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COVID-19-EPIDEMIC :

COVID-19:
Post COVID-19
condition and new onset
diseases after COVID-19
– a rapid review

(New edition dec. 2022)

English Summary

Background

Most people will experience COVID-19 as a mild and transient disease, although some may experience a prolonged period with symptoms. Long-term and nonspecific symptoms have previously been reported following other viral infections, and after bacterial and parasitic infections. 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, mental health problems and reduced lung function after discharge.

Objectives

We aimed to 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. In addition, we summarise differences in the risk of long-term postinfectious symptoms and new onset diseases between COVID-19 and other respiratory tract infections (RTIs).

Methods

This rapid review "Post COVID-19 condition and new onset diseases after COVID-19" is the 4th version replacing our previous report published on February 15th, 2022. In this version we used more stringent inclusion criteria than in previous versions, and we included controlled studies with more than 500 mainly laboratory test positive COVID-19 cases with a follow-up time of six months or longer. We excluded studies mainly reporting on laboratory or radiological finding, uncontrolled studies, and controlled studies that had not been peer-reviewed.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 September 19th, 2022, and a network database search in OpenAlex. One researcher screened the search results. Two researchers selected studies for inclusion and summarised study findings.

We present the results narratively given considerable heterogeneity, supplemented by tables and graphics. We plotted effect estimates reported in the included studies without any pooled synthesis.

Results

Characteristics of included studies
The included 14 studies were conducted in the USA n=5, China n=3, Denmark n=3, UK/England n=2, and South Korea n=1. We included ten retrospective cohort studies and four prospective cohort studies. Seven studies used non-COVID-19 controls, while seven studies used patients with other respiratory tract infections, mainly influenza. The median length of follow-up was around 12 months with some studies following participants for up to two years. Follow-up time was measured from hospital discharge, initial symptoms or from positive test for SARS-CoV-2. Number of COVID-19 participants ranged from 1127 to 1 284 437. The participants in most studies were middle-aged, seven studies included populations below 18 and two studies only enrolled children. The sex distribution was mainly balanced, deviating at most by 11%. Patients were mainly sampled during 2020, three studies continued sampling into 2021, and one study into 2022. Follow ups were performed either at clinics, through online/phone/postal surveys, or by assessing register data. Seven studies included a mix of hospitalised and non-hospitalised COVID-19 patients, seven included only hospitalised patients.

Symptoms compared to non-COVID-19 controls
Two studies looked at self-reported long-term symptoms in COVID-19 cohorts compared to non-COVID 19 cohorts. A Danish cohort study found that eighteen symptoms were more common in positive COVID-19 cohorts (mainly non-hospitalised) than among negative controls after 6 to 12 months, including dysosmia, dysgeusia, fatigue, and dyspnoea. The risk differences tended to decrease over time. A Chinese longitudinal cohort study found hospitalised COVID-19 participants had larger risk of experiencing long-term symptoms at 2-years follow-up relative to their spouses (non-COVID-19 controls). COVID-19 participants reported poorer health-related quality of life but also larger improvements over time in numerous symptoms, such as depression, anxiety, and dyspnoea.

New onset diseases after COVID-19 compared to non-COVID-19 controls
Two British retrospective cohort studies and one Chinese prospective cohort study compared long-term symptoms and new onset diseases in hospitalised COVID-19 survivors and non-COVID-19 controls at 12 months or ≤ 315 days. These studies found that COVID-19 survivors had higher risk of neurological and cognitive impairments, including depression, anxiety, and bipolar disorders. Moreover, one study reported that COVID-19 survivors were more than twice as likely to be re-hospitalised or die during the first year after discharge as compared to the general population.

New onset diseases after COVID-19 compared to other respiratory tract infections
Eight retrospective cohort studies compared long-term symptoms or new onset diseases after COVID-19 with other RTIs. All studies used registered diagnostic codes to extract information on follow-up. A single study used only diagnostic codes registered for re-admission to hospital. Two of the 55 reported diseases were more than twice as likely than the comparator, and only five diseases were less than half as likely among patients with COVID-19 patients compared with other RTIs. Neurological conditions were more common after COVID-19 patients than after other RTIs. Information on mental health consequences was more heterogeneous and without obvious trends in terms of difference between groups. Respiratory illnesses appeared to be

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slightly less common in COVID-19 patients. Reported cardiovascular diagnostic codes did not show a clear pattern of difference, only two of ten cardiovascular conditions differed: heart failure, and intracerebral and subarachnoid bleeding. Musculoskeletal conditions were less common in two studies for COVID-19 patients. Among the infrequently reported diseases there was more variability. It does not appear like length of follow-up up until 2 years changes the outcomes between COVID-19 and other RTIs.

Children
Overall, adolescent and children appear less affected than older age groups based on studies of participants from during the first pandemic year. Compared with non-COVID-19 controls, children who had COVID-19 had more prevalent long-lasting symptoms, but most symptoms appeared to gradually resolve over time. After 6-12 months changes to smell and taste, and reduced appetite were more common among covid positive children compared to controls. Data on mental health and functioning were less clear, with a weak tendency towards better health-related quality-of-life scores among children and adolescents in the COVID-19 group.

Predicting factors for long-term symptoms
Factors predicting the risk of new onset disease and long-term symptoms following COVID-19 and other RTI are similar. Important factors are prior comorbidities, female sex, and severity of disease. Middle aged people appear weakly correlated with higher risk of long-term symptoms and new onset diseases whereas the youngest age groups including children appear least affected.

Discussion

Current evidence suggests that patients who have been hospitalised or undergone non-invasive ventilation due to severe COVID-19 experience similar long-term consequences as patients who have been exposed to similar treatment due to other RTIs. These findings support the current rehabilitation practise of providing similar care to patients post-COVID as after other severe RTIs. Controlled studies also found that most symptoms reported by COVID-19-patients were also reported in the uninfected general population, albeit to a lesser extent. The symptoms that are most specific for COVID-19 seems to be altered smell and taste and neurological diagnoses, although with equally common reporting of dyspnoea and fatigue. Most reported symptoms and new onset diseases are also seen in the follow-up period of other RTIs. Symptom burden appears to decrease over time, but we do not know if or when these symptoms might disappear. The data also reflect that many of the reported symptoms are prevalent in non-infected populations.

Although the evidence base is growing and steadily becomes more trustworthy, some aspects remain uncertain. Our findings continue to reflect long term symptoms in patients who were infected early in the pandemic. New virus variants causing milder disease will likely reduce the overall risk and burden of long-term symptoms. Therapeutic advancements and vaccination impact outcomes and probably lead to milder courses of disease, contributing to a further reduction in the prevalence and burden of long-term symptoms. Studies on consequences of breakthrough infections, and comparative studies on vaccinated versus non vaccinated populations are already pointing in the directions of fewer long-term symptoms. Persons with asymptomatic COVID-19, or those not tested are not well researched.

Conclusion

Severe COVID-19, requiring hospitalisation or intensive care treatment, correlates with more symptoms after six to twelve months. Individuals with COVID-19 appear to experience and get diagnosed with similar conditions as those seen in patients with other severe respiratory tract infections at follow-up, although with some variation and with neurological symptoms standing out as more common after COVID-19. Women have a higher risk for experiencing long-term symptoms than men. Patients who have had mild and moderate COVID-19 (non-hospitalised) report some symptoms beyond six months after infection more often than uninfected persons. The extent of long-term impact of 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 noen opplever at det tar tid å bli kvitt alle symptomer. Slike langvarige og uspesifikke symptomer er tidligere rapportert etter andre infeksjonssykdommer, og det er derfor ikke uventet at en del opplever langvarige symptomer også etter covid-19. Det er også kjent at personer som legges inn på intensivavdeling med alvorlig lungesvikt kan oppleve langvarige funksjonsnedsettelser som nedsatt kognitiv funksjon og redusert lungefunksjon etter utskriving uavhengig av diagnose. I denne rapporten benytter vi begrepet «senfølger etter covid-19» som er basert på en konsensusrapport etter oppdrag fra HOD (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. Vi undersøker også om pasienter som har hatt covid-19 har annen risiko for senfølger eller nyoppstått sykdom sammenliknet med pasienter som har gjennomgått andre luftveisinfeksjoner (LVI).

Metoder

Denne hurtigoppsummeringen er den fjerde versjon i serien «*Senfølger etter covid-19 og nyoppstått sykdom etter covid-19*» og den erstatter versjonen som ble publisert 15. februar 2022. I denne oppdateringen har vi kun inkludert kontrollerte studier med minst seks måneders oppfølging som omfattet mer enn 500 deltakere med hovedsakelig laboratoriebekreftet covid-19. Vi ekskluderte studier som kun presenterte laboratoriefunn og radiologiske funn, studier uten kontrollgrupper og studier som ikke var fagfellevurderte.

Vi gjennomførte systematiske litteratursøk i MEDLINE og WHO Global research on coronavirus disease (COVID-19) database 19. september 2022, og et nettverksdatabasesøk i OpenAlex basert på tidligere inkluderte studier. Én forsker gjennomgikk søkeresultatene, og to forskere valgte ut studier for inklusjon, ekstraherte data og sammenstilte resultater.

Grunnet betydelig heterogenitet mellom studiene presenterte vi resultatene narrativt, supplert med tabeller og grafer. Vi plottet effektestimater rapportert i de inkluderte studiene, men gjennomførte ingen metaanalyser.

Resultater

Kjennetegn på inkluderte studier

Fjorten kontrollerte studier tilfredsstilte våre inklusjonskriterier. Studiene er fra USA n=5, Kina n=3, Danmark n=3, Storbritannia/England n=2 og Sør-Korea n=1. Vi inkluderte ti retrospektive kohortstudier og fire prospektive kohortstudier. Syv studier brukte ikke-covid-19 kontroller, mens syv studier brukte pasienter med andre luftveisinfeksjoner, hovedsakelig influensa. Median oppfølgingstid var rundt 12 måneder, med noen studier som fulgte deltakere i opptil to år. Oppfølgingstid ble målt fra sykehusutskrivning, første symptomer eller fra positiv test for SARS-CoV-2. Antall deltakere med covid-19 varierte fra 1 127 til 1 284 437. De fleste studiene omfattet middelaldrende, syv studier inkluderte også deltakere under 18 år og to studier inkluderte kun barn. Kjønnsfordelingen var i hovedsak balansert, med størst forskjell på 11 %. Pasientene ble i hovedsak rekruttert i 2020, tre studier fortsatte inn i 2021, og én studie inn i 2022. Oppfølging ble utført ved klinikker, gjennom spørreundersøkelse, eller ved å innhente registerdata. Syv studier inkluderte både pasienter som hadde vært innlagt på sykehus og deltakere som ikke hadde vært innlagt, syv inkluderte kun pasienter som hadde vært innlagt.

