSM-5 Checklist for PTSD. The prevalence rate of fatigue symptoms was 18%. Twelve (10%) screened positive for chronic idiopathic fatigue, six (5%) for CFS-like syndrome with insufficient fatigue, three (2.5%) for CFS, and the prevalence rate of PTSD was 5.8%. PTSD in patients with COVID-19 was not associated with increased risk of CFS. The authors concluded that the prevalence of CFS among patients who have recovered from COVID-19 is similar to the prevalence of CFS in the general population.

Trunfio et al. assessed whether SARS-CoV-2 cycle threshold (Ct) value at diagnosis could predict COVID-19 severity, clinical manifestations, and six-month sequelae (25). Hospitalised and outpatient cases were randomly sampled from the diagnoses of March 2020 and data collected at six months by interview and from the regional COVID-19 emergency database. Patients were stratified according to their Ct value in the nasopharyngeal swab at diagnosis. The median time from COVID-19 onset to swab collection was five days. At six months follow-up, 8% reported shortness of breath, 8% taste and smell dysfunction and 4% reported chronic cough.

Walle-Hansen et al. conducted a cohort study including 216 patients aged 60 years and older admitted to four general hospitals in Norway due to COVID-19, from March 1st up until July 1st, 2020 (26). Quality of life and functional status at six months was compared to retrospectively reported status before COVID-19 hospitalisation using the EuroQoL 5L - health-related quality of life (EQ-5D-5L) questionnaire. Six-month follow-up was attended by 106 patients (62%) with a mean age of 74 years. Fifty-seven participants (54%) reported a decrease in health-related quality of life after six months, with no significant difference between persons aged 75 years and older compared to younger participants. Seventy participants (66%) reported a negative change in at least one of the dimensions of the EQ-5D-5L, with impaired ability to perform activities of daily life (35%), reduced mobility (33%) and having more pain or discomfort (33%) being the most commonly reported changes. Forty-six participants (43%) reported a negative change in cognitive function after the COVID-19 hospitalisation.

Overview of studies with non-hospitalised patients

Nine studies followed up non-hospitalised patients after COVID-19 (7, 9, 11-13, 17, 18, 20, 21), including three studies with mixed populations (11, 13, 17). Study population sizes ranged from 171-8 983 participants. The presence of any symptom at around six months after COVID-19 ranged from 8-61%, with fatigue, dyspnoea, and loss of smell and taste being the most reported symptoms. Three studies (7, 11, 17) reported negative impacts on cognitive abilities and activities of daily living. Five studies analysed predicting factors for persistent symptoms after COVID-19 (7, 9, 11, 12, 20), female sex and multiple symptoms at COVID-19 onset stood out as correlating factors for persistent symptoms.

Augustin et al. conducted a longitudinal prospective cohort study to analyse the health consequences of mild COVID-19 in non-hospitalised patients, in Germany (9). A total of 958 patients were observed periodically for long-term symptoms, 353 were followed-up over seven months after disease onset. At four months, follow up on 442 individuals showed that shortness of breath occurred in 9%, loss of smell in 12%, loss of taste in 11%, and fatigue in 10% of the patients. At least one characteristic symptom was present in 28% (123/442) and 35% (123/353) at months four and seven post-infection, respectively. Relative to the initial total cohort 13% (123/958) of the patients presented with long-lasting symptoms. The authors found an association between a lower baseline level of SARS-CoV-2 IgG, loss of smell, and diarrhoea during acute COVID-19 and a higher risk of developing long-term symptoms.

Blomberg et al. conducted a prospective cohort study of 312 SARS-CoV-2 test-positive patients early in the pandemic in Norway (28 February to 4 April 2020, during limited testing capacity)(11). Of the included participants, 247 patients were home-isolated and 65 hospitalised. At six months, 61% (189/312) of all patients had some persistent symptoms. Fifty-two percent (32/61) of home-isolated young adults, aged 16-30 years, had symptoms including loss of taste and/or smell (28%, 17/61), fatigue (21%, 13/61), dyspnoea (13%, 8/61), impaired concentration (13%, 8/61) and memory problems (11%, 7/61). The frequency of most symptoms increased with age in the study population, disturbed smell and/or taste were more frequent in people younger than 46 years. Increased antibody titers as well as pre-existing lung disease were independently associated with both persistent fatigue and total number of symptoms at six months in multivariable analysis. The severity of the initial illness was associated with persistent fatigue and weakly associated with total number of symptoms.

Boscolo-Rizzo et al. evaluated the prevalence of COVID-19 related symptoms twelve months after the onset of mild -to -moderate disease with a prospective study in Italy (12). Patients completed a baseline telephone interview within three weeks after the first positive swab and were re-contacted twelve months after the onset of symptoms. A total of 354 patients completed the baseline telephone interview from which 304 (86%) completed the twelve months follow-up survey. Persistence of at least one symptom at 12 months was reported by 161 (53%) patients with the most frequent being fatigue (27%), followed by smell or taste impairment (22%), shortness of breath (13%), and muscle pain (9%). The risk for persistent symptoms at twelve months was higher for women, patients aged between 40 and 54 years and for those with a body mass index ≥25 kg/m^2. The presence of three to seven symptoms during acute disease was

associated with a higher risk of symptoms after twelve months, with this association being even stronger in those having eight or more symptoms in the acute phase.

Einvik et al. assessed the prevalence and determinants of symptom-defined post-traumatic stress disorder (PTSD) with a population-based study in a cohort of hospitalised and non-hospitalised adults at 1.5-6 months after onset of COVID-19 in Norway (13). Data were acquired from web surveys in June-September 2020 from all PCR positive patients. In total, 211 hospitalised and 938 non-hospitalised subjects received the survey (the non-hospitalised group overlaps with Stavem et al. described in detail below). The prevalence of PTSD was assessed using the PTSD checklist for DSM-5. In total, 583 (51%) of the patients responded at median 116 days (range 41-200) after COVID-19 onset. The prevalence of symptom-defined PTSD was 10% in hospitalised and 7% in non-hospitalised patients. Risk factors for persistent PTSD symptoms were found to be female sex, foreign born and dyspnoea. In non-hospitalised patients, previous depression and COVID-19 symptom were associated with persistent PTSD symptoms.

