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memo

COVID-19-EPIDEMIC :

COVID-19:
Post COVID-19 condition
– a rapid review

(New edition)

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English Summary

Background

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

Objectives

In this rapid review, we summarise research on the proportion of patients who get long-term symptoms, 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 "C*OVID-19: Post COVID-19 condition"* is the 2nd update in the series "*COVID-19: Long-Term Effects of COVID-19"* replacing our previous report published on August 10th, 2021. In this review, we included controlled studies with more than 100 laboratory test positive COVID-19 cases, as well as uncontrolled studies with more than 500 laboratory test positive COVID-19 cases and a follow-up time of six months or longer. We excluded studies mainly reporting on laboratory or radiological findings and uncontrolled studies that had not been peer-reviewed.

The findings are based on systematic searches in MEDLINE and WHO Global research on coronavirus disease (COVID-19) database on October 29th, 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 Case-Control Studies and Observational Cohort and Cross-Sectional Studies. Meta-analysis was not feasible; therefore, we present the results of this rapid review narratively, supplemented by tables and graphics.

Results

Characteristics of included studies

Nine controlled studies met the inclusion criteria, two of which were not peer-reviewed and only published as preprints. Four studies compared SARS-CoV-2-positive versus -negative subjects from the general population, and two studies included a group of influenza patients as controls. Most studies reported outcomes available from registries and medical records, such as hospital stay and health care use. Two studies collected self-reports of sequelae symptoms, and two studies used standardised questionnaires to assess specific symptoms or conditions. The size of the included COVID-19 populations ranged from 291 to 273 618 participants. In addition to the nine controlled studies, we identified eleven eligible uncontrolled studies providing additional information about typical symptoms and symptom burden. The uncontrolled studies mostly included patients hospitalised with non-critical COVID-19, but all studies also included some patients from ICU wards (up to 29% in one study). Three studies included a mixed population of hospitalised and non-hospitalised patients. Study population size ranged from 518 – 8679 participants. One study included only children, the others mainly middle-aged adults. Our quality assessment indicated that all included studies were of good to fair quality. All studies used laboratory testing to diagnose COVID-19, mainly PCR.

Symptoms around six to 12 months follow-up

Patients admitted to the hospital with COVID-19 seem to be at higher risk of subsequent hospital admissions, new diagnoses, and self-reported symptoms at follow-up than those not hospitalised or SARS-CoV-2-negative controls. Health-related quality of life (HRQoL) seemed to be lower in previously hospitalised COVID-19 patients than in the general population, although only compared in one controlled study. As compared with a cohort of hospitalised influenza patients, patient with severe COVID-19 requiring hospitalisation had a higher number of symptoms and longer durations of symptoms. The difference in symptom burden between non-hospitalised influenza patients and patients with mild COVID-19 (non-hospitalised) was less pronounced, as seen in other studies not finding differences in new hospital admissions between patients with mild/moderate COVID-19 disease and general population controls. Some uncontrolled studies showed good improvement of symptoms over time, a trend not clear in all studies at an average of eight months follow-up. Only Children remain little studied but appear much less commonly affected by long-term symptoms.

Overview of grouped signs and symptoms around six to 12 months follow-up

Visualisation of granular data on reported symptoms by ICD symptoms groups of twelve studies with mainly hospitalised patients revealed the broadest range of prevalence of symptoms among *General* symptoms. Symptoms under the *General*, *Neurological* and *Pulmonary* ICD symptom blocks were most prevalent (see Appendix 2 for list of symptom groups and symptoms). Uncontrolled studies and studies with fewer participants appeared to report more extreme values. The *Neurological* symptom block stands out with the largest variety of symptoms, and most frequently reported symptoms.

Predicting factors for long-term symptoms

Across four uncontrolled and one controlled study 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 assessing self-reported symptoms included initially hospitalised COVID-19 patients. The studies with mixed populations were mostly based on registry data lacking information on less severe symptoms that do not require medical attention. It is therefore uncertain how long less severe symptoms persist in people with mild to moderate COVID-19. Few studies reported on health-related quality of life. Although COVID-19 patients seemed to score lower on these outcomes than the general population, the effect of COVID-19 on health-related quality of life remains uncertain due to limited evidence.

Our findings continue to reflect studies conducted early in the pandemic, and we assume that therapeutic advancements, and vaccination may impact outcomes in the future and lead to milder disease and potentially a lower prevalence of long-term symptoms. 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. Large, controlled studies including SARS-CoV-2 test negative and positive participants (vaccinated and unvaccinated) from the general population, questionnaires, clinical measurements, and health-related quality of life are needed to assess the proportion affected by long-term symptoms, as well as type, duration, clustering, and severity of symptoms among people with initial mild to moderate COVID-19.

Conclusion

Severe COVID-19, requiring hospitalisation or intensive care treatment, correlates with more symptoms after six to 12 months. The range of long-term symptoms for hospitalised patients is widest, with *General*, *Neurological* and *Pulmonary* symptoms the most common. Women stand out with a higher risk for developing long-term symptoms. Many patients who have had moderate COVID-19 (non-hospitalised) report prevailing symptoms six to 12 months after infection, but controlled studies now show that many of these symptoms are also reported by uninfected controls. For patients who have had mild covid-19, there may appear to be an increase in some self-reported symptoms, but the symptoms are less pronounced than for patients who have been moderately or severely ill. The extent of long-term impact of mild or moderate COVID-19 on the quality of life in the general population remains unclear, as most studies included patients with severe COVID-19.

Norsk sammendrag

Bakgrunn

For de fleste gir covid-19 mild og forbigående sykdom, men personer som gjennomgår covid-19 kan oppleve at det tar tid å bli kvitt alle symptomer etter sykdommen. Denne formen for langvarige og uspesifikke symptomer er tidligere rapportert i forbindelse med andre infeksjoner, og det er slik sett ikke overraskende at en del pasienter opplever langvarige symptomer etter covid-19. Fra før vet man at personer som legges inn på intensivavdeling etter alvorlig lungesvikt, uavhengig av om de har underliggende sykdom, kan rapportere langvarige funksjonsnedsettelser som nedsatt kognitiv funksjon og redusert lungefunksjon etter utskriving. I denne rapporten benytter vi begrepet «senfølger etter covid-19» som er basert på en konsensusrapport (1).

Problemstilling

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

Metoder

Denne hurtigoppsummeringen er den andre oppdateringen i serien «*Covid-19: Senfølger etter covid-19*» og den erstatter versjonen som ble publisert 10. august 2021. I denne oppdateringen har vi kun inkludert studier med minst seks måneders oppfølging. Kontrollerte studier som omfattet mer enn 100 deltakere med laboratoriebekreftet covid-19 ble inkludert i tillegg til ukontrollerte studier med mer enn 500 deltakere med laboratoriebekreftet covid-19. Vi ekskluderte studier som kun presenterte laboratorie- og radiologiske funn og ukontrollerte studier som ikke var fagfellevurdert.

Vi gjennomførte systematiske litteratursøk i MEDLINE og WHO Global research on coronavirus disease (COVID-19) database 29. oktober 2021. Én forsker gjennomgikk søkeresultatene, og to forskere valgte ut studier for inklusjon, ekstraherte data og sammenstilte resultater. Eksperter fra relevante fagfelt bidro med faglige innspill og til å vurdere studier for inklusjon. Vi vurderte inkluderte studier med tanke på kvalitet og risiko for skjevheter ved hjelp av NIH Quality Assessment Tool for Case-Control Studies og Observational Cohort and Cross-Sectional 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

Ni kontrollerte studier tilfredsstilte våre inklusjonskriterier, hvorav to kun var publisert som «preprints» og ikke fagfellevurdert. Fire studier sammenlignet SARS-CoV-2-positive og SARS-CoV-2-negative personer fra den generelle befolkningen. To studier brukte tidligere influensapasienter som kontrollgruppe. De fleste studiene hentet utfallsdata fra registre og medisinske journalsystemer, slik som sykehusinnleggelser og bruk av helsetjenester. To studier samlet inn data om selvrapporterte symptomer, og to studier brukte standardiserte spørreskjemaer for å undersøke spesifikke symptomer eller tilstander. Størrelsen på covid-19-utvalgene varierte fra 291 til 273 618 deltakere. I tillegg til de ni kontrollerte studiene inkluderte vi elleve ukontrollerte studier for å belyse typiske symptomer og symptombyrde. De ukontrollerte studiene inkluderte hovedsakelig covid-19-pasienter som hadde vært innlagt på sykehus. De fleste var ikke kritisk syke, men alle studiene inkluderte noen pasienter fra intensivavdelinger (opptil 29 % i én studie). To studier inkluderte både pasienter som hadde vært innlagt på sykehus og deltakere som ikke hadde vært innlagt. Størrelsen på utvalgene varierte fra 518 til 8 679 deltakere. Én studie inkluderte kun barn, de øvrige hovedsakelig middelaldrende voksne. Vi vurderte kvaliteten på de inkluderte studiene til å være rimelig til god. Alle studiene brukte laboratorietester til å diagnostisere covid-19, hovedsakelig PCR.

Symptomer ved seks til tolv måneders oppfølging

Pasienter innlagt på sykehus med covid-19 ser ut til å ha høyere risiko for nye sykehusinnleggelser, nye diagnoser og selvrapporterte symptomer enn de som ikke var innlagt og SARS-CoV-2-negative kontrollgrupper. Helserelatert livskvalitet (HRQoL) ser ut til å være lavere hos tidligere sykehusinnlagte covid-19-pasienter enn hos den generelle befolkningen, men dette ble kun målt i én kontrollert studie. Alvorlig syke covid-19-pasienter med behov for sykehusinnleggelse hadde flere symptomer og symptomer med lengre varighet enn pasienter som hadde vært innlagt på sykehus med influensa. Forskjellen i symptombyrde mellom influensapasienter (ikke innlagt på sykehus) og pasienter med mild covid-19 (ikke innlagt på sykehus) var mindre uttalt, et funn som samsvarer med andre studier som ikke fant noen forskjell i nye sykehusinnleggelser mellom pasienter med mild/moderat covid-19-sykdom og kontrollgrupper fra den generelle befolkningen. Enkelte ukontrollerte studier med en gjennomsnittlig oppfølgingstid på åtte måneder fant tydelig nedgang i antall symptomer over tid, men trenden var ikke like tydelig i alle studier. Blant studiene vi har inkludert i denne oversikten er det bare én som i hovedsak omfatter barn og unge, men barn ser ut til å være mindre berørt av senfølger etter covid-19 enn voksne.