Symptomer sammenlignet med kontroller uten covid-19

To studier undersøkte selvrapporterte langvarige symptomer i covid-19-gruppen sammenlignet med ikke-covid19-gruppe. En dansk kohortstudie fant atten symptomer som ble hyppigere rapportert av pasienter som hadde gjennomgått covid-19 (hovedsakelig ikke-innlagte) enn blant negative kontroller etter 6 til 12 måneder, herunder redusert smak og luktesans, tretthet og dyspné. Risikoforskjellene så ut til å avta over tid. En kinesisk kohortstudie fant at pasienter som hadde vært innlagt på grunn av covid-19 rapporterte flere langvarige symptomer ved 2-års oppfølging enn deres ektefeller (ikke- covid-19-kontroller). De som hadde hatt covid-19 rapporterte dårligere helserelatert livskvalitet enn kontrollene, men også forbedringer over tid i en rekke symptomer, som depresjon, angst og dyspné.

Nyoppstått sykdom etter covid-19 sammenlignet med kontroller uten covid-19

To britiske retrospektive kohortstudier og en kinesisk prospektiv kohortstudie sammenlignet langvarige symptomer og nyoppstått sykdom hos innlagte covid-19 og ikke-innlagte, ikke-covid-19-kontroller etter cirka ett år. Studiene fant at covid-19-gruppen hadde høyere risiko for nevrologiske og kognitive svekkelser, inkludert depresjon, angst og bipolare lidelser. En studie rapporterte at covid-19-overlevende hadde mer enn dobbelt så stor sannsynlighet for å bli innlagt på nytt eller for å dø i løpet av det første året etter utskrivning sammenlignet med befolkningen generelt.

Nyoppstått sykdom etter covid-19 sammenlignet med andre luftveisinfeksjoner

Åtte retrospektive kohortstudier sammenlignet langvarige symptomer eller nyoppstått sykdom etter covid-19 med etter andre luftveisinfeksjoner (LVI). Alle studiene brukte registrerte diagnosekoder for å hente ut informasjon om oppfølging. Én studie brukte kun diagnosekoder knyttet til gjeninnleggelse på sykehus. I alt ble 55 mulig nyoppståtte diagnoser rapportert i de inkluderte studiene, hvorav to var mer enn dobbelt så sannsynlig etter covid-19 sammenlignet med etter andre LVI, og fem sykdommer var mindre enn halvparten så sannsynlig blant pasienter med covid-19. Mulige nevrologiske tilstander var vanligere etter covid-19 enn etter andre LVI. Informasjon om psykiske lidelser pekte i ulike retninger uten tydelige forskjeller

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mellom grupper, mens respiratoriske tilstander så ut til å være litt mindre vanlig hos covid-19-pasienter. Kardiovaskulære diagnosekoder viste ingen klare gruppeforskjeller. To studier viste at muskel- og skjelettplager var mindre vanlig etter covid-19. Det ser ikke ut til at oppfølgingstiden opptil to år endret resultatene for sammenligningen mellom covid-19 og andre LVI.

Barn

Samlet sett virker ungdom og barn mindre påvirket enn eldre aldersgrupper, men dette er basert på studier fra det første pandemiåret. Sammenlignet med kontroller uten covid-19 hadde barn med covid-19 mer langvarige symptomer, men de fleste symptomene så ut til å avta gradvis. Etter 6-12 måneder var redusert lukte- og smakssanse og redusert appetitt mer vanlig blant barn som hadde gjennomgått covid-19 sammenlignet med kontroller. Resultatene for psykisk helse og funksjon var mindre entydige, med en svak tendens for bedre skår for helserelatert livskvalitet blant barn og unge i covid-19-gruppen sammenlignet med kontrollgruppen.

Risikofaktorer for senfølger etter covid-19

Faktorene som assosieres med økt risiko for senfølger og nyoppstått sykdom er i stor grad de samme for covid-19 som etter andre LVI. Viktige faktorer er samsykelighet, kjønn og sykdommens alvorlighetsgrad. Middelaldrende mennesker så ut til å ha høyest risiko for langvarige symptomer og nyoppstått sykdom, mens de yngste aldersgruppene så ut til å ha lav risiko.

Diskusjon

Kunnskap tyder på at pasienter som har vært innlagt på sykehus eller gjennomgått ikke-invasiv ventilasjon på grunn av alvorlig covid-19 opplever lignende senfølger som pasienter som har vært utsatt for lignende behandling på grunn av andre LVI. Disse funnene støtter dagens rehabiliteringspraksis med å gi lignende oppfølging og rehabiliteringstilbud til pasienter etter covid-19 som etter annen alvorlig LVI. Kontrollerte studier fant at de fleste symptomene rapportert av covid-19-pasienter også ble rapportert i den generelle befolkningen, om enn i noe mindre grad. Mest spesifikt for covid-19 ser ut til å være endret lukte- og smakssans og nevrologiske diagnoser, mens symptomer som pustevansker og tretthet er omtrent like vanlig. De fleste symptomene og nyoppståtte sykdommer sees også etter andre LVI. Symptombyrden ser ut til å avta over tid.

Selv om kunnskapsgrunnlaget vokser og blir mer pålitelig, er enkelte aspekter fortsatt usikre. Våre funn gjenspeiler fortsatt senfølger hos pasienter som ble smittet tidlig i pandemien. Nye virusvarianter som forårsaker mildere sykdom vil sannsynligvis redusere risikoen for senfølger. Nye og bedre behandlingsmetoder og vaksinasjon gir mildere sykdomsforløp, noe som sannsynligvis bidrar til en ytterligere reduksjon i forekomsten og belastningen av senfølger. Noen studier om konsekvenser av gjennombruddsinfeksjoner og forskjeller mellom vaksinerte og ikke-vaksinerte populasjoner peker i retning av færre senfølger. Her må det imidlertid presiseres at denne hurtigoversikten er gjennomført strenge inklusjonskriterier som ikke ga grunnlag for å gå gjennom slike studier på en systematisk måte.

Konklusjon

Alvorlig covid-19, som krever sykehusinnleggelse eller intensivbehandling, ser ut til å gi flere symptomer ved seks- og tolv-måneders oppfølging sammenlignet med mindre alvorlig covid-19. Pasienter som har gjennomgått covid-19 blir diagnostisert med lignende tilstander som pasienter som har gjennomgått andre alvorlige luftveisinfeksjoner, dog med noen forskjeller som at nevrologiske symptomer er vanligere etter covid-19. Kvinner har høyere risiko for å utvikle senfølger enn menn. Pasienter som har hatt mild og moderat covid-19 (ikke innlagt på sykehus) rapporterer vedvarende symptomer seks til tolv måneder etter infeksjon hyppigere enn personer i kontrollgrupper som ikke har fått påvist SARS-CoV-2. Effekten av senfølger etter covid-19 på livskvalitet i den generelle befolkningen er fortsatt usikker ettersom livskvalitet i hovedsak er målt blant pasienter som har vært alvorlig syke.

Table of content

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 the 4th version of this rapid review, we searched evidence aiming to explore:

1. Which proportion of patients experience long-term symptoms after COVID-19?
2. Which symptoms are specific to post COVID-19 condition?
3. Which factors are associated with long-term symptoms of COVID-19?
4. How does post COVID-19 condition differ from long-term effects of other respiratory tract infections? Are there differences in new onset diseases after COVID-19?

The outbreak team at the Norwegian Institute of Public Health (NIPH) has commissioned this rapid review update, with the previous version published 15th February 2022 (2).

Methods

Literature search

We applied an open search strategy to identify all relevant studies on the 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. We defined the inclusion criteria prior to the search. We included studies of participants with confirmed COVID-19, that reported on symptoms, quality of life, and predicting factors for long-term symptoms. One researcher (JH) conducted the search on September 19th, 2022, in the MEDLINE database for studies published in the period 29.10.2021 -19.09.2022. We expanded this search with a search in the WHO Global research on coronavirus disease (COVID-19) database on September 19th, 2022 (limited to 2021-22; five databases: EMBASE, EuropePMC, Scopus, ProQuest Central, Web of Science, and English language), and an OpenAlex search (based on the controlled studies from previous reports) (3, 4). Combined with the previous reports' search period, we covered the timeframe since 01.01.2020.

Inclusion criteria:

Population:	More than 500 COVID-19 positive participants followed up with non-COVID-19 controls.
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. Studies reporting cumulative/aggregated follow-up data combined for the acute phase (first 3 months) and beyond were excluded, unless compared with another acute illness.
Study types:	Cohort studies (prospective and retrospective), case-controls, registry-based studies, cross-sectional surveys
Excl. criteria:	Non-peer-reviewed studies, abstracts, letters, 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 change is that we only included controlled studies. We changed the inclusion criteria because more studies had been published since the third version.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (JH and JFME) reviewed the studies in full text, selected studies for inclusion, extracted, and summarised data/results from included studies in tables. A senior researcher in the field provided feedback for the study selection process, methodological approach, and results presentation (KGB).

Quality assessment

One reviewer (JH) used the RoB SPEO tool developed by the World Health Organisation and the International Labour Organisation to assess the risk of bias of included studies (5). As we expected to identify many eligible studies, we only assessed what we considered the most relevant of the tool's eight domains: (i) bias of selecting participants into the study. We resolved any uncertainty regarding the risk of bias of a study through discussion among review authors. We did not assess the certainty of the available evidence.

Data extraction

We extracted information on study country, participants, follow-up period, symptom prevalence and statistics (e.g., odds ratio, rate ratio, hazard ratio). We described studies with participants mainly below 18 years of age separately.

Data analysis

We exported data tables of extracted endpoints to Microsoft Excel and PowerPoint for data analysis and visualisation. The choice of visualisation was based on discussion of available datapoints, a graphs ability to convey information, subjective intuition, and the expected ease of understanding. We reported the prevalence of long-term symptoms in COVID-19- and non-COVID-19 cohorts at different time points (e.g., 6 months, 12 months, and 2 years) and expressed the risks among cohorts as Risk Ratios (RRs) or Risk Differences (RDs) alongside accompanying confidence intervals (CIs). Effect sizes were taken directly from the included studies if available, else we calculated these based on symptoms prevalence data per cohort. We used Hazard Ratios (HRs) to express the probability of reporting symptoms or diagnostic codes during follow-up (time-to-event data) in the COVID-19 cohorts relative to either non-COVID cohorts or cohorts with other respiratory tract infections at different timepoints. The heterogeneity of included studies prevented us from compiling data quantitively. The included plots are graphical presentations of extracted endpoints across included studies to convey trends, not equally well reflected in text.

Peer review

Preben Aavitsland (director of surveillance, NIPH), Helena Niemi Eide (MD, NIPH) and Signe Flottorp (research director, NIPH) critically reviewed the draft before publication. Margrethe Greve-Isdahl reviewed the section on the paediatric population (senior physician, NIPH).