Logue et al. characterised long-term sequelae of COVID-19 with a longitudinal prospective cohort of mostly out-patients with laboratory-confirmed COVID-19 in Washington, USA (17). A total of 234 participants with COVID-19 were contacted to complete a single follow-up questionnaire between three and nine months after illness onset. Overall, 177 participants (76%; mean age 48 years, range 18-94; 57% women) completed the survey. Persistent symptoms were reported by approximately 30% of the cohort. The highest prevalence was observed in patients aged 65 years and older (43%). The most common persistent symptoms were fatigue (14%) and loss of smell or taste (14%). Moreover, 31% of patients reported worse health related quality of life compared with baseline and negative impacts on at least one activity of daily living, the most common one being household chores.

Lund et al. examined incident drug use, hospital diagnoses, and overall health-care use from two weeks to six months after a positive SARS-CoV-2 test in a main cohort of 8983 individuals without hospitalisation (median age 43y (IQR 29-56), 64% women), and a smaller cohort of hospitalised patient (18), including also a matched reference group of 80 894 individuals testing negative. The authors conducted a population-based cohort study using the Danish registries for prescription, patient, and health insurance from February 27 to May 31, 2020. From the total of 8983 non-hospitalised test-positive individuals, 31% (2757) initiated new drug treatments during follow-up, 26% received a new hospital diagnosis, and 73% (6557) visited their general practitioner, were seen at a hospital outpatient clinic, or were admitted to hospital. The most frequent persistent symptoms, limited to symptoms recorded during a follow-up hospital visit, were dyspnoea (1.2%), cough (0.2%), headache (0.4%), fatigue (0.2%), and pain (0.3%). SARS-CoV-2 test-positive individuals had an increased risk of receiving hospital diagnoses of dyspnoea (RR 2.00; 95% CI 1.62–2.48) and venous thromboembolism (RR 1.77; 95% CI 1.09–2.86) compared with the reference group, but no increased risk of other diagnoses. Rate ratios of overall general practitioner visits (1.18; 95% CI 1.15–1.22]) and outpatient hospital visits (1.10; 95% CI 1.05–1.16), but not hospital admission, showed increases among SARS-CoV-2 test-positive individuals compared with SARS-CoV-2 test-negative. The authors point out that their analysis only captures specific symptoms leading to hospital contacts, and not patient-reported symptoms, and can therefore not be used as a measure of the overall prevalence of these symptoms.

Peghin et al. conducted a prospective cohort study of 599 consecutive adult in-and out-patients with COVID-19 at a tertiary care teaching hospital in Italy, from March to May 2020 (20). Through telephone interviews by trained nurses, symptoms potentially associated with COVID-19 were investigated at 187 days (22 SD) after COVID-19 onset. The participants were free to answer in their own words. The prevalence of "post-COVID-19 syndrome," (i.e. symptoms that developed during or after COVID-19, that continued for ≥12 weeks, and were not explained by an alternative diagnosis) was 40% (241/599). Female gender (OR 1.55, 95% CI 1.05–2.27), a proportional increase in the number of symptoms at the onset of COVID-19 (OR 1.81; 95% CI 1.59–2.05) and ICU admission (OR 3.10; 95% CI 1.18–8.11) were all independent risk factors for post-COVID-19 syndrome.

Say et al. aimed to describe medium-term clinical outcomes three to six months after diagnosis of 171 children with COVID-19 presenting to an Australian tertiary paediatric hospital (21). Participants, (median age 3 years [IQR 1–8]): 90 (53%) boys and 81 (47%) girls were followed up between March 21, 2020 and March 17, 2021. Most children had mild disease (100 [58%]) or were asymptomatic (61 [36%]), and nine (5%) children had moderate disease. Follow-up data at 3–6 months were available for 151 (88%) of 171 children, of whom 54 (36%) were asymptomatic and 97 (64%) were symptomatic (i.e., with mild, moderate, or severe disease) with acute COVID-19. Twelve (8%) children had post-acute COVID-19 symptoms, all of whom were symptomatic during the acute phase of COVID-19. The most common post-acute COVID-19 symptoms were mild post-viral cough (six [4%] of 151 children), fatigue (three [2%] of 151 children) or both post-viral cough and fatigue (one child). The duration of post-viral cough ranged from three to eight weeks and post-viral fatigue ranged from six to eight weeks from the time of symptom onset. At the most recent review in March 2021, all 151 children had returned to their baseline health status and post-acute COVID-19 symptoms had resolved.

Stavem et al. performed a cross-sectional mixed-mode survey of a non-hospitalised, PCR-positive, geographical cohort of 938 patients in the catchment areas of two Norwegian hospitals (7). A total of 451 patients (48%) responded to the survey. The authors compared prevalence of 23 symptoms during initial illness and at 1.5-6 months. Around 60% of non-hospitalised COVID-19 subjects had no symptoms 1.5–6 months after symptom onset. The authors found an association between symptom load during the acute COVID-19 phase and number of comorbidities with the number of symptoms at follow-up. The authors published two supplementary publications on fatigue and quality of life based on the same population (28, 29). The supplementary publication by Garratt et al. reported EQ-5D-5 L scores on the same population pool (29). Garratt et al. compared the response-based scores with the general population norms in Norway. The questionnaire was completed by 458 (49%) subjects at a median of 117.5 days after COVID-19 onset. Garratt concluded that EQ-5D index scores (0.82; SD 0.17) did not differ from the general population norms. However, several important dimensions of HRQoL, including aspects of mental health, were lower than general population norms 1.5–6 months after COVID-19 onset.

Overview of grouped signs and symptom

Across all studies more than 60 different signs and symptoms were reported. The majority were non-objective, difficult to quantify symptoms, as reported by the participants through interviews, checklists or freely reported. The reported symptoms were mostly translated/converted from patient description into medical terminology. Although a broad spectrum of symptoms was reported in most studies, some authors grouped symptoms into groups of closely related symptoms. Symptoms themselves ranged from less to more impactful, cut-off thresholds for satisfying a symptom were mostly not reported or not applicable in the chosen study design.