Gruppering av kliniske tegn og symptomer ved seks til tolv måneders oppfølging

Kategorisering basert på ICD symptomgrupper fra tolv studier med hovedsakelig sykehusinnlagte pasienter viste størst spredning i forekomsten av allmennsymptomer. Allmennsymptomer, nevrologiske symptomer og lungesymptomer var de vanligste symptomkategoriene. Ukontrollerte studier og studier med færre deltakere later til å rapportere mer

ekstreme verdier. Kategorien med nevrologiske symptomer skilte seg ut med flest enkeltstående symptomer og hyppigst rapporterte symptomer.

Risikofaktorer for senfølger etter covid-19
Én kontrollert og fire ukontrollerte 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 langvarige symptomer.

Diskusjon

De fleste studiene som målte selvrapportert forekomst av symptomer, inkluderte kun covid-19-pasienter som hadde vært innlagt på sykehus. Studiene med både innlagte og ikke-innlagte pasienter er hovedsakelig basert på registerdata som mangler informasjon om mindre alvorlige symptomer som ikke krever medisinsk oppfølging. Det er derfor usikkert hvor lenge mindre alvorlige symptomer vedvarer hos personer med milde til moderate sykdomsforløp. Få studier måler helserelatert livskvalitet. Det ser ut til at covid-19-pasienter skårer lavere på dette utfallet enn den generelle befolkningen, men på grunn av begrenset dokumentasjon forblir effekten av gjennomgått covid-19-sykdom på helserelatert livskvalitet usikker.

Våre funn er fremdeles relatert til studier som ble gjennomført tidlig i pandemien, og vi antar at forbedrede behandlingsmetoder, og vaksinasjon vil kunne påvirke senfølger etter covid-19 i fremtiden og føre til mildere sykdomsforløp og færre senvirkninger. På grunn av heterogenitet på tvers av studier var det ikke mulig å sammenstille resultater i metaanalyser. Vi kan verken bekrefte eller avkrefte årsakssammenhenger mellom gjennomgått covid-19 og langvarige symptomer basert på de inkluderte studiene. Det er behov for store, kontrollerte befolknings-studier som omfatter SARS-CoV-2 test positive og SARS-CoV-2 negative deltakere (vaksinerte og uvaksinerte), og som bruker spørreskjemaer, kliniske målinger og måling av helserelatert livskvalitet for å få bedre kunnskap om ulike symptomers hyppighet, varighet og alvorlighets-grad, samt klynger av symptomer blant personer med initial mild til moderat covid-19.

Konklusjon

Alvorlig covid-19, som krever sykehusinnleggelse eller intensivbehandling, korrelerer med flere symptomer ved seks- og tolv-måneders oppfølging. Spekteret av senfølger er bredest for innlagte pasienter, og generelle-, nevrologiske- og lungesymptomer er de vanligste. Kvinner skiller seg ut med en høyere risiko for å utvikle senfølger. Mange pasienter som har hatt moderat covid-19 (ikke innlagt på sykehus) rapporterer vedvarende symptomer seks til tolv måneder etter infeksjon, men kontrollerte studier viser noen av disse symptomene også rapporteres i uinfiserte kontrollgrupper. For pasienter som har hatt mild covid-19, kan det se ut til at det er en økning i noen selvrapporterte symptomer, men symptomene er mindre uttalt enn for pasienter som har vært moderat eller alvorlig syke. Effekten av senfølger av mild og moderat covid-19 på livskvalitet i den generelle befolkningen er fortsatt uklar ettersom livskvalitet i hovedsak er målt blant pasienter som har vært alvorlig syke.

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Problem statement

COVID-19 has been associated with long-term symptoms. Aiming to offer customised treatment, policy makers, health care professionals and patients need access to up-to-date evidence about long-term 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 are associated with long-term symptoms of COVID-19?

The outbreak team at the Norwegian Institute of Public Health (NIPH) has commissioned this rapid review update, with the previous version published 10th August 2021 (2). Additionally, this update addresses assignment 479 from the Norwegian Ministry of Health and Care Services in which NIPH committed to update the rapid review about post-covid and long-term symptoms. As a part of the work with the present report, we have also prepared a memorandum regarding long-term symptoms among children and adolescents that is included in NIPHs response to assignment 58 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 long-term COVID-19 symptoms, demographic and medical risk factors associated with symptoms on follow-up, and studies analysing the impact of long-term symptoms of COVID-19 on the healthcare system. We defined the inclusion criteria prior to the search. We searched for studies with non-COVID-19 controls with more than 100 participants; in addition, we searched for uncontrolled studies with more than 500 participants with mainly laboratory confirmed COVID-19, that reported on symptoms, quality of life, and predicting factors for long-term symptoms. One researcher (JH) conducted a search on October 29th, 2021, in the MEDLINE database for studies published in the period 17.06.2021 -29.10.2021. This search was expanded with a search in the WHO Global research on coronavirus disease (COVID-19) database on October 29th, 2021 (3). In combination with the previous reports' search period, the timeframe since 01.01.2020 was covered.

Inclusion criteria:

Population:	More than 100 participants followed up with non-COVID-19 controls. More than 500 participants followed up without controls. Participants with 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 median/mean six months or longer
Study types:	Cohort studies (prospective and retrospective), case-controls, case-series, surveys
Exclusion criteria:	Non-peer-reviewed uncontrolled studies, abstracts, studies limited to participants with one main underlying disease

The inclusion criteria listed above are more specific 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 uncontrolled studies with less than 500 participants are not included, in addition to the requirement that six months follow-up time needs to be met by the average, or median of all participants. We changed the inclusion criteria based on the assumption that more studies had been published since the second version.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (JH, AVF) 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 (HLG, KMG, KGB).

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-Control Studies (4). The NIH assessment tool focuses on the key concepts for evaluating the internal validity of studies. Methodological quality rating can be good, fair or poor quality, based on fulfilment of 14 aspects for Observational Cohort and Cross-Sectional Studies and 12 for Case-Control Studies. 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, AVF) extracted relevant information from included studies to Excel. We extracted information on study country, participants, follow-up period, symptom prevalence and statistics (e.g., odds ratio, rate ratio, hazard ratio). For prevalence of symptoms, we calculated percentages based on provided fractions. In case of mixed populations in uncontrolled studies (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 (5) (Appendix 2). Studies with participants mainly below 18 years of age were described separately.

Data analysis

Data tables of extracted endpoints were exported to *plotly,* an online tool for data analysis and visualisation (6). We plotted prevalence of symptoms against individual studies and symptom groups in a scatterplot. We used colours to differentiate between controlled and un-controlled studies. 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. Bar charts were used to illustrate the prevalence of symptoms in cases of COVID-19 and controls.

Peer review

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

Acknowledgements

The authors would like to thank our NIPH colleagues Hanne L. Gulseth, Helena Niemi Eide, Elisabet Hafstad and Ley Muller for their support in preparing previous versions of the report, the literature search and data analysis. We thank the peer reviewers Signe Flottorp and Ernst Kristian Rødland for their critical review of the report.

Results

Description of studies

Results of the literature search

We identified 2938 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 (7). In total, we read 30 references in full text. 20 studies unique studies matched our inclusion criteria, including six studies from our