Acknowledgements

Results

Description of studies

Results of the literature search

We identified 14 127 unique references through the systematic literature searches. JH screened all potentially relevant titles and abstracts in EPPI reviewer (4). In total, we read 54 references in full text. Fourteen unique studies matched our inclusion criteria, including four studies from our previous report, of which three studies were replaced with studies providing updated

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┌────────────────────────┐  ┌────────────────────────┐  ┌────────────────────────┐
│ Records identified      │  │ WHO Global research on │  │ OpenAlex Search on     │
│ through MEDLINE         │  │ coronavirus disease     │  │ previous reports incl. │
│ database                │  │ (COVID-19) database     │  │ studies                │
│ (n = 4757)              │  │ (n = 10 592)            │  │ (n = 826)              │
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│              Records after deduplication                                        │
│              (n = 14 127)                                                       │
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┌────────────────────────┐        ┌──────────────────────────────────────────────┐
│ Records screened by     │        │ Records excluded by screening (n = 1 909)     │
│ human                   │───────▶│                                               │
│ (n =1 963)              │        │ Records excluded due to less than 30%         │
└────────────────────────┘        │ probability of likely relevance (n = 12 164) │
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┌────────────────────────┐        ┌──────────────────────────────────────────────┐
│ Full-text studies       │        │ Full-text articles excluded:                  │
│ assessed for            │───────▶│    Different follow-up (n = 17)               │
│ eligibility and quality │        │    Different population (n =  2)              │
│ (n = 54)                │        │    Sample size (n = 16)                       │
└────────────────────────┘        │    Preprint /Abstract (n =  5)                │
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┌────────────────────────┐
│ Included studies        │
│ (n = 14)                │
└────────────────────────┘
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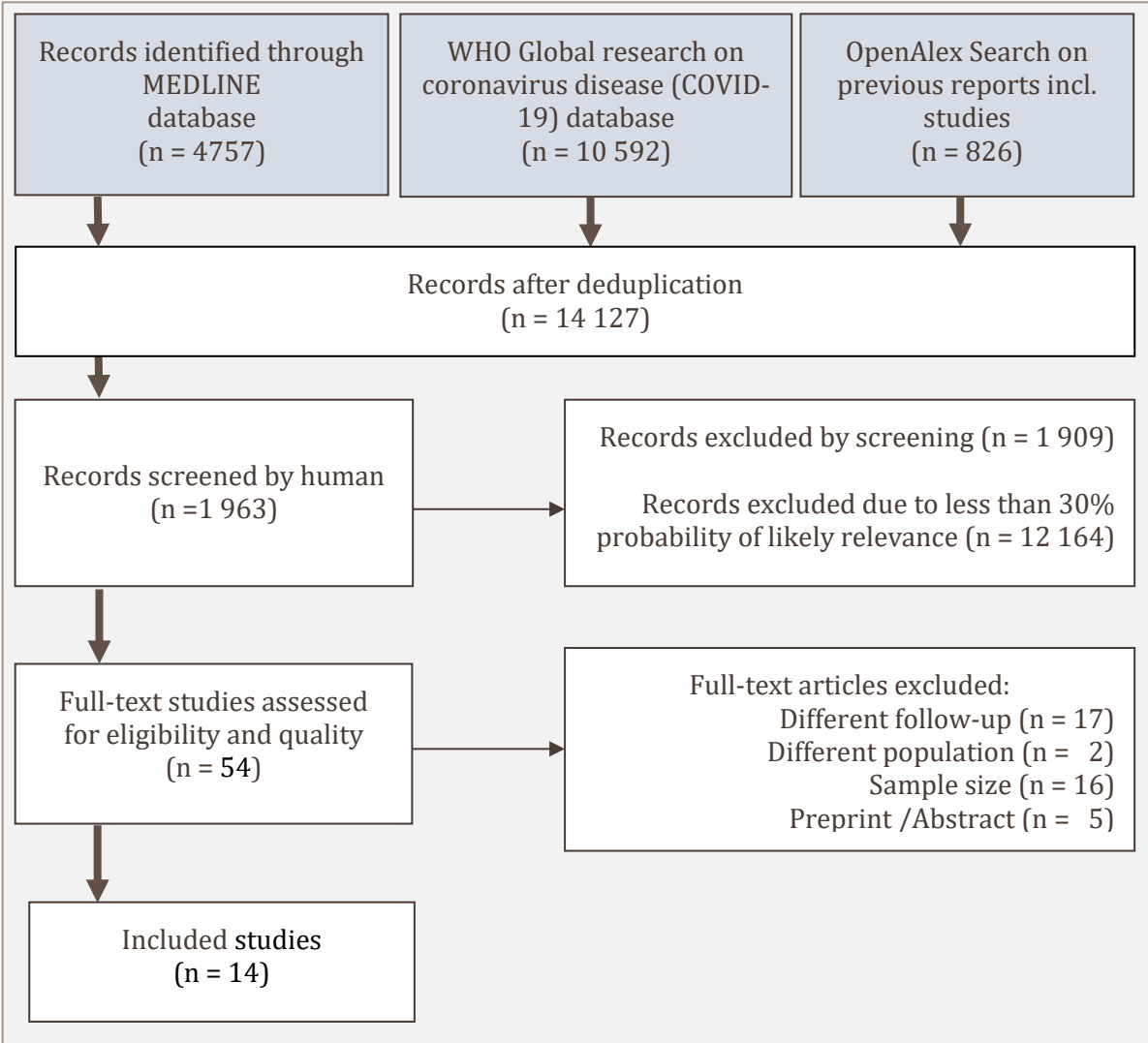
*F*igure 1. Flow diagram of search strategy and study inclusion

information (6-8). 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 (8-14).

Included studies
Table 1 provides an overview of the 14 included studies, categorised by hospitalisation status. We excluded all uncontrolled studies from our previous report, and a list of 40 relevant studies that did not fully match our inclusion criteria (Appendix 2).

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	Controls	Length of follow up
HOSPITALISED							
Bhaskaran (15)	England	24 673	**66 (53-78)**	56	Retro. cohort	Neg covid & RTI (influenza)	315 days
Clift (16)	England	32 525	**49 (18)**	50	Retro. cohort	SARI	12 months
Huang (17)	China	1 276	**59 (49-67)**	53	Pro. cohort	Neg covid	6 and 12 months
Huang (6)	China	1127	**57 (48–65)**	54	Pro. cohort	Neg covid	2 years
Liu (7)	China	1 539	**69 (66-75)**	48	Pro. cohort	Neg covid	6 months
Qureshi (13)	USA	10 691		46	Retro. cohort	Pneumonia	med. 218d
Qureshi (14)	USA	10 403		49	Retro. cohort	Pneumonia	med. 182 days
MIXED							
Lee (18)	S. Korea	21 615		45	Retro. cohort	RTI (influenza)	209 days
Kikkenborg Berg (10)	Denmark	6 630	**10 (7–13)**	52	Retro. cohort	Neg covid	12 months
Kikkenborg Berg (9)	Denmark	10 997	**18 (16–19)**	42	Retro. cohort	Neg covid	12 months
Sørensen (19)	Denmark	61 002	**50 (36-60)**	39	Retro. cohort	Neg covid	6-12 months
Taquet (12)	USA	236 379	**46 (20)**	44	Retro. cohort	RTI (incl. influenza)	6 months
Taquet (11)	USA	273 618	**46 (20)**	43	Retro. cohort	RTI (incl. influenza)	6 months
Taquet (8)	USA	1 284 437	**43 (22)**	58	Retro. cohort	RTI	2 years

RTI: Respiratory tract infection, SARI: severe acute respiratory infections

The included studies were conducted in the USA n=5, China n=3, Denmark n=3, UK/England n=2, and South Korea n=1. Ten studies were retrospective, and four studies were prospective cohort studies. Seven studies used non-COVID-19 controls with very limited matching, mainly for age and sex, seven studies used patients with other respiratory tract infections as controls, mainly influenza patients with more limited matching of participants characteristics. The median length of follow-up was around 12 months in most studies with some studies following participants for up to two years. Follow-up time was measured from hospital discharge, initial symptoms, or from positive test for SARS-CoV-2. The number of COVID-19 participants ranged from 1127 to 1 284 437. The participants in most studies were middle-aged, seven studies included populations below 18 and two studies only enrolled children. The sex distribution was balanced in most studies, deviating at most by 11%. All studies used laboratory testing to diagnose COVID-19 (mainly PCR). Patients were mainly sampled during 2020, three studies continued sampling into 2021, and one study into 2022 (Figure 2). Follow ups were performed either at clinics, through online/phone/postal surveys, or by assessing register data. Seven

studies included a mix of hospitalised and non-hospitalised COVID-19 patients, seven included only hospitalised patients. None of the included studies looked only at non-hospitalised patients.
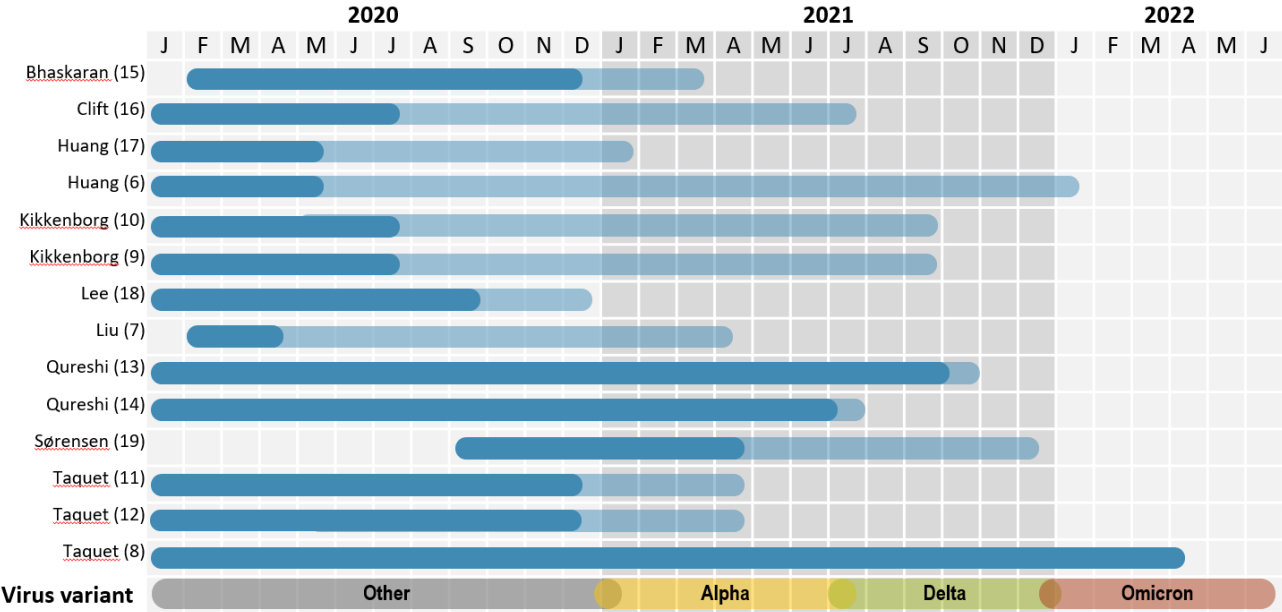
Figure 2. *Overview of timeframes, times for patient sampling (dark blue) and follow-up (light blue), in some studies follow-up was running parallel to sampling. Virus variants dominating at the respective are colour coded.*

Quality assessment

We assessed the included studies with RoB SPEO tool (5) for what we considered was the most relevant of the tool's eight domains for the assessment: (i) bias of selecting participants into the study (Table 2).