We grouped symptoms into blocks based on the ICD-10 Chapter XVIII "*Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)*". 13 blocks were considered for grouping: 1. General, 2. Cardiovascular, 3. Ear, Nose and Throat, 4. Gastrointestinal, 5. Integumentary (related to skin, hair, nails), 6. Neurological, 7. Obstetric/Gynaecological, 8. Ocular, 9. Psychiatric, 10. Pulmonary, 11. Rheumatologic, 12. Urologic and 13. Functional and other (symptoms according symptom groups listed in Appendix 2). Reported symptoms were grouped into eleven groups, as no studies reported symptoms matching with the groups Obstetric/ Gynaecological and Urologic. Our categorisation provides a simplified proxy for related symptoms, independent of severity and without further analysis.

Prevalence of symptom groups by study

We plotted the prevalence of reported symptoms against the authors of the included studies and used categorical colour-coded bubbles to represent individual symptoms according to symptom groups. We subdivided studies by hospitalisation status, to create separate graphs for each population group. Figures 3 and 4 provide an overview of both population groups. Most authors reported on several symptom groups, with several symptoms per group. The graphs indicate that the prevalence of symptoms, independent of symptom group, was higher among mostly hospitalised patients (ICU and non-ICU) compared to non-hospitalised patients at around six months follow-up. In the hospital-based studies most authors reported *General* and *Functional & other* symptoms as most frequent, whereas only two studies did so among the non-hospitalised studies. Furthermore, in the studies of non-hospitalised patients the symptom range, as reflected in the number of symptom groups was less with eight groups, compared to the hospital-based studies with eleven symptom groups.

In Figure 3, the range of the prevalence of separate symptoms varies widely. It looks like most symptoms cluster at a lower prevalence, contrasting with symptoms of the groups *General* and *Functional & other* which appear slightly detached with more than 50% prevalence.

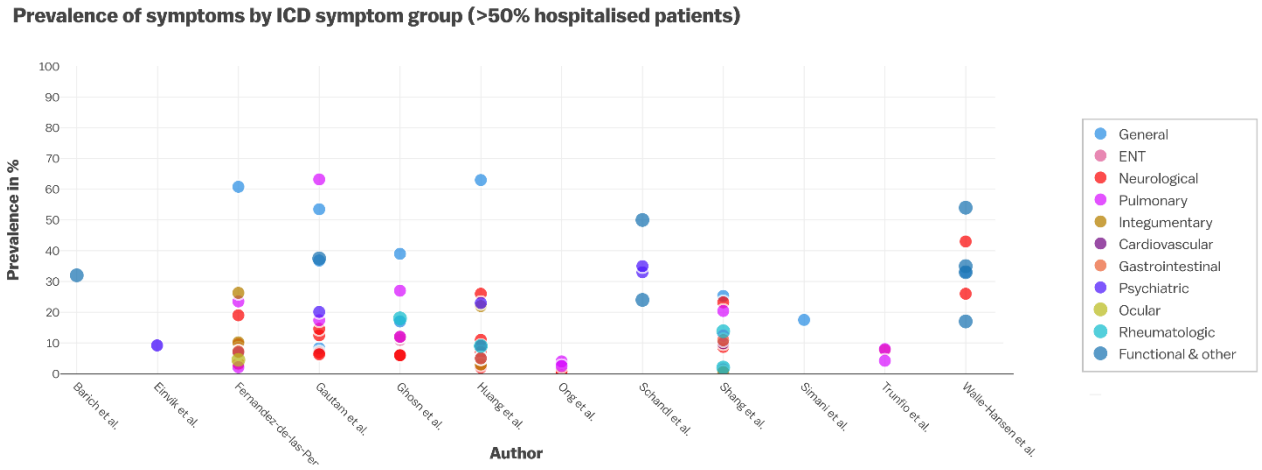

Figure 3. Prevalence of symptoms by ICD symptom groups, symptoms separately shown by author (hospitalised)

In Figure 4, the range of the prevalence of separate symptoms is less than seen in Figure 3. It looks like most symptoms cluster at a lower prevalence, with symptoms of the groups *General, Neurological* and *Pulmonary* most common.

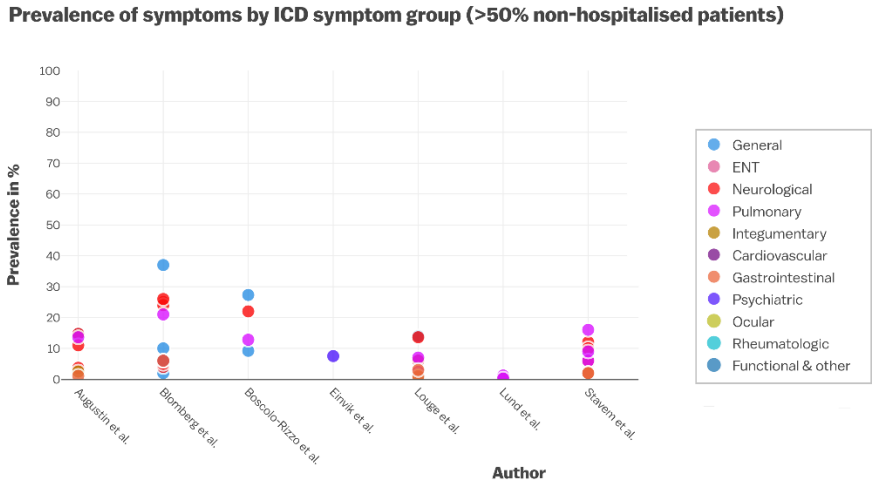

Figure 4. Prevalence of symptoms by ICD symptom groups, symptoms separately shown by author (non-hospitalised)

The prevalence of symptoms by symptom group and study size

In Figure 4 and 5 we plotted the prevalence of reported symptoms against symptom groups and used categorical colour-coded bubbles to represent individual studies. Bubble-size reflects the number of participants (not to scale). For both groups, the broadest range of prevalence is seen among *General* symptoms. *General*, *Neurological* and *Pulmonary* groups appear dominant among both populations, although more clearly seen among the non-hospitalised patients. The studies with mostly non-hospitalised patients reported fewer other symptom groups (8 vs 11), all with lower prevalence.

In Figure 5, similarly as in Figure 3, a higher prevalence of symptoms is seen among studies with mostly hospitalised patients (ICU and non-ICU). The highest prevalence of symptom groups is reported by smaller studies, appearing like outliers compared to less prevalent symptoms groups clustered at lower prevalence. The *General* symptom group stands out with high prevalence, although with a wide range.