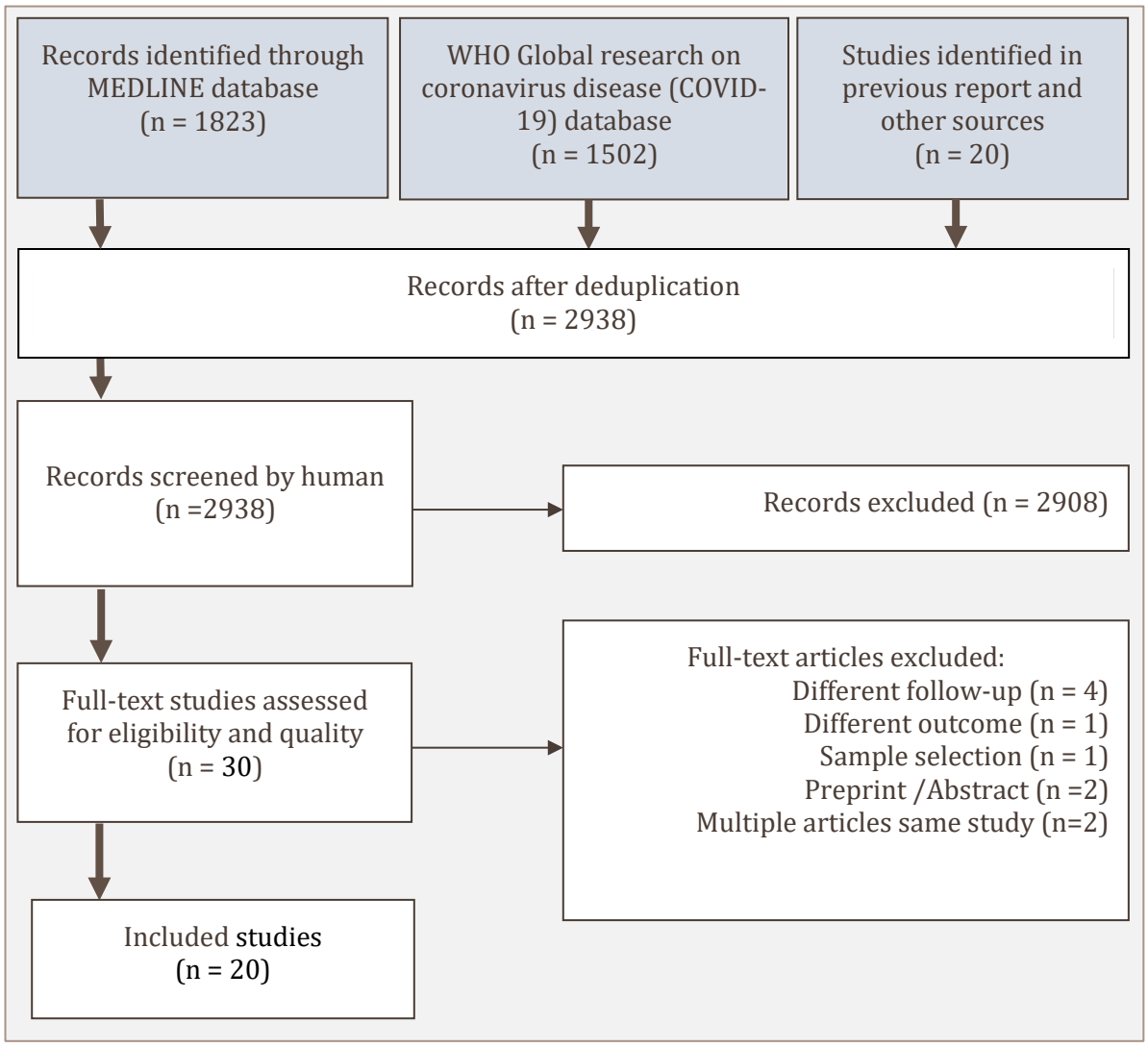

Figure 1. Flow diagram of search strategy and study inclusion

previous report, of which one study was replaced with an update. Most studies from our previous report (n=20) were excluded from this update because of too short follow-up or small sample size (n=14). Figure 1 shows a graphical representation of our search and screening methodology, and Table 1 lists the included studies. Three authors published more than a single publication on their study population, in that case we decided to group the results under the name of the identical first author (8-14).

Included studies

After full text screening we included 20 studies reported in 24 articles, including six out of 20 studies from the preceding report (Table 1). We excluded eight studies not matching our inclusion criteria (Appendix 3).

Table 1. Overview of included studies

Fist author, reference	Country	SARS-CoV-2-pos. participants (n)	Age (mean (SD)/ median (IQR))	Sex % male	Study type	Length of follow up**
HOSPITALISED*						
Bhaskaran (15)	UK	24 673	**66 (53-78)**	56	Retrospective controlled	≤ 315 days
Fernandez-de-las-Penas (8-10)	Spain	1142	61 (17)	52	Cross-sectional uncontrolled	7 months (SD 0.6)
Ghosn (16)	France	1137	**61 (51-71)**	63	Prospective uncontrolled	6 months
Günster (17)	Germany	8679	**72 (57-82)**	54	Retrospective uncontrolled	180 days
Huang (18)	China	1 276	**59 (49-67)**	53	Ambidirectional controlled	6 and 12 months
Liu (19)	China	594	**63 (53-68)**	46	Prospective uncontrolled	12 months
Liu (20)	China	1 539	**69 (66-75)**	48	Cross-sectional controlled	6 months
Maestre-Muñiz (21)	Spain	587	65 (18)	51	Cross-sectional uncontrolled	12 months +/-1m
Munblit (22)	Russia	2 649	**56 (46-66)**	49	Prospective uncontrolled	218 days (200-236)
Osmanov (23)	Russia	518	**10 (3-15)**	48	Prospective uncontrolled	256 days (223-271)
Peghin (24)	Italy	599	53 (16)	47	Prospective uncontrolled	187 days (SD 22)
Shang (25)	China	1 174	**62 (51-69)**	51	Prospective uncontrolled	6 months
Zhang (26)	China	2 433	**60 (49-68)**	50	Retrospective uncontrolled	12 months
NON-HOSPITALISED						
Lund (27)	Denmark	8 983	**43 (30-56)**	39	Prospective controlled	6 months
Kim (28)	S. Korea	900	**31 (24-47)**	30	Retrospective uncontrolled	195 days (191-200)
MIXED						
Caspersen (29)	Norway	774	**≈47**	42	Ambidirectional controlled	1-6 months and 11-12 months
Mainous (30)	USA	325	**≈55**	39	Retrospective controlled	6 months
Park (11, 12)	S. Korea	6 148/7133	**≈45**	39	Retrospective controlled	6 months
Taquet (13, 14)	USA	273 618/236 379	46 (20)	42/45	Retrospective controlled	6 months
Xiong (31)	China	291	37 (9)	19	Cross-sectional controlled	6 months after outbreak

*For uncontrolled studies, categories reflect the hospital status of >50% of participants. Controlled studies with both hospitalised and non-hospitalised participants are categorized as "mixed".
**Length of follow up was reported differently in the included studies

The included studies were conducted in China n=6 (18-20, 25, 26, 31), Denmark n=1 (27), France n=1 (16), Germany n=1 (17), Italy n=1 (24), Norway n=1 (29), Russia n=2 (22, 23), South Korea n= 2 (11, 12, 28), Spain n=2 (9, 21), UK n=1 (15) and USA n=2 (13, 14, 30). Nine of the studies included control groups. The median length of follow-up was six months in most studies with some studies following participants for up to a year. Follow-up time was measured from hospital discharge, initial symptoms or from positive test for SARS-CoV-2. Number of SARS-CoV-2-positive participants ranged from 291 to 273 618. The participants in most studies were middle-aged, one study only enrolled children (23). The sex distribution was mainly balanced apart from two studies where 19% (31) and 30% (28) were male. All studies used mainly laboratory testing to diagnose COVID-19 (mainly PCR). Follow ups were performed either at clinics, through online/phone/postal surveys, or by assessing register data.

Among the nine controlled studies, five included a mix of hospitalised and non-hospitalised COVID-19 patients, three included only hospitalised patients and one focused on non-hospitalised patients but reported on hospitalised patients as well in supplementary material. All nine studies compared results to SARS-CoV-2-negative control groups, either from the general population, previous influenza patients, colleagues or spouses. The eleven uncontrolled studies mainly followed up COVID-19 hospitalised patients, non-ICU and ICU. Three of the uncontrolled studies included a mixed population of hospitalised and non-hospitalised patients. All studies started enrolling patients before May 2020 (Figure 2).

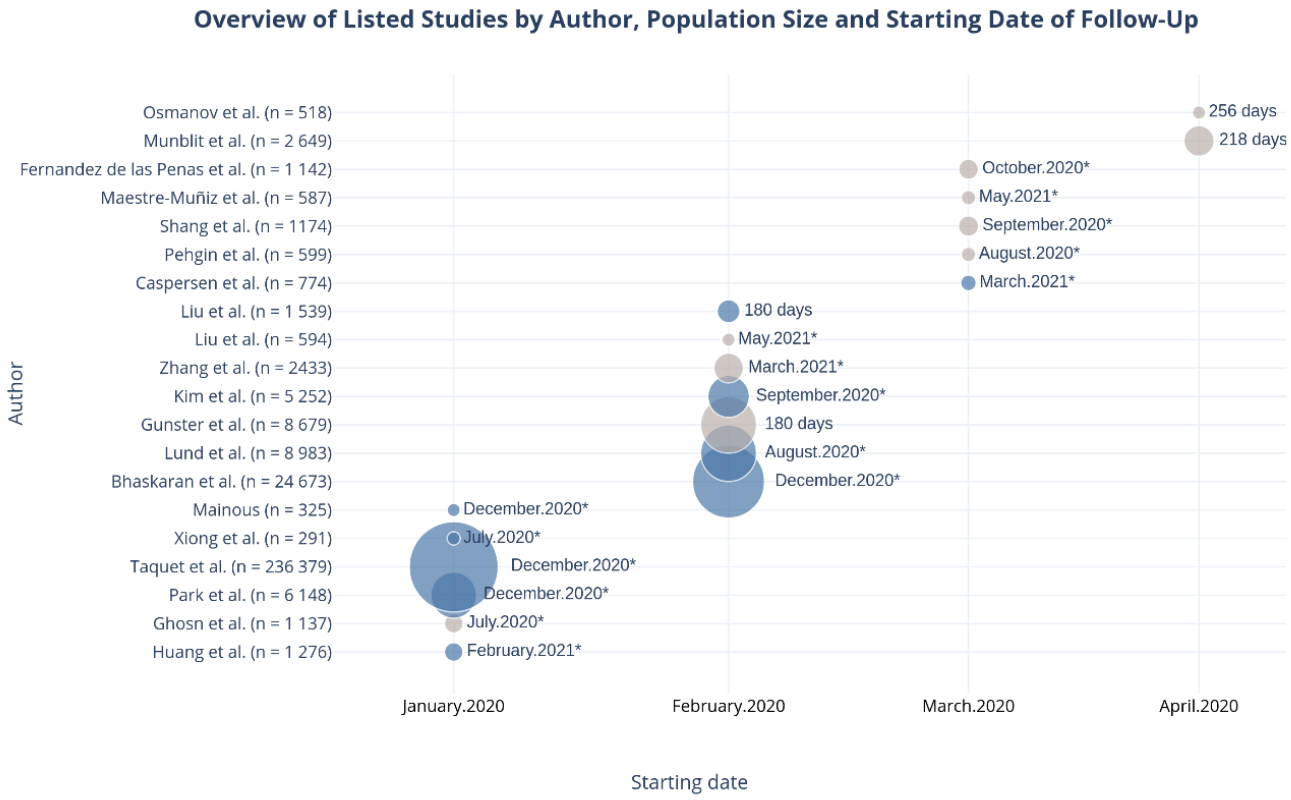

*Figure 2. Start and end date of studies, bubble-size indicating number of study participants, grey bubbles depict un-controlled studies, and blue controlled studies. * indicates the end of follow-up.*

Quality assessment

We assessed study quality to be overall fair to good, ranging from 7-12 points out of 12 possible for case-control studies with no fatal flaws deemed likely to result in a high risk of bias. The lower scored studies had smaller sample sizes and retrospective self-reported outcomes, making blinding of assessors impossible with risk of recall bias (Table 2). Cohort and cross-sectional studies ranged from 8-12 points out of 14, with no fatal flaws deemed likely to result in a high risk of bias. Among the cohort and cross-sectional studies, low participation rate of eligible persons and loss to follow-up after baseline were the most common shortcomings (Table 3).