Table 2. Results of the risk of selection bias assessment

Author	Risk of selection bias	Participant selection	Justification for rating
Bhaskaran (15)	**Probably low**	Routinely collected electronic data from primary care practices covering approximately 40% of the population in England. Individuals discharged between 1 February and 30 December 2020 from a hospitalisation that lasted >1 day. Excluded a small number of people with missing age, sex, or index of multiple deprivation, which are likely to indicate poor data quality. A historic cohort was used as controls.	Data collection independent of study
Clift (16)	**Probably low**	Primary care database that has collected routine clinical data for more than 30 million individuals since 1989 registered to more than 1400 general practices in England using the EMIS software system. This study cohort comprised adults alive and registered with a contributing general practice. A historic cohort was used as controls.	Data collection independent of study
Huang (17) (6)	**moderate**	All patients with laboratory confirmed COVID-19 discharged from Jin Yin-tan Hospital between Jan 7 and May 29, 2020, were eligible for participation. Patients were excluded if they died after discharge; were living in a nursing or welfare home; had psychotic disorder, dementia, or osteoarthropathy; or were immobile. Controls were excluded if they had a history of laboratory confirmed SARS-CoV-2 infection.	First patients with covid, limited testing in the beginning.
Kikkenborg Berg (10) (10)	**Probably high**	The survey was conducted by parent proxy report and was sent to mothers, or to a father or legal guardian if no mother existed, of all children who tested positive and to mothers of children who tested negative or had suspicion of SARS-CoV-2 infection. >30% cases and >25% controls responded to the survey.	Low response rate
Lee (18)	**Probably low**	This is a retrospective cohort study using claims data provided by the Health Insurance Review and Assessment Service (HIRA). South Korea has adopted mandatory universal health coverage; therefore, 97% of South Korea residents are National Health Insurance Service (NHIS) beneficiaries. A historic cohort was used as controls.	Data collection independent of study
Liu (7)	**Probably high**	Participants in this study were the first group of patients Hospitalized with COVID-19 in 2020, from 3 COVID-19–designated hospitals. Uninfected spouses who lived with the patients were recruited as control individuals. Patients were eligible for participation if they were 60 years and older.	First patients with covid, limited testing in the beginning. Spouses as controls.
Sørensen (19)	**Probably high**	430,173 individuals were invited. 36% of participants completed the questionnaire. Compared to non-responders, participants who fully completed the baseline questionnaire were more often: females, born in Denmark, older (50‐70 years old), more often working within healthcare, and living outside of the capital region. To avoid misclassification bias, controls who reported having been found seropositive were excluded.	Distorted response population, low response rate
Taquet (12) Taquet (11) Taquet (8)	**Probably high**	TriNetX's and TriNetX's US Collaborative Network data. The reflected health-care organisations are a mixture of hospitals, primary care, and specialist providers, contributing data from uninsured and insured patients.	Uncertainty in the composition of included participants.
Qureshi (13) Qureshi (14)	**Probably high**	1. Patients diagnosed with pneumonia during a hospitalization lasting >24 hours designed as index hospitalisation. Pneumonia was defined based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) primary diagnosis codes J12–J18. The hospital admission with pneumonia diagnosis was used as the index encounter. All events were recorded relative to this hospitalisation. 2. Patients had at least 4 encounters within 2 years prior to their index encounter. 3. Patients had at least 2 encounters >30 days after the index encounter.	Narrow selection of patients, probably contributing to the severity of outcomes followed up-

Symptoms and new onset diseases compared to non-COVID-19 controls

Symptoms compared to non-COVID-19 controls

Two studies reported symptom prevalence more than six months after the test date: The Danish retrospective cohort study published by Sørensen et al. 2022 (152,880 participants) based on self-reported symptoms six to 12 months after COVID-19 diagnosis, and one Chinese prospective cohort study (2,254 participants) published by Huang et al. 2022, which reported data at 6-, 12-months, and 2-years follow-up.

The Danish study by Sørensen et al. reported risk differences (RD) for 31 different symptoms six to 12 months after the SARS-CoV-2 test date. The difference was calculated based on a comparison of participants with a positive test confirmed between September 2020 to April 2021 and test-negative controls, who were randomly selected using incidence density sampling on the test date with a ratio of 2:3 between test positives and -negatives (19). The study used self-reported symptoms collected via web-based questionnaires. The COVID-19 cases were mostly non-hospitalised males, younger, and more physically active than those in the non-COVID-19 group. Eighteen of the 31 investigated symptoms were more common in positive COVID-19 cases than among negative controls after 6–12 months, with the largest differences noted in dysosmia (smell disorders), dysgeusia (taste disorders), fatigue, dyspnoea, and reduced strength in legs /arms (Figure 3). Risk differences decreased gradually from six to 12 months for all symptoms, except for dysosmia and dysgeusia for which estimates peaked after nine months. This study also presented participants' self-reported diagnoses and self-reported health problems, but these were not further reviewed as the symptoms are more descriptive.
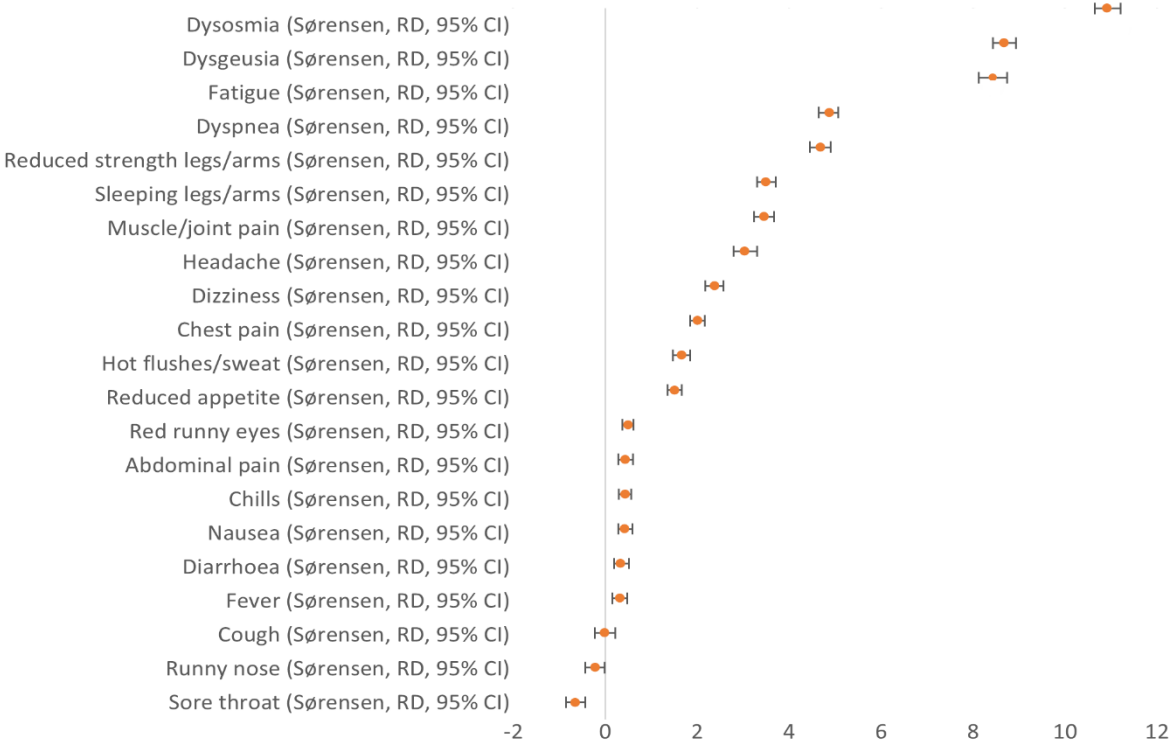

Figure 3. Risk Difference based on self-reported symptoms in COVID-19 cases compared to non-COVID-19 cohort at 6-12 months follow-up (61,002 test-positive and 91,878 test-negative individuals). Detailed values are listed in Appendix 3.

The Chinese study by Huang et al. presented a longitudinal follow-up of health outcomes in hospitalised COVID-19 survivors throughout two years after acute infection (6). The patients represent the earliest cases worldwide, discharged between January and May 2020. COVID-19 survivors were compared to a matched cohort of participants without COVID-19. Health outcomes were measured via either questionnaires, laboratory tests or imaging. Although the study reported symptoms prevalence in the COVID-19 survivors at 6-, 12-months, and 2-years follow-up, the authors did not report prevalence data of the matched non-COVID-19 controls for the first two timepoints. Therefore, we only present data from the 2-years follow-up.