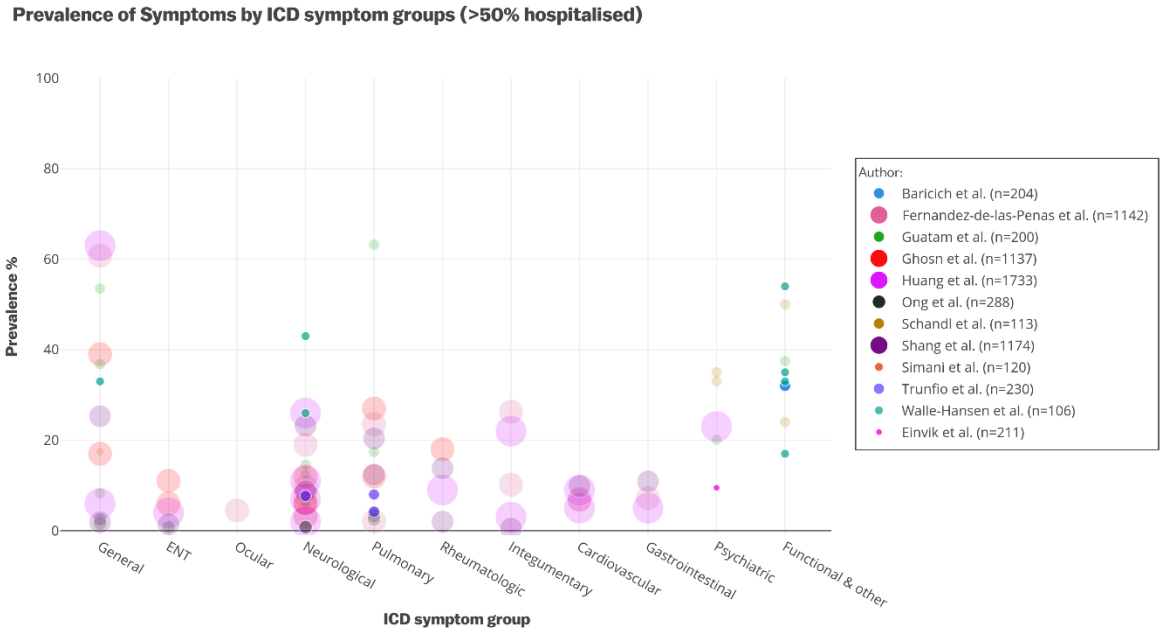

Figure 5. Prevalence of symptoms by symptom groups, bubble-size indicating number of participants (hospitalised)

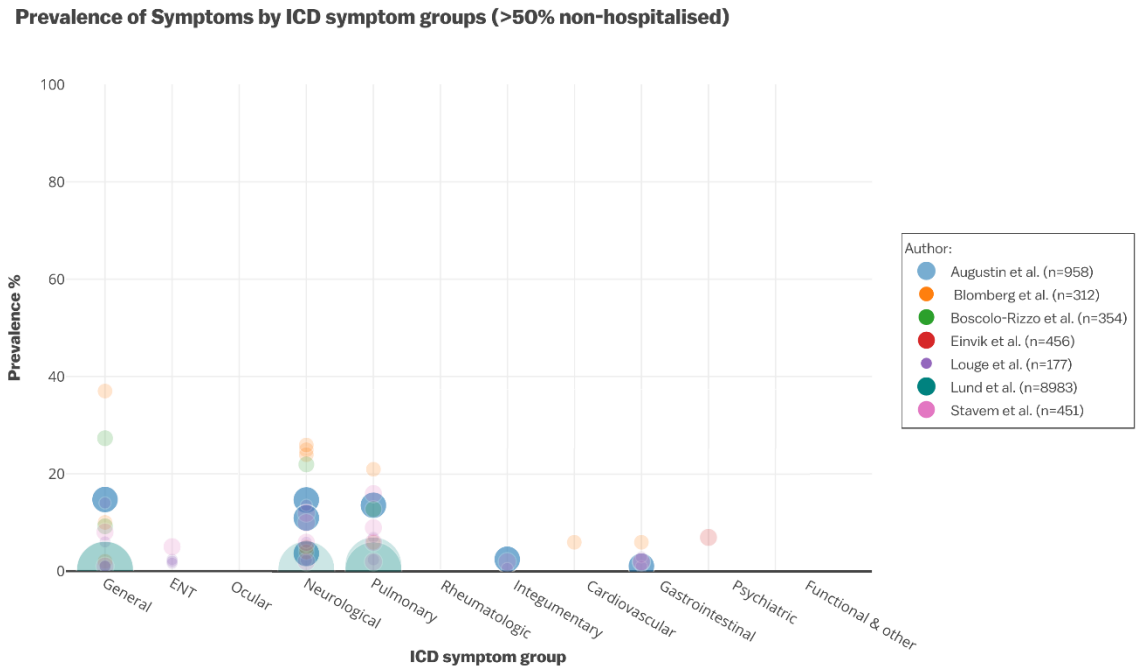

Figure 6. Prevalence of symptoms by symptom groups, bubble-size indicating number of participants (non-hospitalised)

Figure 6 shows that General, Neurological and Pulmonary symptoms were the most common among non-hospitalised participants. Prevalence is generally skewed towards lower prevalence. The three symptoms groups Ocular, Rheumatologic and Functional & other are not reported among the non-hospitalised participants.

Overall, participants reported a wide range of symptoms around and beyond six months after COVID-19. Larger studies with more participants appeared to report a lower range of prevalence of symptoms. Categorisation by symptom groups revealed that *General*, *Neurological* and *Pulmonary* symptoms were the most common. Whereas hospitalised patients reported a physiologically broad spectrum of symptoms beyond the three most common groups, this was less apparent in non-hospitalised patients. Independent of symptoms group, hospitalised patients reported more symptoms more frequently than non-hospitalised patients.

Impact on quality of life

We identified eight studies reporting estimates for health-related quality of life (HRQoL), cognitive and functional status of patients six months or more after COVID-19 (8, 10, 11, 15, 17, 22, 26, 28). Five studies reported outcomes from hospitalised patients (8, 10, 11, 15, 22, 26), and three from mixed or non-hospitalised patients (11, 17, 28). Four studies assessed long-term functional status in hospitalised and critically ill patients, finding a residual functional impairment or reduced mobility and persistent pain in patients who had been mechanically ventilated at around six months after COVID-19 (8, 10, 15, 22).