Table 2. Results of the Quality assessment of Case-Control Studies

First author	1	2	3	4	5	6	7	8	9	10	11	12	Total
Bhaskaran (15)	x	x	-	-	x	x	x	x	x	x	x	x	10
Caspersen (29)	x	x	-	x	x	x	x	x	-	-	-	x	8
Huang (18)	x	x	-	x	x	x	x	x	-	-	-	x	8
Liu (20)	x	x	-	x	x	x	x	x	-	-	-	x	8
Lund (27)	x	x	-	x	x	x	x	x	x	-	-	x	9
Mainous (30)	x	x	-	x	x	x	x	x	x	x	x	x	11
Park (11, 12)	x	x	x	x	x	x	x	x	-	x	x	-	10
Taquet (13, 14)	x	x	x	-	x	x	x	x	x	x	x	x	11
Xiong (31)	x	x	-	x	x	x	-	x	-	x	-	-	7

1. Research question 2. Study population, 3. Sample size justification, 4. Controls from similar population, 5. Selection of cases and controls, 6. Definition of cases and controls, 7. Random selection if less than 100% of eligible selected, 8. Use of concurrent controls, 9. Confirmation that exposure/risk occurred prior to event, 10. Measures of exposure/risk (validity/reliability/consistency), 11. Blinding of assessors, 12. Analyses adjusted for key confounders.

Table 3. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Fernandez-des-las-Penas (9)	x	x	x	x	-	x	x	x	x	NA	x	-	x	-	10
Ghosn (16)	x	x	-	x	-	x	x	-	x	NA	x	-	-	x	8
Gunster (17)	x	x	x	x	-	x	x	x	x	NA	x	x	x	x	12
Kim (28)	x	x	-	x	-	x	x	x	x	NA	x	-	-	x	9
Liu (19)	x	x	-	x	-	x	x	x	x	NA	x	-	x	x	10
Maestre-Muñiz (21)	x	x	x	x	-	x	x	x	x	NA	x	-	-	-	9
Munblit (22)	x	x	x	x	-	x	x	x	-	NA	x	-	x	x	9
Osmanov (23)	x	x	x	x	-	x	x	x	x	NA	x	-	x	-	10
Peghin (24)	x	x	x	x	-	x	x	x	x	NA	x	-	x	x	11
Shang (25)	x	x	x	x	-	x	x	x	x	NA	x	-	-	-	9
Zhang (26)	x	x	x	x	-	x	x	x	x	NA	x	-	-	x	10

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.

Results from controlled studies

We identified nine controlled studies with more than 100 participants followed up for six months or longer, two of which were not peer-reviewed and only published as preprints (15, 29). Two of the studies have multiple publications (11-14). Four studies included cohorts of SARS-CoV-2-positive (both hospitalised and non-hospitalised) and -negative subjects from the general population as cases and controls (11, 12, 27, 29, 30) and two studies (three articles) included a group of influenza patients as controls (13-15). Three studies focused on the subgroup of hospitalised COVID-19 survivors (15, 18, 20) and one study only included frontline health care workers (31). Most studies reported on registry data such as new hospitalisations, health care use and other characteristics recorded in medical records while two studies collected self-reports of long-term symptoms (18, 29) and two studies used standardised questionnaires to assess specific conditions (20, 31). Participant size of the included COVID-19 populations ranged from 291 to 273 618 participants. In general, those hospitalised with COVID-19 had a higher risk of new hospital admissions, new diagnoses, and more self-reported symptoms at follow-up than those who were not hospitalised and SARS-CoV-2-negative controls. Female sex also appears to be a predictor of more symptoms, new diagnoses, or hospital admissions (12, 13, 18, 29). The only controlled study assessing health-related quality of life (HRQoL) found lower scores in formerly hospitalised COVID-19 patients than in the general population controls (18). Results at follow-up suggested more symptoms and longer symptom length for COVID-19 patients than for influenza patients, especially for those with severe COVID-19 (requiring hospitalisation) (13, 15). Other studies found no difference in new hospital admissions between mild/moderate COVID-19 disease (not requiring hospitalisation) and controls in the general population (12, 27, 30). The following section gives a short description of the controlled studies and results reported on the three topics; *prevalence of symptoms*, *re-admissions and use of health care services* and *cognitive and mental tests.*

Bhaskaran et al. (preprint) compared number of readmissions and deaths in 24 673 people discharged after COVID-19 hospitalisation in 2020 (median age 66 years), 123 362 controls in the general population and 16 058 people discharged from influenza-hospitalisation in 2017-2019 in the UK (15). Overall risk of hospitalisation or death (30 968 events) was higher in the COVID-19 group than in general population controls (adjusted-HR 2.23, 95% CI 2.14-2.31) but similar to the influenza group (adjusted-HR 0.94, 95% CI 0.91-0.98). Adjusted-HR for all-cause mortality (7 439 events) was 4.97 (95% CI 4.58-5.40) for COVID-19 vs general population controls and 1.73 (95% CI 1.60-1.87) for COVID-19 vs influenza controls. COVID-19 patients were more likely than influenza patients to be readmitted or die due to their initial infection/other lower respiratory tract infection (adjusted-HR 1.37, 95% CI 1.22-1.54), and to experience mental health or cognitive-related hospital admission or death (adjusted-HR 1.36, 95% CI 1.01-2.83); in particular, COVID-19 survivors with pre-existing dementia had higher risk of dementia death.

Caspersen et al. (preprint) followed 73 727 participants in the pre-existing Mother, Father and Child Cohort Study (MoBa) in Norway from March 2020 to March 2021 (29). Median age was approximately 47 years. Data on COVID-19 diagnosis were obtained from registry data based on PCR confirmed SARS-CoV-2 infection. Those with no COVID-19 diagnosis served as controls. All participants returned completed electronic questionnaires on current symptoms from a list of 22 pre-defined symptoms and duration of such symptoms at the end of follow-up. Only non-vaccinated, adult participants were included. At 11-12 months follow-up, infected subjects had increased risk for 13 of the 22 symptoms when compared to uninfected subjects. The symptom with highest excess risk compared to uninfected subjects was altered smell or taste (17%)

followed by poor memory (15%), fatigue (14%), shortness-of breath (10%) and reduced lung function (7%). Altered smell and taste was weakly correlated with other symptoms. Symptom prevalence was about twice as high in the severe illness group when comparing with those who reported mild illness. Women infected by SARS-CoV-2 reported higher prevalence of heart palpitations, brain fog, fatigue, headache, dizziness, poor memory and altered smell or taste compared to men. 44% of participants with COVID-19 reported no symptoms after 11-12 months and 79% of controls reported no symptoms during follow-up. Anxiety and depression were more common in those with severe illness, but the excess risk was low (2.2% and 1.2%) in the infected group compared with the uninfected. By using factor analysis, the authors found that two underlying factors explained 50% of the variance in the 13 investigated symptoms. One factor comprised brain fog, poor memory, dizziness, heart palpitations and fatigue, and the other factor comprised shortness of breath and cough.

Huang et al. conducted a cohort study of patients who were discharged from one hospital in Wuhan, China between Jan 7 and May 29 2020 (18). 1 276 patients (of the initial 2469) with a median age of 59 years participated in testing 6 and 12 months after discharge and were compared to community-dwelling adults without SARS-CoV-2-infection. The two follow-up visits included a detailed interview, physical examination, laboratory tests, and more. The proportion of patients with at least one sequelae symptom decreased from 68% (831/1227) at 6 months to 49% (620/1272) at 12 months. The proportion of patients with dyspnoea, slightly increased from 26% (313/1185) at 6-month visit to 30% (380/1271) at 12-month visit and more patients had anxiety or depression after 12 months compared to 6 months (26% [331/1271] vs 23% [274/1187]). Number of patients with fatigue or muscle weakness was markedly reduced from 52 % (636/1230) at six months to 20 % (255/1272) at 12 months. No significant difference on 6-minute walking distance test was observed between 6 months and 12 months. 88% (422/479) of patients who were employed before COVID-19 had returned to their original work at 12 months. Compared with men, women had an odds ratio of 1.43 (95% CI 1.04–1.96) for fatigue or muscle weakness, OR 2.00 (95% CI 1.48–2.69) for anxiety or depression, and OR 2.97 (95% CI 1.50–5.88) for diffusion impairment. Matched COVID-19 survivors at 12 months had more problems with mobility, pain or discomfort, and anxiety or depression, and had more prevalent symptoms than did controls. COVID-19 survivors also had lower scores on self-assessed quality of life.

Liu et al. recruited 1539 COVID-19 inpatients aged over 60 years who were discharged from three COVID-19-designated hospitals in Wuhan, China, and 466 uninfected spouses of COVID-19 patients as controls (20). Median age was 69 years. Cognitive status was assessed by telephone interview using the Telephone Interview of Cognitive Status (TICS-40) 6 months after discharge and information about comorbidities was collected from medical records. Subjects' family informants were interviewed to report the cognitive decline of patients and their spouses over the previous 6 months. Severe COVID-19 patients had lower TICS-40 scores than non-severe patients [median (IQR): 24 (18 to 28) vs. 30 (26 to 33), $p < 0.001$] and controls [24 (18 to 28) vs. 30 (26 to 33), $p < 0.001$]. TICS-40 scores were comparable between non-severe COVID-19 cases and controls. No difference was found in the proportion of cases with dementia or MCI between non-severe COVID-19 patients and controls. COVID-19 severity, ICU admission, delirium, and COPD were associated with lower TICS-40 scores. Higher education level and high flow oxygen therapy were associated with higher TICS-40 scores.

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 8 983 individuals without hospitalisation (median age 43 years), and a smaller cohort of 1310 hospitalised patients, including also a matched reference group of 80 894 individuals testing negative (27).

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. 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.