Hospital survivors of COVID-19 showed improvements throughout the follow-up period. The prevalence of reporting at least one long-term symptom decreased from 68% at 6 months to 55% at 2 years in COVID-19 survivors, with fatigue (30%) and sleep difficulties (25%) being the most prevalent symptoms. The prevalence of self-reported anxiety or depression in COVID-19 survivors was reduced by 11% (from 23% at 6 months to 12% at 2 years) at 2 years, regardless of initial disease severity. Fewer patients reported dyspnoea symptoms at 2 years versus at 12 months (14% vs 30%). Despite these improvements, COVID-19 survivors reported poorer Health Related Quality of Life than matched controls at 2 years follow-up. All in all, the COVID-19 survivors had larger risks of experiencing long-term symptoms than matched controls; the risk ratios varied between >1 and 5 for most of the symptoms (Figure 4).
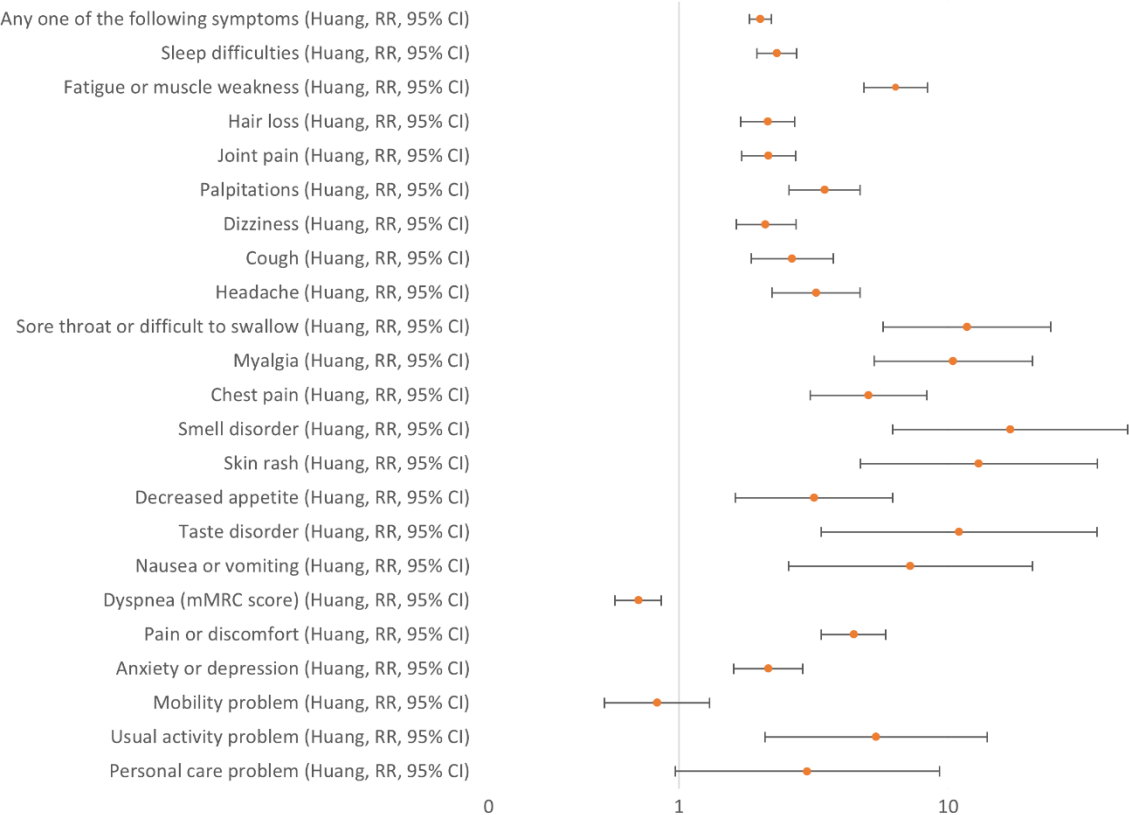

Figure 4. Self-reported symptoms in COVID-19 cases compared to non-COVID-19 controls (spouses, non-COVID-19 cohort) at 24 months follow-up on a logarithmic scale. Risk ratios were calculated from the data reported in the main publication (Huang 22). CI, Confidence Intervals; RR, Risk Ratio. Detailed values are listed in Appendix 3.

New onset diseases after COVID-19 compared to non-COVID-19 controls

Two British retrospective cohort studies by Bhaskaran et al. and Clift et al. (15, 16) and one Chinese prospective cohort study by Liu et al. (7) compared new onset diseases after COVID-19 and non-COVID controls. All studies compared diagnostic codes of hospitalised COVID-19 patients to matched cohorts in the general population from pre-pandemic years (15, 16) or uninfected spouses (7). The studies focused on neuropsychiatric illnesses (32 525 COVID-19 cases) (16), cognitive changes (1438 COVID-19 cases)(7), and hospitalisation, death, and diseases by symptom group (24 673 COVID-19 cases) (15). Follow-up periods were 315 days (15) and 12 months (7, 16).

Overall, these three studies consistently found a higher risk of neurological and cognitive impairments in COVID-19 survivors compared to non-COVID-19 controls. Clift 2022 reported that COVID-19 survivors were between two to three times more likely to report anxiety, dementia, depression, and bipolar disorder. Similar or even higher risks in COVID-19 survivors for other neurological conditions, such as cognitive impairment, progressive- and early/late onset cognitive declines were reported by Liu 2022 (7). The study of Bhaskaran et al. found that COVID-19 survivors were more than twice as likely to be re-hospitalised or die more than a week after discharge (15). The study also reported higher risks of mental health and cognitive impairments, other respiratory infections, circulatory and musculoskeletal problems, and other symptoms in COVID-19 survivors compared to non-COVID controls. We listed diagnosis by overarching symptom groups in a forest plot presenting Hazard Ratios, Risk Ratios and Odds Ratios for getting relevant diagnosis (Figure 5).
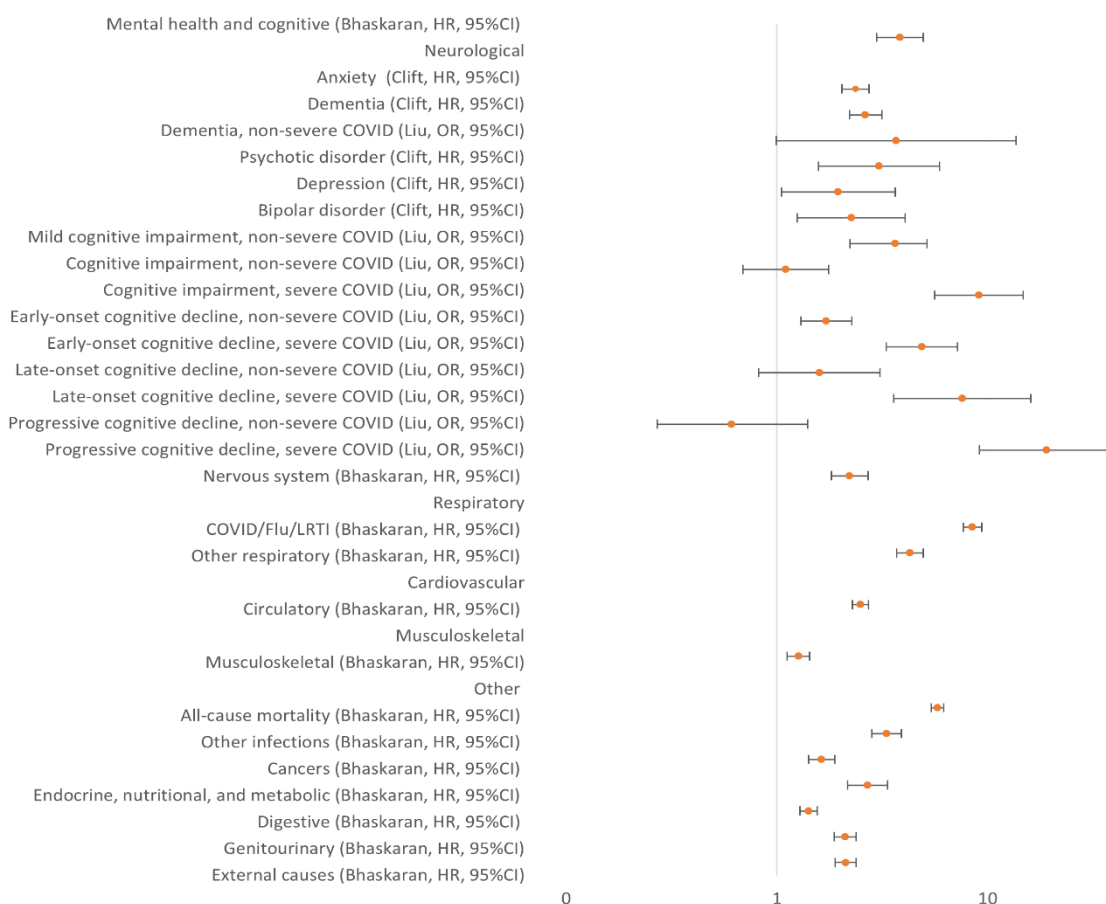

Figure 5. New onset diseases in COVID-19 cases compared to non-COVID controls at around 1 year follow-up on a logarithmic scale. CI, Confidence Intervals, OR, Odds Ratio, RR, Risk Ratio. Detailed values are listed in Appendix 3.

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New onset diseases after COVID-19 compared to other respiratory tract infections

Eight retrospective cohort studies compared the impact of long-term symptoms or new onset diseases after COVID-19 with other respiratory tract infections (RTI) (8, 11-16, 18). Other RTIs were influenza in four studies, pneumonia in two studies, and severe acute respiratory infection, or any other RTI by each one study. Four studies looked only at hospitalised patients (13-16), whereas four studies by two authors looked at mixed populations. COVID-19 patients and RTI cohorts were matched to a limited degree, mainly by demographics. The number of participants with COVID-19 were 10403 in the smallest study, and 1284437 in the largest. Follow-up was from 182 days to more than 2 years. Study populations were mainly from the USA, England, and South Korea. All studies used registered diagnostic codes to extract information on possible sequalae, one study used only diagnostic codes registered for re-admission to hospital (15).

We grouped all reported diagnostic codes by overarching symptom groups and listed these in a forest plot presenting Hazard Ratios and Relative Risks (Figure 6). Across all 55 reported diagnostic codes, two diagnoses were more than twice as likely among COVID-19 patients as among patients with other RTIs, and five diagnostic codes were less than half as likely. For twenty-one diagnostic codes there was no difference in risks, whereas for 34 diagnostic codes there were differences of mostly a smaller degree, with varying clinical significance. The difference was largest for diagnostic codes for neurological conditions, being more prevalent in COVID-19 patients compared to patients with other RTIs. The data on mental health consequences was more variable without a clear trend of difference. Respiratory sequalae appeared to be slightly less common in COVID-19 patients compared with patients with other RTIs. There was no clear pattern regarding differences in reported cardiovascular diagnostic codes. Among ten cardiovascular diagnostic codes only two differed between the groups; heart failure was more likely, and intracerebral or subarachnoid bleeding was less likely among COVID-19 patients compared with patients with other RTIs. Musculoskeletal diagnostic codes were less common among COVID-19 patients in two studies. Among the diagnostic codes which were infrequently reported, or reported by only one author, there was more variability. Nonetheless seven studies showed differences in diagnostic codes, among these, cancer stood out to be slightly less likely among patients with COVID-19. The included studies cannot prove causality, and some illnesses have long prodromal periods without clear symptoms which may have been caught earlier or due to more thorough follow-up.

Four studies looked at the time from COVID-19 diagnosis to any new diagnosis, or risk horizon finding that incidence of new diagnosis decreased over time (8, 13, 15, 18). Longer follow-up time in COVID-19 patients did not appear to greatly increase or reduce the relative risk of outcomes compared with other RTIs.

Eight controlled studies compared the impact of long-term symptoms or new onset disease after COVID-19 with other RTIs. Overall, it appears that risks are quite similar, except for neurological symptoms that seem to be possibly more associated with COVID-19. The largest spread and uncertainty are seen across new onset of mental health disorders.

Figure 6 - Overview of disease groups based on registered diagnostic codes after COVID-19 compared to other RTI on a logarithmic scale. RR/HR>1 indicates COVID-19 worse than other RTI. Bhaskaran, Clift, Qureshi reflect mainly hospitalised patients. Lee and Taquet mainly non-hospitalised patients. Follow-up time: Qureshi and Lee present ca. 6 months, Clift and Bhaskaran ca 12 months, Taquet ca. 2 years. All studies had more than 10 000 participants. Sex distribution was mainly balanced. Detailed values are listed in Appendix 3.