Six studies assessed HRQoL among participants (15, 17, 22, 26, 28, 29). Four study populations were assessed by the EuroQoL 5L - health-related quality of life (EQ-5D-5L) questionnaire and observed a reduction across the five domains (mobility, usual activities, personal care, pain and anxiety/depression) around six months after COVID-19 (15, 22, 26, 29). One study found that 83% of patients did not return to their prior state of health during the first six months (15), whereas another study reported a 50% return to full time work (22). A study on elderly hospitalised patients found that 66% of patients reported a negative change in HRQoL six months post COVID-19. Compromised ability to perform activities of daily living, decreased mobility and pain was most common (26). The fourth study found that 32% of non-hospitalised patients reported some negative impact on HRQoL after COVID-19, most commonly through changes in mobility, pain and anxiety or depression (29). Two studies assessed HRQoL with the RAND-36 questionnaire (22, 28); a study of critically ill patients found a reduction in all domains similar as seen in acute respiratory distress syndrome patients (22). The other study used the fatigue sub-set of the questionnaire to identify a higher prevalence of fatigue, about twice as high as the 22% reported in the general population in Norway (28). One study assed HRQoL on follow-up through impact on activities of daily living (17); 31% of patients reported worse HRQoL compared with baseline, a negative impact on at least one activity of daily living was reported by 8%, the most common being household chores.

We reviewed cognitive impairments and psychological symptoms under quality of life, based on the overlap with HRQoL domains. Three studies assessed cognitive impairments through the Montreal Cognitive Assessment and/or self-reported measures (11,15,26). Two found a compromise of concentration and short-term memory problems in 13% and 19% of participants (11, 15). In a study among elderly, cognitive functions was reduced in 43% of patients as compared to before COVID-19 hospitalisation (26). Three studies assessed residual psychological symptoms with the EQ-5D-5L, RAND-36, Post Traumatic Stress Symptom Scale-14, and Hospital Anxiety and Depression Scale finding a prevalence of anxiety or low mood in 20–33% of participants across the studies (15, 22, 26). One study found that roughly a third of hospitalised patients experienced either post-traumatic stress disorder (PTSD), anxiety or depression on follow-up (22). One study found a correlation between anxiety and depression with mechanical ventilation (invasive and non-invasive) during hospitalisation (8).

Across the studies, a reduction in overall health and health related quality of life was observed for 25%- 83% of hospitalised patients and 25%-46% of non-hospitalised patients after COVID-19. In critically ill patients, pain was the most detrimental symptom to quality of life after

COVID-19. A reduction in mobility, a higher incidence of anxiety and depression, and fatigue impacted patients' quality of life most.

Predicting factors for long-term symptoms

Whereas most studies predominantly focused on the prevalence of symptoms, ten studies included some analysis for identifying factors correlating initially registered information and measured outcomes. For most studies this was not the primary objective, nonetheless some authors collected and analysed data to provide early insights into factors correlated with long-term symptoms, using variable statistics: adjusted Odds ratio (aOR), Odds ratio OR), adjusted Risk Ratio (aRR), Risk Ratio/ incidence rate ratio (RR/IRR) and Hazard ratio (HR).

Based on the collected data, multiple symptoms (7, 9, 14, 16, 20), previous comorbidities (7, 14, 25), female sex (8, 9, 14, 16, 20, 23), severity of COVID-19 and number of days at hospital (8, 14, 16, 19, 20, 23) were identified as factors correlated with length of symptoms. Age was generally not found to be correlated with outcomes. One study found that an initially high SARS-CoV-2 cycle threshold (Ct) was associated with prevalence of six-month sequelae (25). Whereas for IgG titers conflicting results were found, indicating both that low IgG levels during follow up predicted long-term symptoms (9), as well as that IgG titres were significantly higher in long-haulers than in patients without symptoms (20). Table 3 provides a more detailed overview of separate risk factors for four different outcomes (marked in light blue).

Across the ten studies, examining factors predicting long-lasting symptoms, female sex was the most consistent variable, independent of hospitalisation status. In addition, severity of COVID-19, multiple symptoms at diagnosis and prior comorbidities were also correlated with long-lasting symptoms.

Table 3. Overview of ten studies that examined correlating factors at baseline for symptoms on follow-up. A selection of symptoms as provided by the authors, in some instances authors used overlapping terms, some symptoms were not clearly defined. Relative measures are colour-coded, values **more than 3 - red**, **between 2 and 3 - orange**, **more than 1 - bold black**.

