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Associations between SARS-CoV-2 infection and incidence of new chronic condition diagnoses: a systematic review

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ABSTRACT

Because of the large number of infected individuals, an estimate of the future burdens of the long-term consequences of SARS-CoV-2 infection is needed. This systematic review examined associations between SARS-CoV-2 infection and incidence of categories of and selected chronic conditions, by age and severity of infection (inpatient vs. outpatient/mixed care). MEDLINE and EMBASE were searched (1 January 2020 to 4 October 2022) and reference lists scanned. We included observational studies from high-income OECD countries with a control group adjusting for sex and comorbidities. Identified records underwent a two-stage screening process. Two reviewers screened 50% of titles/abstracts, after which DistillerAI acted as second reviewer. Two reviewers then screened the full texts of stage one selections. One reviewer extracted data and assessed risk of bias; results were verified by another. Random-effects meta-analysis estimated pooled hazard ratios (HR). GRADE assessed certainty of the evidence. Twenty-five studies were included. Among the outpatient/mixed SARS-CoV-2 care group, there is high certainty of a small-to-moderate increase (i.e. HR 1.26–1.99) among adults ≥65 years of any cardiovascular condition, and of little-to-no difference (i.e. HR 0.75–1.25) in anxiety disorders for individuals <18, 18–64, and ≥65 years old. Among 18–64 and ≥65 year-olds receiving outpatient/mixed care there are probably (moderate certainty) large increases (i.e. HR ≥2.0) in encephalopathy, interstitial lung disease, and respiratory failure. After SARS-CoV-2 infection, there is probably an increased risk of diagnoses for some chronic conditions; whether the magnitude of risk will remain stable into the future is uncertain.

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Introduction

In addition to disrupting the global economy [1], SARS-CoV-2 has infected millions of people worldwide and more than 4.5 million Canadians [2]. Potential long-term consequences of SARS-CoV-2 infection were raised in the first year of the pandemic [3]. Combined with the large number of infected individuals, it is necessary to derive some estimate of the future burdens of the long-term consequences of SARS-CoV-2 infection so that health policy and other decision makers can make informed decisions and healthcare systems can prepare for a potential increase in need for care and resources.

Many reviews in the literature have examined post-COVID-19 condition (previously called Long COVID) [4–6], and many reviews reporting on other long-term sequalae, such as the development of chronic conditions after SARS-CoV-2 infection, have been limited to a single condition or cluster of conditions [7–9] and/or did not require included studies to have a control group in order to quantify attributable risk [10–12]. In order to understand how SARS-CoV-2 may change the future burden of health outcomes on healthcare resources in the future, it is important to assess whether there is actually an association between SARS-CoV-2 infection and increased risk of long-term sequelae.

Therefore, we set out to conduct a systematic review to answer the question: What are the associations between SARS-CoV-2 infection and the incidence of new diagnoses or exacerbations of chronic conditions in groups based on age and severity of infection?

Methods

This review followed an *a priori* protocol developed in consultation with disease leads (NC, DZ, LS, HG, JM, and others) at the Public Health Agency of Canada. The protocol was prospectively registered and is

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available on PROSPERO (CRD42022364883). This review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 reporting guideline (Appendix 1 in the supplement) [13].

Study eligibility

We included prospective or retrospective observational studies carried out in high-income Organisation for Economic Co-operation and Development (OECD) member countries [14] and comparing individuals with suspected or confirmed SARS-CoV-2 infection (exposed) to those without (controls). Preprints and other reports not peer-reviewed were eligible. Conference abstracts frequently present preliminary results and rarely report sufficient methods to adequately assess quality and were therefore excluded. We limited inclusion to records published in English or French, as these are the official languages of Canada and limits on non-English language studies has not been shown to bias systematic review conclusions [15]. Table S1 in the Supplement outlines our eligibility criteria in greater detail.