Children followed up for longer than 6 months, studies with control groups

Seven studies, by four authors, included a population younger than 18 years, two studies exclusively studied children. Two authors reported on data from Danish children, one author used an international database, and one study used Korean registry data. Participants were mainly infected during 2020 and early 2021, representing earlier variants of the virus.

Kikkenborg Berg et al. conducted a Danish nationwide cross-sectional study and published in two papers (9, 10), including children with COVID-19 (cases) and matched controls from national registers. A survey was sent to participants or mothers, and a control group matched by age and sex (1:4). The survey included the Pediatric Quality of Life Inventory (PedsQL) and the Children's Somatic Symptoms Inventory-24 (CSSI-24) to capture current overall health and wellbeing, and ancillary questions about a selection of 23 common post COVID-19 symptoms. One publication analysed data on children 0-14 years old with 10 997 cases and 33 016 controls (10). Compared with controls, children who had COVID-19 had more prevalent long-lasting symptoms. There was a tendency towards better quality-of-life scores related to emotional and social functioning in cases than in controls in older children. The second publication analysed 24 315 adolescents, 15-18 years old, with COVID-19 and 97 257 controls (9). Participants in the case group had greater odds of having at least one long COVID-19 symptom lasting at least 2 months as well as lower symptom scores (i.e., less somatic distress) on the CSSI-24 and better quality of life scores on the PedsQL compared to controls. Participants with COVID-19 had more long-lasting symptoms and sick leave, whereas participants in the control group had more short-lasting symptoms and marginally lower quality of life. The study size, including all SARS-CoV-2 PCR test results for the total Danish population is a strength, yet low response rates, non-response bias, and recall bias and not sufficient matching with controls limit the generalisability of findings.

Lee et al. conducted a retrospective cohort study in South Korea (18). The authors used claims data to determine the number and types of complications from COVID-19 that patients experienced, and which participants that were more vulnerable to those complications compared with peers with influenza. Looking at factors associated with incidence of complications for both illnesses the study found that younger participants (0-19) had lower odds compared to older patients (20–44); younger age was more strongly associated with less complications for covid patients than for influenza patients.

Sørensen et al. conducted a nationwide survey of post-acute symptoms (19). The authors stratified their findings by sex and age groups (15-19-year-olds). In their supplementary files they published the RD of symptoms after 6-12 months, and self-reported health problems between the test date and until 6-12 months, in COVID-19 compared with test-negative participants. Risk differences of 21 different reported symptoms after 6-12 months showed a greater risk for dysosmia, dysgeusia, reduced appetite and strength in arms/legs among COVID-19 positive children compared to controls. COVID-19 adolescent girls experienced more dyspnoea, chest pain, dizziness, fatigue, headache and sleeping legs/arms than negative controls and boys with COVID-19. COVID-19 adolescent boys experienced less cough, runny eyes and nose, and sore throats than girls with COVID-19 and non-COVID-19 controls. There was no risk difference between participant groups for seven other symptoms (abdominal pain, chills,

diarrhoea, fever, hot flushes, muscle/joint pain, and nausea). Self-reported health problems and self-reported received diagnoses are not included here as the symptom spectrum is more descriptive.

Taquet et al. analysed post-COVID-19 neurological and psychiatric new onset disease trajectories registered in TriNetX electronic health records network (8). New onset disease trajectories differed for the included 185 748 COVID-19 children compared with COVID-19 adults: in the 6 months after COVID-19, children were not at an increased risk of mood or anxiety disorders but for psychotic disorders, and epilepsy or seizures. Children with COVID_19 compared with children with other RTIs had an increased risk for encephalitis, cognitive deficit, insomnia, intracranial haemorrhage, ischaemic stroke, nerve, nerve root, and plexus disorders. Cognitive deficit in children had a finite risk horizon (75 days) and a finite time to equal incidence (491 days) unlike in adults.

Overall, adolescent and children appear less affected than older age groups based on studies of participants from during the first pandemic year. Compared with non-COVID-19 controls, children who had COVID-19 infection had more prevalent long-lasting symptoms. Most symptoms appeared to gradually resolve over time. After 6-12 months changes to smell and taste, and reduced appetite were more common among covid positive children compared with controls. Data on mental health and functioning were less clear.

Predicting factors for long-term symptoms and new onset disease

Whereas most studies predominantly compared diagnoses and symptoms, five authors analysed factors correlating initially registered information and outcomes. For most studies this was not the primary objective, nonetheless some authors collected and analysed data to provide insights into factors correlated with possible sequalae or long-term symptoms, using variable statistics: adjusted odds ratio, odds ratio, hazard ratio, relative risk/risk ratio and risk difference (7, 8, 18, 19).

Comparing potential relevance of predicting factors between COVID-19 and other RTIs there is visible congruence (18). Prior comorbidities, female sex, severity of COVID-19 seem to be correlated with risk of long-term symptoms or a new onset disease (7, 18, 19). Severity of COVID-19 was strongly correlated with long-term symptoms in most studies. Regarding age and risk, middle age appears weakly correlated with symptoms, youngest age groups including children appeared least affected (8, 18, 19). One study looked at virus variant as determinant for neurological and psychiatric outcomes, the data suggested that the Alpha variant was the least consequential, Delta the most and Omicron in the middle (8).

Discussion

We included 14 studies following up participants with COVID-19 and non-COVID-19 controls for six months or longer in this fourth version of our rapid review. The previous report published February 2022 included 20 studies: 11 studies without control groups, and nine studies with controls (2). Four studies, of which three were updated since our previous report matched the updated inclusion criteria, and ten new studies were added. We excluded uncontrolled studies in this update. Other recently published systematic reviews have conducted their searches earlier in the first part of 2022, with mainly few or no controlled studies (20-24). The anticipated increase in number of controlled studies led us to applying more stringent inclusion criteria, requiring 500 or more participants, compared to 100 or more in the previous report. There remains a disbalance between non-hospitalised and hospitalised patients with mainly hospitalised patients captured in studies. Some studies with mixed populations also provide insight into long-term symptoms and new onset diseases among non-hospitalised patients.

This update provides new insights and strengthens our earlier findings. The focus on controlled studies reveals that most reported symptoms were also seen in the follow-up period of other RTIs. The comparison of COVID-19 with other RTIs revealed that many symptoms or new onset diseases after COVID-19 were also commonly reported in non-COVID respiratory tract infected populations. The comparison with non-COVID-19 controls revealed a greater difference in reported symptoms, especially for altered sense of smell and taste, dyspnoea, and fatigue. The risk of a new diagnosis appeared not to be higher among COVID-19 patients compared with patients with other RTIs, with higher or lower risks only among a few of the reported diagnostic codes. This suggests that the severity of the acute disease may be more relevant than the pathogen. Altered smell and taste and increased risk of a neurological diagnosis seem to be most specifically related to COVID-19. Studies reporting symptoms both at six months, twelve months and two years follow-up indicated a decrease in prevalence of symptoms over time.

The previous version included only one study of the paediatric population, while this report included seven studies, by four authors. This provides a clearer picture of how a COVID-19 infection may affect children and adolescents. Compared with adults, children appear overall less affected. Compared with controls, children who had a SARS-CoV-2 infection had more prevalent long-lasting symptoms. Most symptoms tended to gradually resolve over time. After 6-12 months altered smell and taste, and reduced appetite were more common symptoms among COVID-19 positive children compared with COVID negative controls. Data on mental health and functioning were less clear. These findings are generally consistent with other systematic reviews in the field, but the research on children is still limited, heterogeneous, and based on low-quality studies (23, 24). With more relevant studies being published continuously, as with a

study consistent with our findings was just prior to publication of this report (25), we can expect more robust findings with time.

Basic statistical analysis within the studies elucidated risk factors for long-term symptoms and new onset diseases. Hospitalisation, severity of COVID-19, co-morbidities and female sex are factors correlated with increased risk of long-term symptoms. The youngest populations including children appear to be less affected, while middle aged populations seem to be most affected. As to be expected, the estimates on rarer symptoms and diagnoses are less precise given small sample sizes.

Even though the evidence base has improved with the publication of larger controlled studies, our findings still reflect persons with COVID-19 from the beginning of the pandemic, mainly 2020 and early 2021. As follow-up time was often reported in aggregate form, we only included studies with a mean or median follow-up time of at least six months for 500 participants, with many studies reporting on up to 12 months and until two years. Our updated and narrowed inclusion criteria led to including only controlled studies, which are more complex to set up and may discriminate against settings in which these types of studies are less common. Many studies have narrow selection criteria and mainly included hospitalised patients with registry data available. Our quality assessment revealed a continued common presence of selection bias of participants, although limiting us to controlled study designs strengthens our findings. By not excluding studies based on our quality assessment, it may be that studies with serious limitations or with publicly expressed concerns remained included, as the case for one included study (26). Our criteria may reflect patients who were more seriously affected and those more often in contact with the healthcare system. Studies mainly used diagnostic codes which may be more objective, but do not capture prevalence nor severity of symptoms (27). The included registry studies aggregated symptoms to time periods, blurring the distinction between symptoms at a specific time point or over a period. The aggregated data presentation for studies with non-COVID non-RTI controls led us to exclude studies reporting cumulative/ aggregated data combining acute and chronic phase (before and after 3 months) in case of non-COVID controls. For controls with other RTIs we decided to include aggregated data from discharge, as differentiation of the acute and chronic phases was more comparable among patients ill with any respiratory tract infection than non-COVID controls without an acute illness at the start of follow-up. Matching between controls and comparators was in many cases limited to demographic characteristics or not performed. Our methodological choices might have an impact on the type of patients investigated. By excluding pre-prints and limiting us to peer-reviewed publications we also limited the number of identified studies, but this might contribute to greater reliability of our findings. No Norwegian studies met the selection criteria of this update, which might limit the generalizability of our findings to the local context. Similarly, we still need more information regarding asymptomatic and mildly affected patients, which would be most applicable to most of those who have been infected with COVID-19 in Norway. Our findings represent an overview of the largest controlled studies, as part of a growing body of evidence, yet the heterogeneity in the available studies continues to prevent quantitative synthesis of findings, any pooled meta-analysis might lead to misleading inferences/conclusions.

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 (28). The findings of this review indicate that the health consequences are quite similar for critically ill COVID-19 patients treated with invasive mechanical ventilation and other patients who have undergone similarly severe non-COVID illnesses with intensive care. These findings support the current rehabilitation practise of providing similar care to patients with PICS after COVID as after other severe RTIs. The increased risk for women to suffer from long-term symptoms is an interesting finding. Men have a higher risk than women of becoming more severely ill in the acute phase of COVID-19 (29). The controlled studies included in this rapid review confirmed findings from previous rapid reviews that patients who have been admitted to the hospital or intensive care unit with COVID-19 seemed to be at greatest risk for developing long-term symptoms. Controlled studies also found that most symptoms reported by COVID-19-patients were also reported 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 the reporting of some symptoms. These measures were not limited to COVID-19 patients only but applied to the whole population.