	Augustin et al.	Blomberg et al.	Fernandez-de-las-Penas et al.	Ghosn et al.	Peghin et al.	Huang et al.	Shang et al.	Stavem et al.	Trunfio et al.	Ong et al.
Participant size	958	312	1142	1137	599	1733	1174	451	230	288
Hospitalisation status	Non-hospitalised	Mixed	Hospitalised	Hospitalised	Mixed	Hospitalised	Hospitalised	Non-hospitalised	Mixed	Hospitalised
Risk factors at diag. for: symptom on follow up										
Older age	OR 0.99 (0.97-1.01)	aRR 1.08 (0.98–1.19)			No correlation for all age groups		HR 0.84 (0.62-1.14)	IRR 0.94 (0.82-1.07)	aOR 1.02 (0.98–1.04)	**aOR 8.75 (1.7–48)** (particpants >65)
Female sex		**aRR 1.35 (1.01–1.81)**	**IRR 1.37 (1.26–1.49)**	**aOR 2.40 (1.75-3.30)**	**OR 1.55 (1.05–2.27)**		**HR 1.62 (1.20-2.18)**			aOR 3.05 (0.9–10.6)
Male sex	**OR 0.49 (0.31-0.77)**							IRR 0.74 (0.53-1.03)	aOR 0.59 (0.26–1.35)	
Previous comorbidities	OR 0.88 (0.53-1.46)		**IRR 1.11 (1.05–1.16)**					**IRR 2.52 (1.58-4.02)**	**aOR 1.01 (0.68–1.48)**	
Asthma/COPD		**aRR 1.57 (1.05–2.37)**								
Former/current smoker								IRR 1.16 (0.83-1.62)		
Chronic heart disease		aRR 1.23 (0.71–2.18)								
Multiple symptoms	**aOR 1.29 (1.08-1.55)**		**IRR1.24 (1.17–1.31)**	**aOR 2.04 (1.45-2.89)**	**OR 1.81 (1.59–2.05)**					
6–9 symptoms								**IRR 1.97 (1.20-3.23)**		
10–23 symptoms								**IRR 4.16 (2.57-6.72)**		
Loss of taste	**OR 2.16 (1.36-3.43)**									
Loss of smell	**aOR 5.12 (2.43-10.8)**									
Cough	aOR 0.94 (0.53-1.67)									
Diarrhoea	aOR 1.5 (0.78-2.91)									
Fever	OR 0.78 (0.50-1.21)									
Headache	aOR 0.84 (0.48-1.47)									
Muscle and/or body aches	OR (1.21 (0.78-1.88)									
Severity of COVID		aRR 1.17 (1.00–1.37)								**aOR 4.23 (1.02–18)**
ICU vs ward			**IRR 1.20 (1.03–1.38)**	**aOR 1.55 (1.09-2.18)**	OR 1.65 (0.61–4.46)	**OR 2.42 (1.15-5.08)**	HR 0.94 (0.47-1.89)			
Ward *vs.* Outpatients					**OR 1.87 (1.19-2.94)**					
Baseline IgG titers										
<1.1	aOR 2.05 (0.9- 4.37)									
1.2 – 4	**aOR 1.90 (1.13-3.18)**									
>4	ref									
SARS-CoV-2 cycle threshold									**aOR 0.90 (0.85–0.96)**	
Risk factors for: Fatigue on follow-up										
Age						**OR 1.17 (1.07-1.27)**				
Female sex			**OR 1.75 (1.37–2.24)**			**OR 1.33 (1.05–1.67)**	**HR 1.54 (1.11-2.12)**			
Severe COVID						**OR 2.69 (1.46–4.96)**	HR 0.97 (0.55-1.69)			
Risk factors for: anxiety and depression										
Age						OR 0.96 (0.87-1.06)				
Female sex						**OR 1.80 (1.39- 2.34)**				
Severe COVID						**OR 1.77 (1.05–2.97)**				
Risk factors for: dyspnoea on follow-up										
Female sex			**OR 1.70 (1.29–2.24)**							

Discussion

We included 20 peer-reviewed studies following up the participants for about six months or longer in this update of our rapid review. This is an addition of 18 new studies from our first version of this report (March 3rd, 2021). Only two studies from our previous report were included, as some remained non peer-reviewed or did not match the updated inclusion criteria. The previous review included mostly smaller studies scoring lower in quality assessment. Interestingly these studies found a much higher skewed prevalence of any symptoms at six months than our update, suggesting that more rigorously conducted studies capture a more nuanced picture. High loss to follow-up and participant selection bias might have contributed to an overrepresentation of the most severely affected, a continuing limitation in this update. The range of symptoms did not change greatly. The previous review provided early insights into the range of symptoms, and duration of symptoms after COVID-19, and suggested some correlations for long lasting symptoms, but the heterogeneity of findings made it challenging to draw conclusions. This update provides a more reliable foundation for key symptoms and risk factors. Even though five months have passed since the previous literature search, all included studies enrolled participants during the first part of the pandemic. We shifted our focus to studies with the longest available follow-up, studies with around six months or longer. As most studies enrolled patients over time, the range of follow-up was broad. As follow-up time was commonly reported in aggregate form, studies were included if a fraction of participants were followed-up for six months. On the other end, studies with longer follow-up were also included, again aggregated data or heterogenous reporting did not allow for stratification by exact follow-up time. Therefore, our findings are an approximation of findings for at around six months. The quality of included studies has improved, but loss to follow-up and lack of control groups remain common limitations. Our inclusive approach continues to reflect the early stage of research and emphasises that current findings need to be critically assessed. Our findings represent an overview of the limited available evidence without quantitative synthesis of findings.

Nevertheless, this update provides new insights and strengthens our earlier findings. Differences by hospitalisation status have become clearer. Basic statistical analysis within the studies begin to elucidate risk factors for long-lasting symptoms and severity, and a visualisation of the symptomatology has revealed dominant symptoms groups. Overall participants reported a wide range of symptoms at around and beyond six months after COVID-19. Categorisation by symptom groups reveals that *General*, *Neurological* and *Pulmonary* symptoms are the most common. Whereas hospitalised patients report a physiologically broad spectrum of symptoms beyond the three most common groups, this is less apparent in non-hospitalised patients. Independent of symptoms group, hospitalised patients reported more symptoms more frequently than non-hospitalised patients.

Insights into predicting factors for symptom duration and severity were analysed by ten studies, reporting some form of statistical analysis of their data. Female sex was the most consistent variable to be associated with duration of symptoms, independent of hospitalisation status. In addition, across most participants, severity of COVID-19, multiple symptoms at diagnosis and prior comorbidities were also correlated with long-lasting symptoms. Some included studies also assessed quality of life on follow-up, finding reduced health and quality of life among hospitalised and non-hospitalised patients. A higher prevalence of reduced quality of life was observed in hospitalised patients, in accordance with greater symptom load. In critically ill patients, pain was the most detrimental symptom to quality of life after COVID-19. A reduction in mobility, a higher incidence of anxiety and depression, and fatigue impacted patients' quality of life most.

This update includes for the first time a study on the paediatric population, although limited in size and representativeness it appears that children are much less affected from prolonged symptoms. After our literature search a large British prospective cohort study with 1734 COVID-19 positive children between 5-17 years was published, their results support that children usually experience a short duration of COVID-19 with low symptom burden (30). Additionally, they found that some children experience prolonged illness duration, although not with increasing symptom burden, and most recovered by day 56. Non-peer-reviewed studies or studies with fewer participants point in a similar direction. Due to apparent differences between the adult and child population, we chose not to summarise the paediatric findings together with adults.