To be eligible, studies had to report on severity of SARS-CoV-2 infection (i.e. hospitalization status), adjust for possible confounding by at least sex and two or more comorbidities (i.e. by matching, propensity scores, or multivariable regression), and report outcomes by age to allow for allocation to the most appropriate age group for analysis and synthesis of findings by key life-course stages: 0–17y, 18–64 y, and ≥65y. Study outcomes reported using differing age groupings were analysed within the most appropriate age group. Where a study reported an age group that spanned two of our categories, we weighted the data based on the number of years contributed to the age category. For example, data reported for 60–69 year-olds contributed to both the 18–64-year-old and ≥65-year-old groups but was given half of the 60–69-year-old age group's overall weight. We included studies comparing people with confirmed (e.g. by laboratory testing) or suspected (e.g. physician diagnosed, regardless of test status) SARS-CoV-2 infection to those without. To ensure we would have some relevant studies to include, we did not require control groups to test negative for SARS-CoV-2. There was also no requirement for control groups to be healthy individuals (i.e. they could include hospitalized patients or individuals with other respiratory infections such as influenza but without SARS-CoV-2), to control for possible confounding, such as due to hospitalization not specific to SARS-CoV-2 infection.

Primary outcomes of interest were incidence and exacerbations of chronic conditions after SARS-CoV-2 infection compared to controls. Conditions of interest fell into the following categories: cardiovascular diseases, neurological conditions, cancer, chronic kidney disease, diabetes (excluding gestational diabetes), musculoskeletal disorders (e.g. osteoarthritis, gout, etc.), respiratory diseases, mental disorders, and stroke. Individual conditions within each category were also evaluated. Because of the limited clinical and epidemiologic relevance [16], we did not look at dementia/cognitive impairment outcomes in individuals <18 years. Outcomes could be ascertained at any time after the acute phase of infection (i.e. immediately after discharge in hospitalized patients and ≥4 weeks in outpatients) and no minimum follow-up time was required. We attempted to only include studies reporting on diagnoses of chronic conditions, defined as those that were at a minimum documented by a healthcare provider in medical records; however, there may not have been standard diagnostic testing performed in all cases. Variables of interest for subgroup analyses were time since infection, vaccination status, and different SARS-CoV-2 variants of concern.

Search strategy

An information specialist (MT) developed a search strategy combining concepts for SARS-CoV-2 infection, post-acute/follow-up, outcomes (e.g. incidence), and chronic conditions of interest using vocabulary and syntax specific to each database searched. The search strategy was peer-reviewed by a second research librarian using the PRESS 2015 checklist [17]. Searches were carried out on 4 October 2022 in Ovid MEDLINE® ALL 1946 to 3 October, and EMBASE 1974 to 3 October 2022. Search results were limited to those on or after 1 Jan 2020, and filters were applied to remove case reports, commentaries, and conference abstracts. The full searches for MEDLINE and EMBASE are available in Appendix 2 in the Supplement. In addition to database searches, a review lead (LG or JP) screened the reference lists of included studies and pertinent systematic reviews identified during screening for potentially relevant studies. Screening of reference lists and systematic reviews was completed on 7 November 2022.

Study selection

Search results were uploaded to an EndNote library (v. 20.3, Clarivate Analytics, Philadelphia, PA) and deduplicated before screening. Unique records were then uploaded to DistillerSR (Evidence Partners, Ottawa, Canada) and screened in a two-stage process, first by title and abstract (screening) and then by full-text (selection). Using standardized forms, all reviewers involved in screening and selection (LG, JP, SS) piloted the screening form with a random sample of 200 records and piloted the selection form with 16

full-text records from the database searches. Screening and selection proceeded once sufficient agreement between reviewers was reached.