Mainous et al. followed a cohort of 10 646 persons who were tested for COVID-19 in the University of Florida health system (30). 325 of these tested positive (median age approximately 55 years), of which 211 had mild or moderate symptoms and 114 had severe symptoms (were hospitalised). New hospitalisations during the following 6 months after testing were assessed. There was no difference in hospital admittance between SARS-CoV-2 test positive and SARS-CoV-2 test negative participants (hazard ratio [HR] 1.31; 95 % CI 0.98-1.74), but those with severe COVID-19 had a significantly increased risk of hospitalisation of any cause compared to both mild/moderate COVID-19 patients (HR 2.20; 95 % CI 1.13-4.28) and SARS-CoV-2 test negative participants (HR 2.24, 95 % CI 1.52-3.30). Hospitalisation risk was comparable between SARS-CoV-2 test negative participants and SARS-CoV-2 test positive participants with mild/moderate symptoms.

Park et al. (multiple publications) used data from the National Health Insurance Service COVID-19 database in South Korea (NHIS-COVID-19 DB) to investigate the prevalence of mental illness and the associated factors for its development among COVID-19 patients (median age approximately 45 years) (11) and whether COVID-19 patients were at a higher risk of dementia diagnosis compared to controls at 6 months follow-up (12).

The authors found a higher prevalence of mental illness in the COVID-19 patients than in the control group (12. 0% vs. 7.7 %; odds ratio (OR) = 2.40, 95% CI 2.21–2.61) (11). This trend was more evident in COVID-19 patients who received specific treatment for COVID-19 than in the COVID-19 patients who did not receive specific treatment (OR = 3.27, 95% CI 2.77–3.87 for specific treatment vs. controls and OR = 2.23, 95% CI 2.03–2.45 for no specific treatment vs. controls). However, the causal relationship between COVID-19 and mental illness cannot be established in this study.

The incidence of new-onset dementia among COVID-19 patients was 1.39-fold higher (HR: 1.39, 95% CI 1.05–1.85) than in the control group. Hospitalised COVID-19 patients had a 1.62-fold higher incidence of dementia than the control group, while non-hospitalised COVID-19 patients showed no increased incidence of dementia (12). In both studies, several potential confounders such as BMI, smoking and alcohol use were not adjusted for in the multivariable models. Also, adjusting for duration of isolation because of COVID-19 attenuated the associations between mental illness and dementia – and COVID-19 down to HR 1.02 (95% CI 1.01-1.02) and HR 1.03 (95% CI 1.02-1.03) in COVID-19 patients, which has no clinical significance.

Taquet et al. (multiple publications) used data from a federated network of linked electronic health records (TriNetX Analytics), primarily from the USA, to estimate incidence rates and relative risks of neurological and psychiatric diagnoses in patients following a COVID-19

diagnosis (14) and to estimate incidence of long-term symptoms (13). Both studies were comprised of patients with a COVID-19 diagnosis and a matched control cohort of influenza patients.

The authors found that among patients diagnosed with COVID-19 (mean age 46 years), the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 34% (95% CI 33–34), with 13% (95% CI 12–13) receiving their first such diagnosis. Most diagnostic categories were more common among COVID-19 patients than among the influenza patients: HR 1.44 (95% CI 1.40–1.47) for any diagnosis, and HR 1.78 (95% CI 1.68–1.89) for any first diagnosis. As with incidences, HRs were higher in patients with more severe COVID-19 (e.g, those admitted to an intensive care unit compared with those who were not: HR 1.58 (95% CI 1.50–1.67) for any diagnosis and HR 2.87 (95% CI 2.45–3.35) for any first diagnosis (14).

The incidence and co-occurrences were estimated for nine core symptoms of post-COVID condition. Among COVID-19 survivors, 37% had one or more long-term symptoms recorded during the 90–180-day period while the corresponding number in a group of 114,449 patients in the influenza-group was 30%. The incidence of all symptoms, except pain, was lower in the 90- to 180-day period than in the 1- to 90-day period. All nine symptoms were more frequently reported after COVID-19 than after influenza. Overall, there was a higher incidence of post-COVID symptoms in the elderly (aged 65 years and older), in more severely affected patients, and in women (13).

Xiong et al. included 291 frontline health care workers (HCWs) in China with a mean age of 37 years who had been diagnosed with COVID-19 and 42 age- and gender-matched COVID-19-free frontline HCWs as controls (31). The study examined the prevalence, correlates, and clinical symptoms of possible PTSD in surviving HCWs 6 months after the COVID-19 outbreak. Surviving HCWs had significantly higher rates of possible PTSD than controls (19.9% vs. 4.8%, P = 0.017). Correlates of PTSD in survivors were ICU admission (OR = 8.73, P = 0.003), >10 respiratory symptoms during the most symptomatic period of COVID-19 (OR = 3.08, P = 0.006), the residual symptom of dizziness (OR = 2.43, P = 0.013), the residual symptom of difficult breathing (OR = 2.23, P = 0.027), life in danger due to COVID-19 (OR = 16.59, P = 0.006), and exposure to other traumatic events (OR = 2.94, P = 0.035). The prevalence of possible PTSD in the control group was also higher than in the Chinese general population where the lifetime, 12-month, and 1-month prevalence rates of PTSD were previously estimated to be 0.30%, 0.20%, and 0.195%, respectively.

Prevalence of symptoms

Caspersen et al. (29) and Huang et al. (18) measured self-reported symptoms in COVID-19 cases and uninfected controls from a pre-existing study cohort (Figures 3 and 4). Most symptoms occurred in both COVID-19 cases and in the controls. The symptoms most frequently reported in Caspersen et al. were altered smell or taste, poor memory, fatigue, shortness-of breath, headache, and brain fog. The most frequently reported symptoms in Huang et al. were fatigue, hair loss, heart palpitations, joint pain, sleep problems and anxiety or depression. Symptoms are generally reported in a larger proportion of the population in the study by Huang et al. which consisted of more severely ill patients initially hospitalised with COVID-19 while most participants in Caspersen et al. were never admitted to hospital. The prevalence of symptoms at 12 months follow up was approximately half in the group who reported mild illness in the study by Caspersen et al. compared to those with moderate to severe COVID-19 disease.

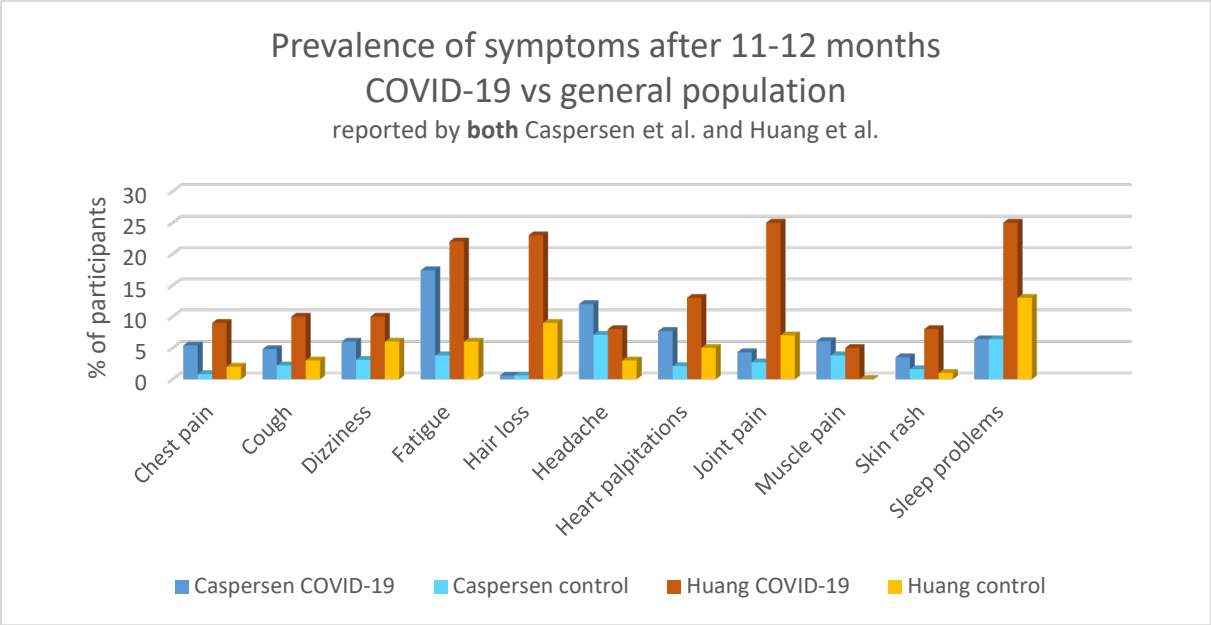

Figure 3. Prevalence of self-reported symptoms in COVID-19 cases and non-cases at 11-12 months follow-up. Based on data from Caspersen et al. (29) and Huang et al. (18).

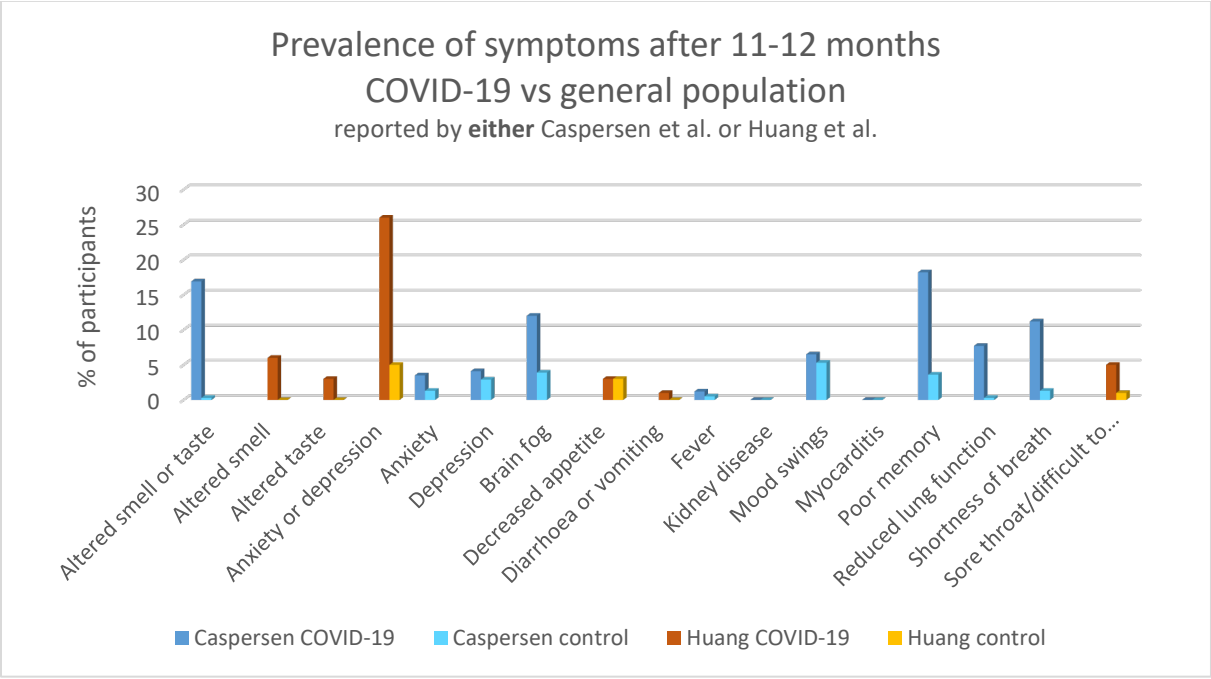

Figure 4. Prevalence of self-reported symptoms in COVID-19 cases and non-cases at 11-12 months follow-up. Based on data from Caspersen et al. (29) and Huang et al. (18).