Although we were able to broaden the knowledge base, our findings continue to rely on mostly smaller studies without a control/ reference group conducted at the beginning of the pandemic. Our quality assessment found studies to be mostly of fair quality, a slight improvement to our last report, yet a high loss to follow-up, recall bias and lack of controls remain strong limitations. Our broad inclusion criteria contributed to finding many new studies but contributed equally to heterogeneity among them. Despite roughly half of all studies including non-hospitalised patients, it is unclear how well these participants reflect the general population. The studies' general validity or specific validity for the population in Norway remains uncertain.

Patients who have been admitted to the hospital or intensive care unit with COVID-19 seem to be at greatest risk for developing long lasting symptoms, but without controlled studies it remains unclear to what extent their symptoms are COVID-19 specific or reflects more general consequences of hospital/intensive care. It is well-known that many patients who are admitted to intensive care units after invasive medical treatment experience post-intensive care syndrome (PICS). PICS shares many similarities with long-term COVID-19 symptoms. In line with some studies on long-term effects of COVID-19, typical risk factor for PICS are older age, female sex and disease severity (31). The apparent increased risk for women to suffer from long-lasting symptoms is an interesting finding, especially as a NIPH review on risk factor for COVID-19 hospital admission or death showed women to be at a lower risk of becoming more severely ill in the first place (32).

The majority of studies did not include matched controls, a strong limitation in evaluating COVID-19 specific effects. Due to lack of controls, it remains uncertain how far prevailing symptoms are specific to COVID-19 or more generally attributable to a period of illness.

Populations assessed for changes in quality of life, may have had compromised life quality prior to COVID-19, and measurements may include more than COVID-19 specific reductions. Equally, pandemic related infringements on personal liberty, lockdowns, social isolation and changes to pre-pandemic lifestyle might also be factors underlying reporting of some symptoms. These factors are not limited to COVID-19 patients only but apply to the whole population. The long-termed effects of COVID-19 and long-termed effect of the pandemic situation are difficult to single out in un-controlled studies. Generally, differences in reporting may also represent differences in target populations and characteristics, as for example ethnical groups in one location may not be representative for another location. The existing heterogeneity impairs direct comparison of risk estimates across studies, and hence meta-analysis was not feasible. It should be noted that causal relationships cannot be confirmed or refuted based on the included study designs.

Many aspects remain uncertain, and important questions remain unanswered. Although symptoms appear to decrease over time, we do not know if or when these symptoms might disappear. Our findings reflect the early pandemics survivors, and we don't know how therapeutic advancements, new virus variants or vaccination efforts might impact outcomes in the future. Persons with asymptomatic COVID-19, or those not tested are not well researched, yet studies on these populations may reveal to us yet unknown consequences. Future studies need to be more standardised, include more participants in number and diversity with according control groups, and minimal loss to follow-up needs to be ensured to shape a more reliable evidence base.

Conclusion

Based on 20 studies of fair quality we have found that many COVID-19 patients report prevailing symptoms long after infection, with a large proportion continuing to experience one or more symptoms at six months or longer follow-up. Severe COVID-19, requiring hospitalisation or intensive care treatment, correlates with longer and more functional limitations on follow up. The range of symptoms for hospitalised patients is widest, with *General*, *Neurological* and *Pulmonary* symptoms the most common among both hospitalised and non-hospitalises patients. Women stand out with a higher risk for developing long-term symptoms. The extent of long-term impact of COVID-19 on the quality of life in the general population remains unclear.

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Appendix

Appendix 1; Search strategy

Search: 2021-06-17

Ovid MEDLINE(R) ALL <1946 to June 16, 2021 >

#	Query	Results
1	chronic covid*.ti,ab,kf.	23
2	long covid*.ti,ab,kf.	258
3	persistent covid*.ti,ab,kf.	29
4	(Post acute covid* or postacute covid*).ti,ab,kf.	64
5	(Post covid* adj3 (illness* or syndrome* or symptom*)).ti,ab,kf.	138
6	(Prolonged adj3 covid*).ti,ab,kf.	114
7	or/1-6	558
8	(chronic adj3 (complication* or infect* or symptom* or syndrome*)).ti,ab,kf.	89906
9	(Long-haul* OR longhaul*).ti,ab,kf.	941
10	((long-term or longterm) adj3 (complication* or consequence* or outcome*)).ti,ab,kf.	111011
11	(Persistent adj3 (infecti* or symptom* or syndrome*)).ti,ab,kf.	26287
12	(Prolonged adj3 recovery).ti,ab,kf.	2552
13	sequelae*.ti,ab,kf.	66720
14	or/8-13	290379
15	exp Coronavirus/	78216
16	exp Coronavirus Infections/	95426
17	(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.	161969
18	((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	5322
19	(2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.	161969
20	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	5322
21	or/15-20	146906
22	7 or (14 and 21)	2575
23	(2021012* or 2021013* or 202102* or 202103* or 202104* or 202105* or 202106*).dt.	658850
24	22 and 23	1153

Search: 2021-06-17
WHO COVID-19 Global literature on coronavirus disease

TW:(long-covid OR "long covid" OR long-haul* OR "long haul" OR "long hauler" OR "long-haulers" OR "lingering complications" OR "long term complications" OR "longterm complications" OR "long-term complications" OR "persistent complications" OR "prolonged complications" OR "sustained complications" OR "lingering effects" OR "long term effects" OR "longterm effects" OR "long-term effects" OR "persistent effects" OR "prolonged effects" OR "sustained effects" OR "lingering symptoms" OR "long term symptoms" OR "longterm symptoms" OR "long-term symptoms" OR "persistent symptoms" OR "prolonged symptoms" OR "sustained symptoms" OR "post-covid syndrome" OR "post covid syndrome" OR survivors OR survivorship OR "post-covid syndrome" OR "post covid syndrome" OR survivors OR survivorship) OR SU:time

Timeperiode: 2021

Results: 1304

Appendix 2; List of symptom groups and symptoms

General

- anorexia (R63.0)
- weight loss (R63.4)
- cachexia (R64)
- chills and shivering
- convulsions (R56)
- deformity
- discharge
- dizziness / Vertigo (R42)
- fatigue (R53)
  - malaise
  - asthenia
- hypothermia (T68)
- jaundice (P58, P59, R17)
- muscle weakness (M62.8)
- pyrexia (R50)
- sweats
- swelling
- swollen or painful lymph node(s) (I88, L04, R59.1)
- weight gain (R63.5)