During screening, DistillerSR's machine learning feature (DistillerAI) was enabled. DistillerAI learns from human reviewers' inclusion decisions to assign a likelihood score (0–1, with values closer to 1 indicating higher likelihood of inclusion) for each unscreened record and prioritizes the most relevant records for screening by the human reviewers (i.e. the most relevant records are screened first) [18]. Further, when threshold likelihood score for inclusion is applied, DistillerAI can act as a second reviewer with high specificity and sensitivity [19]. Thus, two reviewers independently screened the first 50% of titles and abstracts, after which DistillerAI acted as a second reviewer with likelihood threshold of 0.7. All remaining records with a DistillerAI-assigned likelihood >0.7 proceeded to selection and the rest were manually screened by one human reviewer for final exclusion. After screening, attempts were made to retrieve the full texts of all potentially relevant records. Two reviewers independently reviewed all retrieved full-texts and came to consensus on inclusion, with adjudication by a review lead or other reviewer (e.g. statistician) when necessary.

Data extraction and management

We developed standardized data extraction forms in Microsoft Office Excel (v. 2019, Microsoft Corporation, Redmond, WA) which were independently piloted by all reviewers involved in extraction (LG, JP, SS). Thereafter, one reviewer extracted data from the included studies, and a second reviewer independently verified results data for accuracy and completeness. Disagreements were resolved by discussion. When relevant findings were reported in figures, data was extracted using Web Plot Digitizer (https://automeris.io/WebPlotDigitizer/). We only recorded zero events of a condition when it was explicitly reported.

We extracted the following information from each study: study characteristics (i.e. author, year, country, funding source, location of registration/protocol, design), population characteristics (i.e. inclusion and exclusion criteria, sample size, population demographics (age, sex, ethnicity, relevant comorbidities), SARS-CoV-2 infection confirmation method and timing), care setting during acute phase (outpatient, inpatient, mixed out- and inpatients), comparator(s), length of follow-up, analysis details (i.e. variables considered in analysis), outcome details (i.e. methods of ascertainment), and findings. For each condition category and/or individual condition of interest we extracted both relative (i.e. incidence rate ratios [IRRs] or hazard ratios [HRs]) and per-group incidence rates or cumulative incidence, when available. If an adjusted incidence rate or cumulative incidence was not reported (but participants were matched by at least sex and comorbidities), we extracted the crude number of events and estimated the cumulative incidence based on the denominator for each group. When results were reported for multiple time points, we took the longest follow-up. We extracted outcome data even when it was not able to be meta-analysed, for example if only a *p*-value between groups was reported, to help interpret data and document possible reporting biases. Adjusted findings (i.e. from the most adjusted model) were prioritized in all cases. We extracted any within-study analyses by time since infection, SARS-CoV-2 vaccination status, and different SARS-CoV-2 variants of concern and synthesized these narratively. Data extracted for this review are available on reasonable request from the authors.

Risk of bias assessment

To assess risk of bias of included studies we used the JBI critical appraisal checklist for cohort studies [20]. After piloting, a review lead (LG) assessed the risk of bias for each study and brought any questions or concerns about included studies to the review team for discussion and consensus. We specifically considered in our assessment the validity of SARS-CoV-2 infection confirmation, with laboratory confirmed (using RT–PCR or antigen test) based on medical records being low risk and all others having some concerns. We also had concerns when a prospective study did not censor control participants who contracted COVID-19 during the follow-up period. We assigned an overall risk of bias rating (low, moderate or high) based on the number of questions answered "No" for each study (0 for low, 1 for moderate, ≥ 2 for high). Final assessments were incorporated into our certainty of evidence assessments guided by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (see below) [21].

Data synthesis

We conducted random-effects meta-analysis using inverse variance weighting in Review Manager (RevMan; v5.4, The Cochrane Collaboration, 2020) to estimate a pooled hazard ratio when two or more studies reported on a condition category, or individual condition, by age category and COVID-19 care setting (inpatient vs. outpatient/mixed). Because our analysis was based on planned sub-groups, we did not investigate further into potential sources of heterogeneity. Forest plots were generated in RevMan to visually display results of the meta-analyses. Data not appropriate for meta-analysis were synthesized narratively. For all

meta-analyses, a relative effect of 0.75–1.25 was considered little-to-no association; 0.51–0.74 and 1.26–1.99 small-to-moderate association (decrease or increase, respectively), and ≤0.50 or ≥2.00 large association. All studies with useable data were included in the meta-analyses for each condition category or individual condition they reported on. Since we identified no eligible studies with data on exacerbations of pre-existing conditions and new diagnosis of a condition can only occur once, we considered reported hazard ratios and incidence rate ratios to be interchangeable. When only cumulative incidence or crude events were reported, we estimated the incidence rates for each group by dividing the number of events by the average follow-up period (in years) multiplied by the number of participants.