Readmissions and use of health care services

Five studies investigated differences in readmissions and use of health care services in COVID-19-cases and controls (11-15, 27, 30) using registry data.

Taquet et al. (13) and Bhaskaran et al. (15) compared COVID-19 patients to influenza patients and found that risks for most outcomes were broadly comparable to those experienced by hospitalised influenza patients, however COVID-19 patients were more likely to be readmitted

or die due to their initial infection/other lower respiratory tract infection than influenza controls (15). Taquet et al. found that the prevalence of symptoms reported upon any health care service contact was generally higher in COVID-19 patients compared to influenza patients (Figure 5) and the risk of post-COVID symptoms was higher in patients who had more severe COVID-19 illness (13).

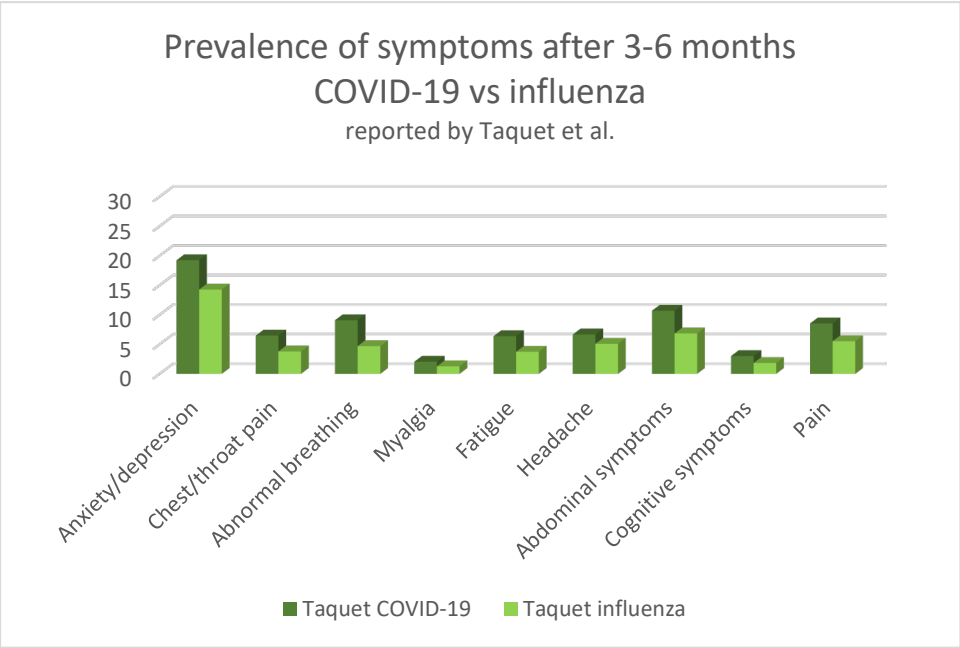

Figure 5. Prevalence of symptoms reported upon contact with health care services three to six months after diagnosis in matched COVID-19 patients and previous influenza patients. Based on data from Taquet et al. (13).

The likelihood of hospitalisation, development of mental illness or dementia or initiating new drug therapies following severe COVID-19 was found to be increased compared to non-COVID-19 patients (11, 12, 27, 30) and those who had mild/moderate COVID-19 (27, 30), but there are reasons to question the causal relationship between COVID-19, mental illness and dementia. Some studies found that non-hospitalised COVID-19 patients with mild/moderate disease did not have different risks for a subsequent hospitalisation or for developing dementia than COVID-19-negative patients (12, 27, 30).

Cognitive and mental tests

Two studies used validated questionnaires to assess signs of cognitive impairments (20) and post-traumatic stress disorder (PTSD) (31) in COVID-19 cases and controls after six months. In the study on cognitive impairments, all participants were older than 60 years and initially hospitalised with COVID-19. They concluded that COVID-19 patients, especially patients with severe disease, had a higher risk of long-term cognitive decline than their uninfected spouses (20). The study on PTSD included mainly female frontline health care workers (HCW) who were infected with SARS CoV-2 and compared to colleagues not infected. Forty-two percent of the infected HCWs with severe COVID-19 and 16% of the infected HCWs with mild/moderate COVID-19 had possible PTSD 6 months after the COVID-19 outbreak versus 5% of the uninfected controls (31). Only crude analyses were performed.

Results from uncontrolled studies

We identified eleven studies without controls, with more than 500 participants followed up for six months or longer (9, 16, 17, 19, 21-26, 28). All studies followed up mostly hospitalised COVID-19 patients, the majority were non-critical patients without need of intensive care treatment, however all studies also included some patients from ICU wards (up to 29% in one study). Three studies included a mixed population of hospitalised and non-hospitalised patients (21, 24). One study included only children, the others mainly middle-aged adults (23). Study population size ranged from 518 – 8679 participants. The presence of any one symptom at six months to 12 months after COVID-19 hospitalisation in adults ranged from 28% to 90%, with fatigue, dyspnoea, anxiety and sleeping problems most reported across the studies. Critically or severely ill patients appear to be more affected over time. Some of the reviewed studies showed good improvement of symptoms over time, a trend not clear in all studies at an average of eight months follow-up. Symptoms on follow-up were more common among women and the initially severely ill. Two studies assessed changes in Health-related quality of Life (HRQoL) or limitations on daily living activities, finding that both decreased on follow-up (8, 22). Children remain little studied but appear to be less affected by long-term symptoms (23).

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 (9). SARS-CoV-2 PCR confirmed patients discharged from four Spanish hospitals between March 10th to May 31st 2020 were included. Researchers interviewed patients by telephone. In total, 1142 (48% women, mean age 61 years) were included. At seven months, 19% (n=212) of patients were completely free of any post-COVID symptom, 21% (n=238) had one symptom, 23% (n=267) had two symptoms, and 37% (n=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 (10). 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. In a further follow-up publication the authors found that at least 20% of COVID-19 survivors self-reported limitations in daily living activities eight months after hospitalisation (8).

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 three and six months after admission. In total, data was available for 1137 patients (median age 61 years). 655 (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. After six months, 24% (n=255) of the patients had three or more persistent symptoms. 125 (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 after six months was independently associated with female gender, having three or more symptoms at admission and ICU admission during the acute phase.

Günster et al. conducted an observational study with claims data from the German Local Health Care Funds of adult patients hospitalised in Germany (17). PCR-confirmed COVID-19 cases between February 1 and April 30, 2020, for whom 6-month readmission rates for the first 180 days after admission or until death were available. Of the 6 235 patients discharged alive, 1 668 were readmitted a total of 2 551 times within 180 days, resulting in an overall readmission rate of 27%.

Kim et al. conducted a survey of patients diagnosed with COVID-19 between February 18, 2020 and March 14, 2020 in South Korea (28). An online survey was conducted in September 2020 with a very low response rate of 17.1% (900/5252). Clinical characteristics and self-reported clinical sequelae of the responders were analysed to investigate the prevalence of, and factors associated with sequelae. The patients responded after a median period of 195 days. The median age was 31 years (42 years in non-respondents), and 70% of responders were female (63% in non-responders). Regarding the initial disease severity, 29 (3%) were asymptomatic, 763 (85%) mild, 86 (10%) moderate, 17 (2%) severe, and 5 (1%) critical. In total, 591 (66%) responders suffered from COVID-19-related long-term sequelae and 78 (9%) responders were receiving outpatient treatment for COVID-19-related long-term sequelae. The most common symptoms identified during the isolation period were loss of smell and taste at 45% and 44%, respectively. Fatigue was the most common long-term sequelae, accounting for 253 (26%) responders, followed by concentration difficulty, amnesia, cognitive dysfunction, anxiety, and depression, which accounted for over 20%. Female gender was identified as a factor associated with mental and psychological long-term sequelae.

Liu et al. followed 594 (of 1422 contacted) COVID-19 patients (median age 63 years) discharged from a hospital in Wuhan, from February 2020 to May 2021 (19). Demographic and clinical characteristics (including comorbidities and symptoms), laboratory and radiological findings, pulmonary function tests and electro-cardiogram were analysed. Of 594 enrolled patients, 502, 422, and 486 patients completed three-, six- and 12-month post-discharge follow-up visits. 257 (51%) patients had at least one symptom at three months post-discharge, which decreased to 169 (40%) at six-month visit and 138 (28%) at 12-month. During follow-up period, insomnia, chest tightness, and fatigue were the most prevalent symptoms. Most laboratory parameters returned to normal, whereas prevalence of organs damage persisted at 12-month follow-up. Abnormalities of pulmonary function was found at six months in 10% of participants, and 7% at 12 months. Electro-cardiogram abnormalities occurred in 51% of patients at three months post-discharge, including arrhythmia, ST-T change and conduction block, which increased to 61% of cases at six-month visit and were maintained at high prevalence with 50% at 12-month visit.