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 experiences for patients from the early phase of the pandemic. Newer virus variants (omicron), vaccination and therapeutic advancements, seem to lead to milder disease and potentially a lower prevalence of long-term symptoms (30). Studies on consequences of breakthrough infections, and comparative studies on vaccinated versus non vaccinated populations is beginning to appear. These will with time provide valuable insights into populations not addressed in this report (31-33). New virus variants causing milder disease are also expected to reduce the risk of long-term symptoms. Only one included study analysed patients with the Omicron variant indicating slightly milder consequences, further research into this is required. Persons with asymptomatic COVID-19, or those not tested are not well researched. Although the research landscape is rapidly developing, the marginal scientific value of new updates is decreasing. We need research on post-COVID-19 condition by vaccination status, virus variant, and low COVID-19 clinical severity to provide up to date knowledge to clinicians and policymakers.

Conclusion

Severe COVID-19, requiring hospitalisation or intensive care treatment, correlates with more symptoms after six to twelve months. Individuals with COVID-19 appear to experience and get diagnosed with similar conditions as those seen in patients with other severe respiratory tract infections at follow-up, although with some variation and with neurological symptoms standing out as more common after COVID-19. Women have a higher risk for experiencing long-term symptoms than men. Patients who have had mild and moderate COVID-19 (non-hospitalised) report some symptoms beyond six months after infection more often than uninfected persons. The extent of long-term impact of 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: 2022-09-19: *Ovid MEDLINE(R) ALL <1946 to October 29, 2021 >*

#	Query	29.10.21	19.09.22
1	chronic covid*.ti,ab,kf.	33	63
2	long covid*.ti,ab,kf.	545	1797
3	persistent covid*.ti,ab,kf.	43	132
4	(Post acute covid* or postacute covid*).ti,ab,kf.	141	390
5	(Post covid* adj3 (illness* or syndrome* or symptom* or condition*)).ti,ab,kf.	301	939
6	(Prolonged adj3 covid*).ti,ab,kf.	181	323
7	or/1-6	1059	3067
8	(chronic adj3 (complication* or infect* or symptom* or syndrome*)).ti,ab,kf.	92094	96840
9	(Long-haul* OR longhaul*).ti,ab,kf.	1009	1173
10	((long-term or longterm) adj3 (complication* or consequence* or outcome*)).ti,ab,kf.	114984	124216
11	(Persistent adj3 (infecti* or symptom* or syndrome*)).ti,ab,kf.	27044	28885
12	(Prolonged adj3 recovery).ti,ab,kf.	2610	2763
13	sequelae*.ti,ab,kf.	68354	72288
14	or/8-13	298750	318041
15	exp Coronavirus/	102548	150500
16	exp Coronavirus Infections/	125455	198109
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	312119
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	29572
20	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	5549	8708
21	or/15-20	214812	318301
22	21 and 20191201:20301231.(dt). /20210122:20301231.(dt)/20210617:20301231.(dt)./ **20211029:20301231.(dt)**	46125	105024
23	14 and 22	957	2402
24	7 or 23	1823	**4757**

*Alterations since last search marked in red

Search: 2021-09-19: *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 "post covid condition" OR survivors OR survivorship)

*Alterations since last search marked in red

Results:
22.01.21: 1 291 (until 22.01.21)
17.06.21: 1 304 (for all 2021)
29.10.21: 1 502 (for 17.06-29.10)
19.09.22: 10 592 (2021-22; EMBASE, EuropePMC, Scopus, ProQuest Central, Web of Science, language EN)

Search: 2022-09-19: *OpenAlex via EppiReviewer*:
11 controlled studies from previous report were used as a basis to search from 29.10.21-19.09.2022. The search returned n=826 articles.

Overview of searches:
Medline   4 757
WHO   10 592
OpenAlex   826
_____

Sum   16 175

   -   Duplicates   **2 048**
_____

Sum   **14 127**

Appendix 2; List of excluded studies

Table of excluded studies

First Author	Reason for Exclusion
Abel (34)	Too short follow-up
Al-Aly (33)	Aggregated follow-up
Beauchamp (35)	Participant selection
Caspersen (36)	Follow-up, participant size
Caspersen (37)	Publication type, pre-print
Deuel (38)	Participant size
Edlow (39)	Participant size
Fjelltveit (40)	Participant size
Haberland (41)	Participant size
Hodgson (42)	Participant size
Huang (43)	Update available and included
Ioannou (44)	participant selection
Jacob (45)	Unclear follow up
Johnson (46)	Participant size
Kerchberger (47)	Aggregated follow-up
Krishnan	Pre-print
Lapin (48)	Aggregated follow-up
Liu (Yu-Hui)	update available and included
Lopez (49)	Too short follow-up
Lund (50)	Aggregated follow-up
Mainous(51)	Participant size
Mainous	Participant size
Murata (52)	Too short follow-up
Nehme (53)	Participant size
Ollila (54)	Participant size
Park (55)	Aggregated follow-up
Park (56)	Aggregated follow-up
Patel (57)	Too short follow-up
Petersen (58)	Participant size
Rezel-Potts (59)	Aggregated follow-up
Rivera-Izquierdo (60)	Participant size
Sandmann (61)	Participant size
Schulz (62)	Publication type, letter
Selvaskandan (63)	Unclear follow up
Vaira (64)	Participant size
Wang (65)	Aggregated follow-up
Whittaker (66)	Too short follow-up
Wollborn (67)	Unclear follow up
Xie (68)	Aggregated follow-up
Xiong (69)	Participant size

Appendix 3; Figure data

Figure 3

Name	Effect size	lower	higher
Dysosmia (Sørensen, RD, 95% CI)	10,92	10,64	11,2
Dysgeusia (Sørensen, RD, 95% CI)	8,68	8,43	8,93
Fatigue (Sørensen, RD, 95% CI)	8,43	8,12	8,74
Dyspnea (Sørensen, RD, 95% CI)	4,87	4,64	5,07
Reduced strength legs/arms (Sørensen, RD, 95% CI)	4,68	4,45	4,9
Sleeping legs/arms (Sørensen, RD, 95% CI)	3,5	3,3	3,71
Muscle/joint pain (Sørensen, RD, 95% CI)	3,46	3,24	3,68
Headache (Sørensen, RD, 95% CI)	3,04	2,79	3,3
Dizziness (Sørensen, RD, 95% CI)	2,38	2,18	2,58
Chest pain (Sørensen, RD, 95% CI)	2,01	1,85	2,16
Hot flushes/sweat (Sørensen, RD, 95% CI)	1,66	1,48	1,84
Reduced appetite (Sørensen, RD, 95% CI)	1,51	1,36	1,67
Red runny eyes (Sørensen, RD, 95% CI)	0,5	0,38	0,62
Abdominal pain (Sørensen, RD, 95% CI)	0,44	0,29	0,6
Chills (Sørensen, RD, 95% CI)	0,44	0,3	0,56
Nausea (Sørensen, RD, 95% CI)	0,43	0,28	0,59
Diarrhoea (Sørensen, RD, 95% CI)	0,34	0,2	0,51
Fever (Sørensen, RD, 95% CI)	0,32	0,16	0,48
Cough (Sørensen, RD, 95% CI)	-0,01	-0,23	0,22
Runny nose (Sørensen, RD, 95% CI)	-0,22	-0,43	-0,01
Sore throat (Sørensen, RD, 95% CI)	-0,65	-0,85	-0,43

Figure 4

Symptoms (self-reported) at 24 months	Effect size	lower	higher
Any one of the following symptoms (Huang, RR, 95% CI)	2,01	1,83	2,21
Sleep difficulties (Huang, RR, 95% CI)	2,31	1,95	2,74
Fatigue or muscle weakness (Huang, RR, 95% CI)	6,38	4,86	8,38
Hair loss (Huang, RR, 95% CI)	2,14	1,7	2,69
Joint pain (Huang, RR, 95% CI)	2,15	1,71	2,71
Palpitations (Huang, RR, 95% CI)	3,48	2,57	4,71
Dizziness (Huang, RR, 95% CI)	2,1	1,63	2,72
Cough (Huang, RR, 95% CI)	2,63	1,86	3,74
Headache (Huang, RR, 95% CI)	3,24	2,22	4,71
Sore throat or difficult to swallow (Huang, RR, 95% CI)	11,75	5,74	24,07
Myalgia (Huang, RR, 95% CI)	10,44	5,3	20,59
Chest pain (Huang, RR, 95% CI)	5,06	3,07	8,33
Smell disorder (Huang, RR, 95% CI)	17	6,22	46,4
Skin rash (Huang, RR, 95% CI)	13	4,72	35,82
Decreased appetite (Huang, RR, 95% CI)	3,18	1,62	6,23
Taste disorder (Huang, RR, 95% CI)	11	3,38	35,76
Nausea or vomiting (Huang, RR, 95% CI)	7,25	2,56	20,56
Dyspnea (mMRC score) (Huang, RR, 95% CI)	0,71	0,58	0,86
Pain or discomfort (Huang, RR, 95% CI)	4,46	3,38	5,87
Anxiety or depression (Huang, RR, 95% CI)	2,15	1,6	2,88
Mobility problem (Huang, RR, 95% CI)	0,83	0,53	1,3
Usual activity problem (Huang, RR, 95% CI)	5,4	2,09	13,97
Personal care problem (Huang, RR, 95% CI)	3	0,97	9,27