We conducted separate analyses for each of the following categories of chronic conditions: cardiovascular disease, neurological conditions, chronic kidney disease, diabetes, musculoskeletal disorders (e.g. osteoarthritis, gout, etc.), respiratory diseases, mental disorders, and stroke. Although cancer was also among our chronic conditions of interest, we did not identify any eligible studies reporting on this outcome. The disease leads helped to ensure conditions reported by each included study were appropriately categorized. We also analysed individual conditions within each condition category (e.g. dementia/mild cognitive disorder within the category of neurological conditions) when there was condition-specific data and a sample size of >2000 in the SARS-CoV-2 infection group.

For studies that reported data for multiple diagnoses falling within the label of an individual condition (e.g. tachycardia and ventricular arrhythmia, which would both contribute to the condition labelled "arrhythmias"), we calculated an estimated average for the condition weighted by the inverse of the variance to give more weight to results with more reliable estimates. This process was also used when a study reported multiple individual conditions within a condition category, if the study did not report a suitable composite outcome for the condition category.

For all categories and individual conditions with low, moderate or high certainty of some direction of effect (i.e. small-to-moderate or large increase/decrease), we estimated the excess incidence in the SARs-CoV-2 group per 1000 people over 6 months. We used a hierarchy to identify the most relevant data to use for the control (non-SARS-CoV-2) event rate. If at least one study reported a composite outcome (e.g. any cardiovascular event) within a condition category, we used the study's reported incidence for that composite outcome. When a condition category had no directly reported composite incidence, we looked at the individual conditions in that condition category. Where we considered conditions within a condition category to be mutually exclusive (broadly speaking), we took the sum of their incidence in the control group as an estimate of the control event rate. Where conditions within a condition category were not mutually exclusive, we used the individual condition with the highest incidence as a conservative estimate. When multiple studies reported a control event rate for a condition category or individual condition, we took an average weighted by sample size. We converted all control event rates to a standard 6-month period, which was most representative of follow-up duration in the included studies. For example, a 1-year incidence rate was divided by 2 to estimate the incidence over 6 months. We estimated excess incidence by subtracting the control event rate from the product of the control event rate and the relative effect.

Other than age and COVID-19 care setting, we did not conduct any quantitative subgroup or sensitivity analyses. However, we planned to narratively summarize any time-varying effects and any within-study sub-group analyses for different SARS-CoV-2 variants of concern or by SARS-CoV-2 vaccination status.

Certainty of evidence

Two reviewers reached consensus through discussion on the certainty about conclusions in relation to our thresholds of effect of the relative effects for each outcome, guided by GRADE [21,22]. We started the evidence at high certainty [23] and down rated to lower levels (i.e. moderate, low, and very low certainty) based on study quality in five domains (i.e. risk of bias, indirectness, inconsistency, imprecision, reporting biases). For each domain, we rated down by 0, 1, or 2 levels depending on the seriousness of the concerns, i.e. how much the domain appeared to impact the conclusions. We used thresholds as the targets of our certainty: a relative effect of 0.75–1.25 was considered little-to-no association, 0.51–0.74 and 1.26–1.99 was considered small-to-moderate, and ≤0.50 or ≥2.00 large. For example, we did not rate down for risk of bias when both high and low risk of bias studies had estimates surpassing the threshold for magnitude of association. Similarly, we did not rate down if some of our concerns in one domain likely stemmed from another domain, for example, we did not rate down for inconsistency if differences in estimates across studies were judged to be primarily related to risk of bias. If only one or two conditions contributed to a condition category estimate, we considered this an indirectness concern. To assess reporting biases, we compared outcomes specified in each report's Methods section (or protocol if available) with the outcomes reported in the Results section. Outcomes in the results section that were not specified in the methods or specified in the methods but not reported in the results were considered concerns.