Maestre-Muniz et al. conducted telephone interviews of patients discharged from one hospital after acute COVID-19 in the first wave of the pandemic in Spain (21). Functional assessment was performed in patients aged over 65. Clinical and hospital records were reviewed, and mortality causes assessed. A total of 587 patients with COVID-19 were discharged from hospital, including 266 with severe-to-critical COVID-19 after hospital admission (median age 71.5 years) and 321 mild-to-moderate patients from the emergency room (56.2 years). Post-COVID-19 syndrome was assessed in 543 patients at one year from discharge. Any clinical complaint was reported by 90% of patients who needed hospitalisation and 80% of those discharged from the emergency room, with breathlessness (42%), tiredness (35%), loss of taste (30%), and loss of smell (26%)

being the most common complaints. Ongoing symptoms attributed to COVID-19 were reported by 67% and 50% of patients, respectively. Newly developed COPD, asthma, diabetes, heart failure, and arthritis—as well as worsening of pre-existing comorbidities—were found.

Munblit et al. followed up 2649 of 4755 (56%) patients six to eight months after discharge from four hospitals in Moscow between 8 April and 10 July 2020 via telephone interviews (22). COVID-19 diagnosis was clinical in 1291 patients and PCR based in 1358. Most cases were mild (63%), 902 (34%) required supplemental oxygen and 68 (3%) needed ventilatory support. Median age was 56 years and 51% were women. Persistent symptoms were reported by 1247 (47%) participants, with fatigue (21%), shortness of breath (15%) and forgetfulness (9%) as the most common symptoms. Chronic fatigue (25%) and respiratory (17%) were the most common symptom categories. Female sex was associated with any persistent symptom category OR 1.8 (95% CI 1.6 to 2.2) with association being strongest for dermatological (OR 3.3, 95% CI 2.4 to 4.6) symptoms. Asthma and chronic pulmonary disease were not associated with persistent symptoms overall, but asthma was associated with neurological (OR 2.0, 95% CI 1.3 to 3.0) and mood and behavioural changes (OR 2.0, 95% CI 1.2 to 3.2), and chronic pulmonary disease was associated with chronic fatigue (OR 1.7, 95% CI 1.2 to 2.3).

Osmanov et al. conducted a prospective cohort study among children (≤18 years old) admitted with confirmed COVID-19 (23). Children admitted to a children's hospital in Moscow between April and August 2020, were followed up via telephone interviews. Of 853 eligible children, 518 (61%) were available for the follow-up assessment and included in the study. Median age was 10 years and 52% were girls; median follow-up since hospital discharge was 256 days. At the time of the follow-up interview 126 (24%) parents of children reported persistent symptoms among which fatigue (53, 11%), sleep disturbance (36, 7%,) and sensory problems (29, 6%) were the most common. Multiple symptoms were experienced by 44 (8%) participants. Risk factors for persistent symptoms were older age "6-11 years" (odds ratio 2.7 (95% CI 1.4 to 5.8) and "12-18 years" (2.7, 95% CI 1.4 to 5.4) compared to age <2 years, and a history of allergic diseases (1.7, 95% CI 1.0 to 2.7).

Peghin et al. conducted a prospective cohort study of 599 consecutive adult in-and out-patients (mean age 53 years) with PCR-confirmed COVID-19 at a tertiary care teaching hospital in Italy, from March to May 2020 (24). 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. Most patients had been symptomatic (91%) and presented mild (76%) and moderate (17%) disease in the acute phase. A total of 26% had been hospitalised (3.8% in ICU). 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). The most common symptoms were fatigue (13%), anosmia/dysgeusia (10%), neurological symptoms (10%) and dyspnoea (6%). The persistence of fatigue and neurological symptoms was associated with moderate/severe disease at onset, whereas altered sense of smell and taste were associated with mild disease. Female gender (OR 1.6, 95% CI 1.0–2.3), a proportional increase in the number of symptoms at the onset of COVID-19 (OR 1.8; 95% CI 1.6–2.0) and ICU admission (OR 3.1; 95% CI 1.2–8.1) were all independent risk factors for post-COVID-19 syndrome.

Shang et al. followed up 1174 patients with severe COVID-19 via telephone interviews six months after discharge from three hospitals in Wuhan, China (25). Median age was 62 years. In total, 55% (441 of 796 participants who provided data) 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.

Zhang et al. conducted a retrospective cohort study at two hospitals in Wuhan, China. All adult patients with COVID-19 discharged between February 12 and April 10, 2020, were screened for eligibility (26). Of a consecutive sample of 3988 discharged patients, 1555 were excluded (796 declined to participate and 759 were unable to be contacted) and the remaining 2433 (61%) patients were enrolled. All patients were interviewed via telephone from March 1 to March 20, 2021. Of 2433 patients at 1-year follow-up, 50% were men and 680 (28%) categorized as severe cases; the median age was 60 years (IQR 49-68). In total, 1095 patients (45%) reported at least one symptom. The most common symptoms included fatigue (28%), sweating (17%), chest tightness (13%), anxiety (10%), and myalgia (8%). Older age, female sex, and initial severe disease were associated with higher risks of fatigue. Older age and severe disease were associated with higher risks of having at least three symptoms.

Overview of grouped signs and symptoms

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. 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)*" (see Appendix 2 for list of symptom groups and symptoms). 13 blocks were considered for grouping: 1. General, 2. Cardiovascular, 3. Ear, Nose and Throat, 4. Gastro-intestinal, 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 12 blocks, no studies reported symptoms matching with the group Obstetric/ Gynaecological. Our categorisation provides a simplified proxy for related symptoms, independent of severity and without further analysis.

The prevalence of symptoms by symptom group and study size

We plotted the prevalence of reported symptoms between six and 12 months against symptom groups, highlighting difference between non-controlled and controlled studies by grey and blue bubbles respectively (Figure 6). Twelve studies provided granular enough data to be include in the graph. The majority of patients included represent hospitalised patients. The bubble-size reflects the number of study participants (not to scale). The broadest prevalence range of symptoms is seen among *General* symptoms. Symptoms under the *General*, *Neurological* and

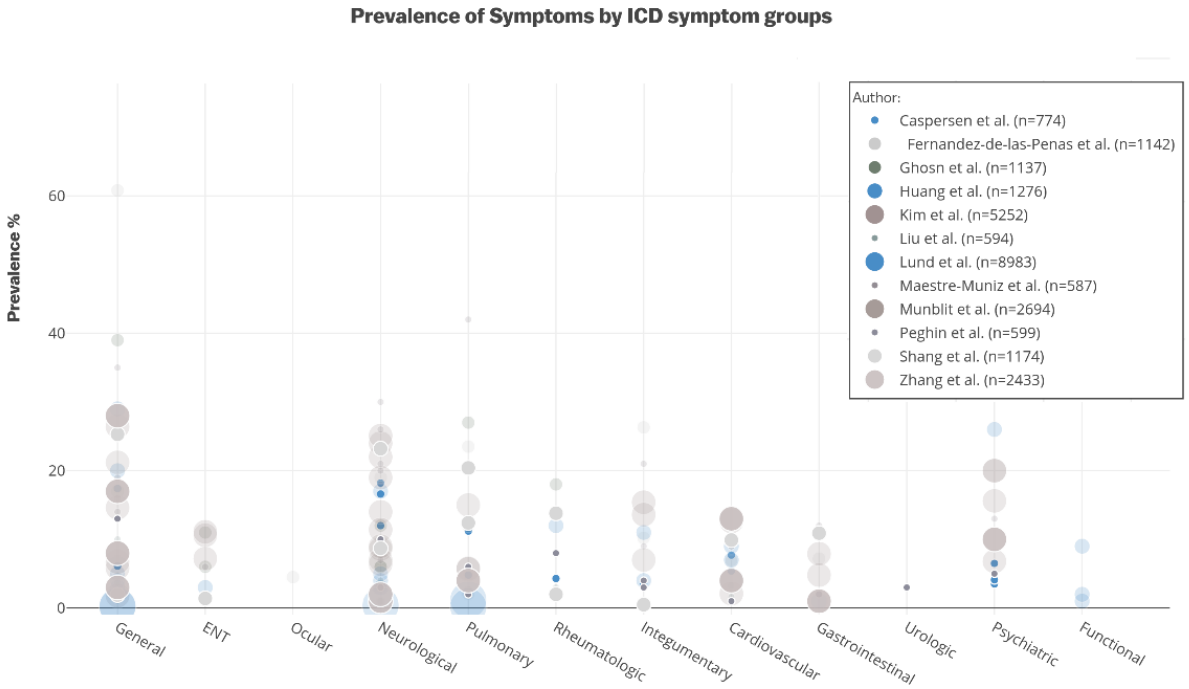

Figure 6. Prevalence of symptoms by symptom groups, bubble-size indicating number of participants (bubble size indicates study size, blue bubbles: controlled studies, grey bubbles: uncontrolled studies)

Pulmonary ICD blocks are most prevalent. Studies without controls and studies with fewer participants reported more extreme values, although it should be noted that the uncontrolled studies reflected a shorter than average follow-up time. The *Neurological* block stands out with the most separate symptoms, and most frequently reported symptoms.

Predicting factors for long-term symptoms

Whereas most studies predominantly focused on the prevalence of symptoms, one controlled and four uncontrolled 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), Risk Ratio/ incidence rate ratio (RR/IRR) and Hazard ratio (HR).

Based on the collected data, multiple symptoms (9, 16, 24), previous comorbidities (9), female sex (9, 16, 24, 25, 32) and severity of COVID-19 (9, 16, 24, 25, 32) were identified as factors correlated with length of symptoms. Age was generally not found to be correlated with outcomes. One study found that IgG titres were significantly higher in patients with than in patients without symptoms (24). Table 3 provides a more detailed overview of separate risk factors for four different outcomes (marked in light blue).