Figure 5

Name	Effect size	lower	higher
Mental health and cognitive (Bhaskaran, HR, 95%CI)	3,84	2,97	4,96
Neurological			
Anxiety (Clift, HR, 95%CI)	2,36	2,03	2,74
Dementia (Clift, HR, 95%CI)	2,63	2,21	3,14
Dementia, non-severe COVID (Liu, OR, 95%CI)	3,68	0,99	13,63
Psychotic disorder (Clift, HR, 95%CI)	3,05	1,58	5,9
Depression (Clift, HR, 95%CI)	1,95	1,05	3,65
Bipolar disorder (Clift, HR, 95%CI)	2,26	1,25	4,07
Mild cognitive impairment, non-severe COVID (Liu, OR, 95%CI)	3,64	2,22	5,15
Cognitive impairment, non-severe COVID (Liu, OR, 95%CI)	1,1	0,69	1,76
Cognitive impairment, severe COVID (Liu, OR, 95%CI)	9,1	5,61	14,75
Early-onset cognitive decline, non-severe COVID (Liu, OR, 95%CI)	1,71	1,3	2,27
Early-onset cognitive decline, severe COVID (Liu, OR, 95%CI)	4,87	3,3	7,2
Late-onset cognitive decline, non-severe COVID (Liu, OR, 95%CI)	1,59	0,82	3,09
Late-onset cognitive decline, severe COVID (Liu, OR, 95%CI)	7,58	3,58	16,03
Progressive cognitive decline, non-severe COVID (Liu, OR, 95%CI)	0,61	0,27	1,4
Progressive cognitive decline, severe COVID (Liu, OR, 95%CI)	19	9,14	39,51
Nervous system (Bhaskaran, HR, 95%CI)	2,21	1,81	2,71
Respiratory			
COVID/Flu/LRTI (Bhaskaran, HR, 95%CI)	8,47	7,66	9,37
Other respiratory (Bhaskaran, HR, 95%CI)	4,28	3,7	4,95
Cardiovascular			
Circulatory (Bhaskaran, HR, 95%CI)	2,49	2,28	2,72
Musculoskeletal			
Musculoskeletal (Bhaskaran, HR, 95%CI)	1,27	1,12	1,43
Other			
All-cause mortality (Bhaskaran, HR, 95%CI)	5,79	5,41	6,2
Other infections (Bhaskaran, HR, 95%CI)	3,32	2,82	3,9
Cancers (Bhaskaran, HR, 95%CI)	1,63	1,41	1,88
Endocrine, nutritional, and metabolic (Bhaskaran, HR, 95%CI)	2,69	2,17	3,35
Digestive (Bhaskaran, HR, 95%CI)	1,41	1,29	1,55
Genitourinary (Bhaskaran, HR, 95%CI)	2,11	1,87	2,38
External causes (Bhaskaran, HR, 95%CI)	2,12	1,89	2,38

Figure 6

Name	Effect size	lower	higher
Mental health			
Anxiety (Clift, RR)	0,71		
Anxiety disorder (Taquet, HR, 95% CI)	1,13	1,11	1,15
Bipolar affective disorder (Clift, RR)	0,55		
Depression (Clift, RR)	0,29		
Mood disorder (Lee, RR, 95% CI)	1,73	1,56	1,93
Mood disorder (Bhaskaran, HR, 95% CI)	1,61	0,54	4,79
Mood disorder (Taquet, HR, 95% CI)	1,08	1,06	1,11
Neurotic disorders (Bhaskaran, HR, 95%, CI)	2,59	0,71	9,52
Schizophrenic disorder (Bhaskaran, HR, 95% CI)	0,2	0,03	1,12
Neurological			
Dementia (Clift, RR)	0,44		
Dementia (Lee, RR, 95% CI)	1,96	1,52	2,55
Dementia (Taquet, HR, 95% CI)	1,33	1,26	1,41
Dementia (Qureshi, OR, 95% CI)	1,3	1,1	1,5
Dementia (Bhaskaran, HR, 95% CI)	2,32	1,48	3,64
Delirium (Bhaskaran HR, 95% CI)	1,1	0,7	1,72
Cognitive deficit (Taquet, HR, 95% CI)	1,36	1,33	1,39
Psychotic disorder (Clift, RR)	0,62		
Psychotic disorder (Taquet, HR, 95% CI)	1,27	1,18	1,37
Encephalitis (Taquet, HR, 95% CI)	0,96	0,85	1,08
Epilepsy or seizures (Taquet, HR, 95% CI)	1,14	1,09	1,19
Guillain-Barré syndrome (Taquet, HR, 95% CI)	1,12	0,97	1,3
Insomnia (Taquet, HR, 95% CI)	1,13	1,1	1,16
Myoneural junction or muscle disease (Taquet, HR, 95% CI)	1,89	1,76	2,04
Nerve, nerve root, and plexus disorder (Taquet, HR, 95% CI)	0,89	0,87	0,91
Parkinsonism (Taquet, HR, 95% CI)	1,04	0,92	1,17
Nervous (Bhaskaran, HR, 95% CI)	1,01	0,78	1,3
Respiratory			
Asthma (Lee, RR, 95% CI)	0,36	0,28	0,47
COPD (Lee, RR, 95% CI)	0,79	0,54	1,15
Pneumonia (Lee, RR, 95% CI)	1,02	0,9	1,16
Other respiratory (Bhaskaran, HR, 95% CI)	0,78	0,68	0,88
Cardiovascular			
Cardiovascular (Lee, RR, 95% CI)	1,05	0,83	1,32
Heart failure (Lee, RR, 95% CI)	1,88	1,42	2,5
Cerebrovascular disease (Lee, RR, 95% CI)	1,21	0,91	1,6
Intracranial haemorrhage (Taquet, HR, 95% CI)	1,09	1,01	1,18
Ischaemic stroke (Taquet, HR, 95% CI)	1,11	1,06	1,17
Any cardiovascular event (Qureshi, HR, 95% CI)	0,9	0,8	1,02
Ischaemich heart disease (Qureshi, HR, 95% CI)	1	0,87	1,04

Ischaemic stroke (Qureshi, HR, 95% CI)	0,84	0,7	1,02
Intracerebral or subarch. Hemorrage (Qureshi, HR, 95% CI)	0,42	0,26	0,69
Circulatory (Bhaskaran, HR, 95% CI)	0,94	0,84	1,06
Muscoloskeletal			
Muscoloskeletal (Lee, RR, 95% CI)	0,75	0,7	0,81
Muscoloskeletal (Bhaskaran, HR, 95% CI)	0,78	0,66	0,93
Other			
Peridontal disease (Lee, RR, 95% CI)	0,65	0,61	0,7
Skin disease (Lee, RR, 95% CI)	0,89	0,82	0,98
Hair loss (Lee, RR, 95% CI)	1,52	1,18	1,97
Cancers (Bhaskaran, HR, 95% CI)	0,77	0,66	0,9
Other infection (Bhaskaran, HR, 95% CI)	0,76	0,64	0,91
COVID/Flu/ LRTI (Bhaskaran, HR, 95% CI)	1,37	1,22	1,54
Autoimmune (Lee, RR, 95% CI)	1,03	0,86	1,25
Gastro (Lee, RR, 95% CI)	0,78	0,73	0,84
Digestive (Bhaskaran, HR, 95% CI)	0,96	0,84	1,1
Endocrine, nutritional and metabolic (Bhaskaran, HR, 95% CI)	1,11	0,84	1,47
External causes (Bhaskaran, HR, 95% CI)	1,15	0,97	1,35
Genitoirinary (Bhaskaran, HR, 95% CI)	0,96	0,82	1,13
Death (Bhaskaran, HR, 95% CI)	0,95	0,91	0,98

Appendix 4; Characteristics used for matching controls

Author	Study type	Controls	Criteria for matching controls
Bhaskaran (15)	Retro. cohort	Neg covid / RTI (incl. influenza)	*"Two comparison groups were also selected. First, we identified people under follow-up in the general population in 2019, individually matched 5:1 to the COVID-19 group on age (within 3 years), sex, Sustainability and Transformation Plans (STP, a geographical area used as in NHS administration, of which there were 32 in our data), and calendar month (e.g., a patient discharged from a COVID-19 hospitalisation in April 2020 was matched to 5 individuals of the same age, sex, and STP who were under follow-up in general practice on 1 April 2019).... Second, we identified all individuals discharged from hospital in 2017 to 2019 where influenza was coded as the primary reason for hospitalisation and who were alive and under follow-up 1 week after discharge."*
Clift (16)	Retro. cohort	SARI	*"We extracted a temporally distinct historic cohort to compare incidence rates of post-SARI discharge neuropsychiatric sequelae with the remaining population, intending to statistically compare those in the prepandemic period with those in the contemporary pandemic period. This cohort identified adults aged 18 years and older entering the cohort from January 24, 2015, to January 23, 2020."*
Huang (17)	Pro. cohort	Neg covid	*"COVID-19 survivors and controls were further matched 1:1 by age, sex, and comorbidities including cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes. The maximum allowed age difference between COVID-19 patients and their controls was 10 years."*
Huang (6)	Pro. cohort	Neg covid	*"COVID-19 survivors who attended the three follow-up visits were matched (1:1) by age, sex, and comorbidities (including cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes) to control participants. The maximum allowed age difference between COVID-19 survivors and their matched controls was 5 years."*
Liu (7)	Pro. cohort	Neg covid	*"Their uninfected spouses (N = 466) were recruited as a control population. Participants with preinfection cognitive impairment, a concomitant neurological disorder, or a family history of dementia were excluded, as well as those with severe cardiac, hepatic, or kidney disease or any kind of tumor."*
Qureshi (13)	Retro. cohort	Pneumonia	*"Each SARS-CoV-2–infected patient was matched with a pneumonia patient without SARS-CoV-2 infection using age, gender, race/ethnicity, and reference encounter admission date."*
Qureshi (14)	Retro. cohort	Pneumonia	*"Each SARS-CoV-2–infected patient was matched with a pneumonia patient using age, gender, race/ethnicity, and index encounter admission date."*
Lee (18)	Retro. cohort	RTI (influenza)	Not closer described.
Kikkenborg Berg (10)	Retro. cohort	Neg covid	*"At the same time, controls who had never had a positive SARS-CoV-2 test were identified from the Danish Civil Registration System and included using exposure density matching by sex and age in a 1:4 ratio at the time of the cases' positive tests*
Kikkenborg Berg (9)	Retro. cohort	Neg covid	*"A group of controls without a positive SARS-CoV-2 test, matched 1:4 (n=97 257) by sex and age at the time of the case's positive test was identified from the Danish Civil Registration System."*
Sørensen (19)	Retro. cohort	Neg covid	Not described in detail: *"time-matched control population"*
Taquet (12)	Retro. cohort	RTI (incl. influenza)	*"We used propensity score matching19 to create cohorts with matched baseline characteristics, done within the TriNetX network. Propensity score with 1:1 matching*

Taquet (11)	Retro. cohort	RTI (incl. influenza)	*used a greedy nearest neighbour matching approach with a calliper distance of 0·1 pooled SDs of the logit of the propensity score. Any characteristic with a standardised mean difference between cohorts lower than 0·1 was considered well matched."* "*Propensity score 1:1 matching (with greedy nearest neighbor matching, and a caliper distance of 0.1 pooled standard deviations of the logit of the propensity score) was used to create cohorts with matched baseline characteristics and carried out within the TriNetX network. Characteristics with a standardized mean difference (SMD) between cohorts 0.1 was considered well matched. Because we used EHR with coded health events, if an event was not present, it was considered absent. Missing data for race and ethnicity were assigned their own category and that category was included in the propensity score matching, so that the 2 matched cohorts had approximately equal numbers of patients with unknown race/ethnicity."*
Taquet (8)	Retro. cohort	RTI	"*The COVID-19 and other respiratory infection cohorts were stratified by age group (age <18, 18–64, and ≥65 years) and by date of the index events in 2-monthly periods. Within each stratum, cohorts were propensityscore matched (1:1) for 82 covariates*"

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