We rated down for inconsistency/lack of consistency when there was a single study in an analysis, when there was concerning variation not accounted for in other domains in study estimates (in relation to our thresholds), or when a single study contributed >80% weight to an estimate. Finally, we rated down once or twice for imprecision when one or both of the ends, respectively, of the confidence interval extended across an effect threshold (i.e. from effect into little-to-no difference or vice versa). When considering imprecision, we made conclusions about the results for which we had the highest certainty; for example when a point estimate surpassed our threshold for a large association but with imprecision, we instead made conclusions about a small-to-moderate association without imprecision concerns.

Results

The flow of records through the selection process is depicted in Figure 1, and Appendix 3 in the Supplement lists relevant studies that did not meet key eligibility criteria, with reasons for exclusion. After screening 4,648 unique database records and 24 records identified from other sources, we included 25 studies from six countries: United States (15), Germany (4), United Kingdom (3), Denmark (1), Korea (1), and Sweden (1). The included studies (median sample size [IQR] N = 488,552 [226,380–2,568,874]) are summarized in Table 1. Eight (32%) of the included studies confirmed that the control group was negative for SARS-CoV-2 using laboratory testing. Only 2 (8%) eligible studies reported on chronic conditions after hospitalization with SARS-CoV-2. We did not identify any eligible studies reporting on cancer, osteoarthritis, or gout after SARS-CoV-2 infection, nor did we identify any eligible studies reporting exacerbations of pre-existing chronic conditions.

Risk of bias assessments are presented in Table 2. The majority of studies (18/25, 72%) were considered moderate risk of bias with only three having low risk. The most frequent concern for risk of bias was the potential for misclassification, largely due to differential exposure ascertainment methods between groups mostly from not confirming the absence of exposure with negative tests in the control group. Our assessment of potential reporting biases did not identify evidence of missing outcome data in any of the studies included in the meta-analysis.

Appendix 4 in the Supplement contains all forest plots. Table 3 presents the summary of findings, including the certainty of evidence for the relative effects and estimates of the excess cumulative incidence in 1000 people over 6 months (for outcomes with low, moderate or high certainty of a direction of effect). The GRADE domain(s) that led to rating down our certainty are documented in the table footnotes. One study included in our review reported on 31 conditions in 7 categories, but only provided non-stratified numeric results for adults (≥18y; ~15% of sample was ≥65 y); [35] this study reported results for children (<18 y) as a broad statement of no difference without effect estimates or variance, and thus was unable to be included in the meta-analysis, although it still met the inclusion criteria detailed in our protocol. We do not report directions of effect for outcomes in which we had very low certainty. The