Table 3. Overview of 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 2 - orange****,* ***more than 1 - bold black****.*

	Fernandez-de-las-Penas et al.	**Ghosn et al.**	**Peghin et al.**	**Huang et al.**	**Shang et al.**
Participant size	1142	1137	599	1733	1174
Hospitalisation status	Hospitalised	Hospitalised	Mixed	Hospitalised	Hospitalised
Risk factors for: symptom on follow up					
Older age			No correlation for all age groups		HR 0.84 (0.62-1.14)
Female sex	**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)**
Previous comorbidities	**IRR 1.11 (1.05–1.16)**				
Multiple symptoms	**IRR1.24 (1.17–1.31)**	**aOR 2.04 (1.45-2.89)**	**OR 1.81 (1.59–2.05)**		
Severity of COVID *ICU vs ward* *Ward vs. Outpatients*	**IRR 1.20 (1.03–1.38)**	**aOR 1.55 (1.09-2.18)**	OR 1.65 (0.61–4.46) **OR 1.87 (1.19-2.94)**	**OR 2.42 (1.15-5.08)**	HR 0.94 (0.47-1.89)
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 studies following up participants for six months or longer in this rapid review update. Six studies from our August 2021 update matched our updated inclusion criteria, and 14 new studies were added. The previous report included one single study with controls, this update includes nine controlled studies, a clear advance of the research landscape. Other recently published systematic reviews have only investigated long-term symptoms up to three months following COVID-19 and have included few or no controlled studies (33, 34). The anticipated advance led us to applying more stringent inclusion criteria for uncontrolled studies, requiring 500 or more participants, a fivefold increase compared to the previous report. Even though still eleven uncontrolled studies matched our inclusion criteria, the balance of non-hospitalised and hospitalised patients was lost, with now mainly hospitalised patients being represented in the uncontrolled studies. Long-term symptoms among non-hospitalised patients are, however, captured in the controlled studies. Our quality assessment revealed a slight increase in overall quality of uncontrolled studies, in addition to the nine studies of a more trustworthy, controlled study design. Among the uncontrolled studies low participation rate of eligible persons and loss to follow-up after baseline were the most common shortcomings, in addition to the lack of a control group. The controlled studies scored better based on more objective measures representing a lower risk of bias. Five of the nine controlled studies include a mix of hospitalised and non-hospitalised patients and compared outcomes with non-COVID controls from the general population, previous influenza patients, colleagues, or spouses. Comparing the findings by study design revealed that the uncontrolled studies indicated higher prevalence and larger variety of symptoms as well as greater severity on follow-up. The controlled studies showed that most symptoms are also commonly reported in non-COVID populations. Several studies reported altered sense of smell and taste to be the most specific acute and long-term symptoms of COVID-19.

As follow-up time was commonly reported in aggregate form, we only included studies with a mean or median follow-up time of at least six months, with some studies following participants up to 12 months. Consequently, our findings do not reflect a single timepoint but a broader interval beyond six months. Studies reporting symptoms both at six- and twelve-months follow-up indicated a decrease in prevalence over time. Our findings represent an overview of a growing body of evidence, yet the heterogeneity in the available studies continues to prevent quantitative synthesis of findings.

This update provides new insights and strengthens our earlier findings. The addition of controlled studies reveals that many of the reported symptoms also are prevalent in non-infected populations and the burden of long-term symptoms in those with mild and moderate COVID-19 is therefore less pronounced in controlled studies than in uncontrolled studies. Basic

statistical analysis within the studies begin to elucidate risk factors for long-term symptoms and severity of symptoms. A visualisation of the symptomatology has revealed dominant symptom groups across included studies. Overall participants reported more than 60 symptoms beyond six months after COVID-19. The broadest range of prevalence of symptoms remains among *General* symptoms. Symptoms under the *General*, *Neurological* and *Pulmonary* ICD symptom blocks continue to be most prevalent (Appendix 2). Studies without controls and studies with fewer participants reported more extreme values.

One of the controlled and four of the uncontrolled studies analysed associations between participants' baseline and general characteristics and the prevalence of symptoms at follow-up. Female sex seems to be the factor most consistently associated with duration of symptoms, independent of hospitalisation status. We also see that severity of COVID-19, multiple symptoms at diagnosis and prior comorbidities were correlated with long-term symptoms.

Two studies 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 among patients who had been hospitalised, and they scored significantly worse than uninfected controls.

A single study on the paediatric population was identified. The study reflected children with hospital contact, an uncommon subgroup among children with COVID-19. Nevertheless, symptoms appeared to be less prevalent than in adults. A separate rapid NIPH review of peer-reviewed paediatric studies with 100 children or more found that children with severe acute COVID-19 experienced more symptoms for a longer time than children with mild or asymptomatic COVID-19, as seen in adults[1]. The review also found that the general incidence of symptoms seemed to be considerably lower among children, but with greater uncertainty as to how many that were affected. Frequently reported symptoms were fatigue, tiredness, difficulty concentrating, stuffy nose, sleep problems and pain. The number of reported symptoms appeared to decrease over time.

Even though the evidence base has significantly improved with the publication of larger uncontrolled and controlled studies, our findings continue to reflect persons with COVID-19 from the beginning of the pandemic. While long follow-up periods are a strength in several of the controlled studies, subjective reporting of symptoms up to a year after the initial diagnosis opens up for recall bias. Outcomes as new hospital admissions or use of health care services as utilised in registry studies are more objective, but do not capture less severe symptoms not requiring medical consultation or hospital admission. The included registry studies aggregated symptoms to time periods, blurring the distinction between symptoms at a specific time point or over a period. Our updated and narrowed inclusion criteria lead to including fewer but larger uncontrolled studies, and nearly equally many controlled studies. This methodological choice has impacted the type of patients investigated. Current findings from studies reporting self-reported symptoms are now mostly limited to hospitalised patients, and 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. The only Norwegian study included

[1] https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2022-01-07-svar-pa-oppdrag-58-om-dose-to-til-12-15-aringer.pdf

participants from the MoBa cohort which consists of the families of babies born between 1999 and 2008 and is not entirely representative for the Norwegian population. There is an evidence gap around asymptomatic and mildly affected patients.

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 (35). Although there is uncertainty if COVID-19 patients stand out as more severely impacted by invasive mechanical ventilation than other patients which have undergone invasive ventilation for non-COVID illnesses (36). The apparent increased risk for women to suffer from long-term 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 acute phase of COVID-19 (37). The controlled studies included in this rapid review confirm findings from previous rapid reviews that patients who have been admitted to the hospital or intensive care unit with COVID-19 seem to be at greatest risk for developing long-term symptoms. Several studies suggested that the burden of symptoms was similar in COVID-19-patients not requiring hospitalisation and uninfected controls. Controlled studies also show that most symptoms reported by COVID-19-patients were also found in the uninfected general population, albeit to a lesser extent. Pandemic related infringements on personal liberty, lockdowns, social isolation, and changes to pre-pandemic lifestyle might therefore explain reporting of some symptoms. These factors were not limited to COVID-19 patients only but applied to the whole population. 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.

Although the evidence base is growing and steadily becomes more trustworthy, some aspects remain uncertain. Symptom burden appears to decrease over time, but we do not know if or when these symptoms might disappear. Our findings continue to reflect the early pandemics patients, and we assume that therapeutic advancements, and vaccination will impact outcomes in the future and lead to milder disease and potentially a lower prevalence of long-term symptoms. New virus variants causing milder disease are also expected to reduce the risk of long-term symptoms. Persons with asymptomatic COVID-19, or those not tested are not well researched, yet studies on these populations may reveal yet unknown consequences. The rapid advance of the research landscape shows that iterative updates are necessary to provide most up to date knowledge to clinicians and policymakers alike.

Conclusion

Severe COVID-19, requiring hospitalisation or intensive care treatment, correlates with more symptoms after six to 12 months. The range of long-term symptoms for hospitalised patients is widest, with *General*, *Neurological* and *Pulmonary* symptoms the most common. Women stand out with a higher risk for developing long-term symptoms. Many patients who have had moderate COVID-19 (non-hospitalised) report prevailing symptoms six to 12 months after infection, but controlled studies now show that many of these symptoms are also reported by uninfected controls. For patients who have had mild covid-19, there may appear to be an increase in some self-reported symptoms, but the symptoms are less pronounced than for patients who have been moderately or severely ill. The extent of long-term impact of mild and moderate COVID-19 on the quality of life in the general population remains unclear, as most studies included patients with severe COVID-19.

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Appendix

Appendix 1; Search strategy

Search: 2021-10-29

Ovid MEDLINE(R) ALL <1946 to October 29, 2021 >

#	Query	
1	chronic covid*.ti,ab,kf.	33
2	long covid*.ti,ab,kf.	545
3	persistent covid*.ti,ab,kf.	43
4	(Post acute covid* or postacute covid*).ti,ab,kf.	141
5	(Post covid* adj3 (illness* or syndrome* or symptom*)).ti,ab,kf.	301
6	(Prolonged adj3 covid*).ti,ab,kf.	181
7	or/1-6	1059
8	(chronic adj3 (complication* or infect* or symptom* or syndrome*)).ti,ab,kf.	92094
9	(Long-haul* OR longhaul*).ti,ab,kf.	1009
10	((long-term or longterm) adj3 (complication* or consequence* or outcome*)).ti,ab,kf.	114984
11	(Persistent adj3 (infecti* or symptom* or syndrome*)).ti,ab,kf.	27044
12	(Prolonged adj3 recovery).ti,ab,kf.	2610
13	sequelae*.ti,ab,kf.	68354
14	or/8-13	298750
15	exp Coronavirus/	102548
16	exp Coronavirus Infections/	125455
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.	208786
18	((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	6072
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.	193062
20	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	5549
21	or/15-20	214812
22	21 and 20210617:20301231.(dt)	46125
23	14 and 22	957
24	7 or 23	1823

Search: 2021-10-29

WHO COVID-19 Global literature on coronavirus disease: 2021

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

Results: 1502 (for 17.06-29.10)

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
Chauhan et al.	Only abstract
Fisher et al.	Length of follow-up
Galván-Tejada et. al.	Length of follow-up
Guo et al.	Pre-print
Horton et al.	Different outcome
Oh et al.	Length of follow-up
Park et al.	Length of follow-up
Rizvi et al.	Different population
Terlizzi et al.	Length of follow-up

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