Cardiovascular

- arrhythmia
- bradycardia (R00.1)
- chest pain (R07)
- claudication
- palpitations (R00.2)
- tachycardia (R00.0)

Ear, Nose and Throat

- dry mouth (R68.2)
- epistaxis (R04.0)
- halitosis
- hearing loss
- nasal discharge
- otalgia (H92.0)
- otorrhea (H92.1)
- sore throat
- toothache
- tinnitus (H93.1)
- trismus

Gastrointestinal

- abdominal pain (R10)
- bloating (R14)
- belching (R14)

bleeding:
Hematemesis
blood in stool: melena (K92.1), hematochezia
constipation (K59.0)
diarrhea (A09, K58, K59.1)
dysphagia (R13)
dyspepsia (K30)
fecal incontinence
flatulence (R14)
heartburn
nausea (R11)
odynophagia
proctalgia fugax
pyrosis (R12)
Rectal tenesmus
steatorrhea
vomiting (R11)

Integumentary

Hair:
alopecia
hirsutism
hypertrichosis
nail:
Main article: Nail_disease § Nail_changes_and_conditions_associated_with_them
Skin:
abrasion
anasarca (R60.1)
bleeding into the skin
petechia
purpura
ecchymosis and bruising (Sx0 (x=0 through 9))
blister (T14.0)
edema (R60)
itching (L29)
Janeway lesions and Osler's node
laceration
rash (R21)
urticaria (L50)

Neurological

abnormal posturing
acalculia
agnosia
alexia
amnesia
anomia
anosognosia
aphasia and apraxia
apraxia
ataxia

- cataplexy (G47.4)
- confusion
- dysarthria
- dysdiadochokinesia
- dysgraphia
- hallucination
- headache (R51)
- hypokinetic movement disorder:
  - akinesia
  - bradykinesia
- hyperkinetic movement disorder:
  - akathisia
  - athetosis
  - ballismus
  - blepharospasm
  - chorea
  - dystonia
  - fasciculation
  - muscle cramps (R25.2)
  - myoclonus
  - opsoclonus
  - tic
  - tremor
    - flapping tremor
- insomnia (F51.0, G47.0)
- Lhermitte's sign (as if an electrical sensation shoots down back & into arms)
- loss of consciousness
  - Syncope (medicine) (R55)
- neck stiffness
- opisthotonus
- paralysis and paresis
- paresthesia (R20.2)
- prosopagnosia
- somnolence (R40.0)

Obstetric / Gynaecological

- abnormal vaginal bleeding
  - vaginal bleeding in early pregnancy / miscarriage
  - vaginal bleeding in late pregnancy
- amenorrhea
- infertility
- painful intercourse (N94.1)
- pelvic pain
- vaginal discharge

Ocular

- amaurosis fugax (G45.3) and amaurosis
- blurred vision
- Dalrymple's sign
- double vision (H53.2)
- exophthalmos (H05.2)

- mydriasis/miosis (H570)
- nystagmus

Psychiatric

- amusia
- anhedonia
- anxiety
- apathy
- confabulation
- depression
- delusion
- euphoria
- homicidal ideation
- irritability
- mania (F30)
- paranoid ideation
- phobia:
- Main article: list of phobias
- suicidal ideation
- post-traumatic stress disorder

Pulmonary

- apnea and hypopnea
- cough (R05)
- dyspnea (R06.0)
  - bradypnea (R06.0) and tachypnea (R06.0)
  - orthopnea and platypnea
  - trepopnea
- hemoptysis (R04.2)
- pleuritic chest pain
- sputum production (R09.3)

Rheumatologic

- arthralgia
- back pain
- sciatica

Urologic

- dysuria (R30.0)
- hematospermia
- hematuria (R31)
- impotence (N48.4)
- polyuria (R35)
- retrograde ejaculation
- strangury
- urethral discharge
- urinary frequency (R35)
- urinary incontinence (R32)
- urinary retention

Functional

- impaired physical performance
- impaired mobility
- impaired ability to perform daily tasks

impaired ability for self care
reduced quality of life
Impaired ability to work

Appendix 3; List of excluded studies

Table of excluded studies

First Author	Reason for Exclusion	Study Type	Country
Buonsenso (33)	Different follow-up	Cross-sectional	Italy
Damanti (34)	Sample size	Retrospective cohort	Italy
Delbressine (35)	Different testing	Prospective cohort	Netherlands/Belgium
Desgranges (36)	No peer review	Prospective cohort	Switzerland
Dulery (37)	Sample selection	Retrospective cohort	France
Ferdenzi (38)	No peer review	Prospective cohort	France
Fernandez de las Penas (39)	Sample selection	Case-control	Spain
Frontera (40)	Sample selection	Prospective cohort	USA
Garcia Abellan (41)	No peer review	Prospective cohort	Spain
Graham (42)	Different follow-up	Prospective cohort	USA
Han (43)	Different outcome	Prospective cohort	China
Heightman (44)	No peer review	Prospective cohort	UK
Hopkins (45)	Sample selection	Prospective cohort	UK
Li (46)	Different follow-up	Prospective cohort	China
Munblit (47)	No peer review	Prospective cohort	Russia
O'Keefe (48)	No peer review	Cross-sectional	USA
Orrù (49)	Different follow-up	Prospective cohort	Italy
Osmanov (50)	No peer review	Prospective cohort	Russia
Penner (51)	Sample size	Retrospective cohort	UK
Perlis (52)	No peer review	Prospective cohort	USA
Pilotto (53)	No peer review	Prospective cohort	Italy
Peluso (54)	No peer review	Prospective cohort	USA
Radtke (55)	No peer review	Prospective cohort	Switzerland
Raw (56)	Different outcome	Cross-sectional	UK
Romero-Duarte (57)	Different follow-up	Retrospective cohort	Spain
Shabaka (58)	Sample selection	Retrospective cohort	Spain
Shoucri (59)	Different follow-up	Retrospective case series	USA
Taboada (60)	Sample size	Prospective cohort	Spain
Twomey (61)	Different testing	Prospective cohort	Canada
Walker (62)	Different follow-up	Cross-sectional	UK
Vaes (63)	Different testing	Prospective cohort	Netherlands
Yan (64)	Different outcome	Prospective cohort	China

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