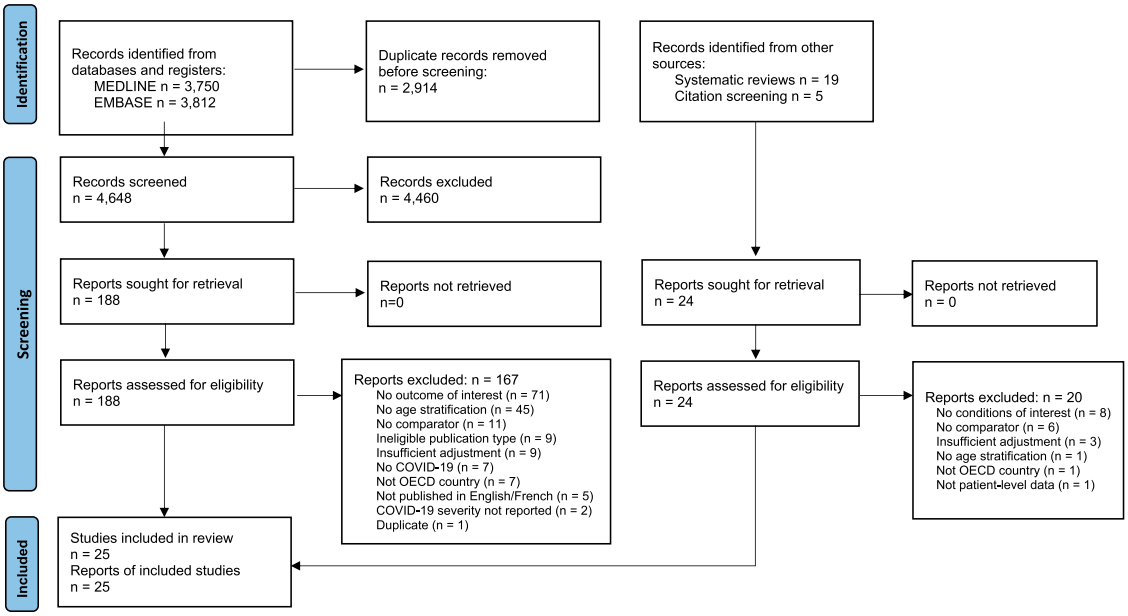

Figure 1. PRISMA flow diagram for a systematic review of the associations between SARS-CoV-2 infection and incidence of new chronic condition diagnoses. Template From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting.

Table 1. Study characteristics of included studies for a systematic review of new diagnoses of chronic conditions after SARS-CoV-2 infection.

Study Country Data source	Index time for SARS-CoV-2 infections	Study design N	Mean/ median follow-up, range If not reported, maximum range of FU?	Care type/setting for SARS-CoV-2 infected cases	Age range (years) % Female	% Hospitalized % in ICU	Comparator timing Test status of comparator group	Outcomes
Abel 2021 [32] United Kingdom Clinical Practice Research Datalink Aurum	Feb 2020 to Dec 2020	Retrospective cohort *N* = 11,923,105	Median (IQR) – 6.3 (4.0–9.3) weeks	Outpatient	16–80+ 50%	NA	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Mental disorders (anxiety disorders, depression, psychosis)
Ayoubkhani 2021 [33] United Kingdom Hospital Episode Statistics Admitted Patient Care and General Practice Extraction Service Data for Pandemic Planning and Research	Jan 2020 to Aug 2020	Retrospective cohort *N* = 95,560	Cov: Mean (SD) – 140 (50) days Con: Mean (SD) – 153 (33) days	Inpatient	0–70 + 45%	100 NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (composite of arrhythmia, heart failure, myocardial infarction, and stroke); Chronic kidney disease (dialysis and kidney transplant); Diabetes (type 1 & type 2); Respiratory disorders
Bohlken 2022 [34] Germany IQVIA Disease Analyzer database	Mar 2020 to Sept 2021	Retrospective cohort *N* = 134,092	Cov: Mean – 158 days Con: Mean – 165 days	Outpatient	18–70+ 53.3%	NA	Concurrent >90% had test negative	Neurological conditions (mild cognitive disorder)
Chevinsky 2021 [35] United States Premier Healthcare Database Special COVID-19 Release	Mar 2020 to Jun 2020	Prospective cohort *N* = 148,892	Range 1–4 mos	Mixed	<18 (adult data not stratified by age)	11.4 NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	31 different conditions across 7 categories, but only reports "Children with COVID-19 were not more likely to experience new diagnoses than children without COVID-19," with no effect size or variance reported and was thus unable to be included in the meta-analysis. Attempt to contact authors to obtain the data was not successful.
Cohen 2022 [36] United States UnitedHealth Database	Jan 2020 to Dec 2020	Retrospective cohort *N* = 226,380	Median (IQR) – 78 (30–175) days	Mixed	65+ 58%	27 6.4	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (acute coronary disease, cardiogenic shock, cardiac arrhythmia, cardiomyopathy, congestive heart failure, coronary disease, hypertension, myocardial infarction, tachycardia); Chronic kidney disease; Diabetes (type 2); Mental disorders (mental health diagnosis, psychosis); Neurological conditions (dementia, encephalopathy, Guillain-Barre syndrome, migraine, peripheral neuropathy, seizure); Respiratory disorders (chronic respiratory failure, interstitial lung disease); Stroke
Daugherty 2021 [37] United States UnitedHealth Database	Jan 2019 to Oct 2020	Retrospective cohort *N* = 488,552	Median (IQR) – 87 (45-124) days	Mixed	18–65 52.5%	8.2 1.1	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (acute coronary disease, arrythmia, cardiogenic shock, cardiomyopathy, congestive heart failure, coronary disease, hypertension, myocardial infarction, tachycardia); Chronic kidney disease; Diabetes (type 2); Mental disorders (mental health diagnosis, psychosis); Neurological conditions (Alzheimer's disease, dementia, encephalopathy, Guillain-Barre syndrome, migraine, peripheral neuropathy, seizure); Respiratory disorders (chronic respiratory failure, interstitial lung disease); Stroke
Donnachie 2022 [38] Germany Bavarian COVID-19 Cohort	Jan 2020 to Jun 2021	Retrospective cohort *N* = 454,649	NR Followed up for 2 years	Outpatient	0–60+ 54%	NA	Concurrent >90% had test negative	Mental disorders (anxiety disorders, mood disorders); Neurological conditions (mild cognitive impairment)

Jacob 2022 [39] Germany IQVIA Disease Analyzer database	Mar 2020 to May 2021	Retrospective cohort *N* = 112,700	NR Maximum of 14 mos	Outpatient	18–70+ 52.3%	NA	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Mental disorders (anxiety disorders, depression)
Kompaniyets 2022 [40] United States HealthVerity	Mar 2020 to Jan 2022	Retrospective cohort *N* = 3,125,676	NR Minimum of 60 days to maximum of 365 days	Mixed	2to 17 50%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (cardiac dysrhythmias); Chronic kidney disease; Diabetes; Mental disorders (anxiety disorders, mood disorder); Musculoskeletal disorders; Neurological conditions (nervous system disorder); Respiratory disorders (asthma); Stroke
Park 2021 [41] Korea National Health Insurance Service Database	Jan 2020 to Dec 2020	Retrospective cohort *N* = 260,883	NR Minimum of 0 days to maximum of 12 mos	Mixed	20–60+ 54.3%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Mental disorders (mental illness)
Pietropaolo 2022 [42] United States TriNetX COVID-19 Research Network	Jan 2020 to Jun 2021	Retrospective cohort *N* = 4,070,133	NR Minimum of 1 d to maximum of 18 mos	Mixed	0–30 45%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Diabetes (type 1 & type 2)
Qureshi 2022 [43] United States Cerner Real-World Data	Until July 2021	Retrospective cohort *N* = 20,806	Median (IQR) – 182 (113–277) days	Inpatient	0–70+ 39%	100 NR	Concurrent >90% had test negative	Neurological conditions (dementia)
Rao 2022 [44] US Electronic health record data from PEDSnet institutions	Mar 2020 to Oct 2021	Retrospective cohort *N* = 659,286	Cov: Mean (SD) – 4.6 (0.7) Weeks Con: Mean (SD) – 4.7 (0.7) weeks	Mixed	0–21 47.2%	6 2.2	Concurrent >90% had test negative	Mental disorders (mental health treatment); Neurological conditions (communication/motor disorders)
Rezel-Potts 2022 [45] United Kingdom Clinical Practice Research Datalink Aurum	Feb 2021 to Jan 2022	Retrospective cohort *N* = 857,300	Median – 12 mos	Mixed	— 56%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (atrial arrhythmias, heart failure, myocardial infarction and ischaemic heart disease); Diabetes (type 1 & type 2); Stroke
Roessler 2022 [46] Germany Data from 6 German statuatory health insurance organizations: AOK Bayern – Die Gesundheitskasse, AOK PLUS, BARMER, BKKen, DAK Gesundheit, and Techniker Krankenkasse	By Jun 2020	Retrospective cohort *N* = 314,268	Cov: Mean (SD) – 236 (44) days Con: Mean (SD) – 254 (36) days	Mixed	0–18 48.1%	1 0.4	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (cardiac arrhythmias, heart failure, heart murmurs, myocardial infarction, other cardiac arrhythmias); Mental disorders (adjustment disorder, anxiety disorders, depressive disorders, emotional and behavioural disorders, obsessive-compulsive disorder); Neurological conditions (chronic fatigue syndrome, developmental delay, dyslexia, facial nerve paralysis, headache, movement disorders, other coordination disorders/ataxia, seizures, speech and language disorders); Stroke
Tartof 2022 [16] United States Vaccine Safety Datalink	Mar 2019 to Mar 2021	Retrospective cohort *N* = 255,718	NR Maximum of 6 mos	Inpatient	0–85+ 53.7%	100 NR	Concurrent >90% had test negative	Diabetes; Mental disorder (anxiety disorders, psychosis); Stroke Only <18y data eligible for meta-analysis
Taquet 2022 [47] United States TriNetX COVID-19 Research Network	Jan 2020 to Mar 2022	Retrospective cohort *N* = 2,568,874	Cov: Mean (SD) – 213 (204) days Con: Mean (SD) – 223 (203) days	Mixed	0–65+ 57.8%	NR	Concurrent >90% had test negative	Mental disorders (anxiety disorders, mood disorders, psychotic disorder); Neurological conditions (cognitive deficit, dementia, Guillain-Barre syndrome, myoneural junction/muscle disease, nerve/nerve root/plexus disorder, Parkinsonism, seizure); Stroke
Taquet 2021 [48] United States TriNetX COVID-19 Research Network	Jan 2020 to Apr 2022	Retrospective cohort *N* = 89,558	NR 14 days to 90 days	Mixed	65+	NR	Concurrent >90% had test negative	Neurological conditions (dementia; other outcomes not analysed by age strata)

(*Continued*)

Table 1. Continued.

Study Country Data source	Index time for SARS-CoV-2 infections	Study design N	Mean/ median follow-up, range If not reported, maximum range of FU?	Care type/setting for SARS-CoV-2 infected cases	Age range (years) % Female	% Hospitalized % in ICU	Comparator timing Test status of comparator group	Outcomes
Wang 2022a [49] United States TriNetX COVID-19 Research Network	Feb 2020 to May 2021	Retrospective cohort *N* = 820,956	NR Maximum of 360 days	Mixed	65–85+ 57%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Neurological conditions (Alzheimer's disease)
Wang 2022b [50] United States TriNetX COVID-19 Research Network	Jan 2019 to Mar 2022	Retrospective cohort *N* = 1,381,784	NR Minimum of 30 days to maximum of 12 mos	Mixed	20–65+ 54%	NR	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (acute coronary disease, angina, atrial fibrillation and flutter, bradycardia, cardiac arrest, cardiogenic shock, cardiomyopathy, heart failure, ischaemic cardiomyopathy, myocardial infarction, tachycardia, ventricular arrhythmias); Stroke
Westman 2022 [51] Sweden SmiNET, Swedish National Patient Register	Feb 2020 to Dec 2021	Prospective cohort *N* = 2,445,113	NR Maximum of 22 mos	Mixed	21–100+ 51%	NR	Historical NA	Neurological conditions (epilepsy)
Xie 2022a [52] United States Department of Veterans Health Administration	Mar 2020 to Sept 2021	Prospective cohort *N* = 4,299,721	Cov: Median (IQR) – 352 (244–406) days Con: Median (IQR) – 352 (245–406) days	Mixed	0–65+ 11.5%	8.3 2.2	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Diabetes
Xie 2022b [53] United States Department of Veterans Health Administration	Mar 2020 to Jan 2021	Prospective cohort *N* = 5,827,407	Cov: Median (IQR) – 347 (317–440) days Con: Median (IQR) – 348 (318–441) days	Mixed	0–65+ 10%	10.9 3.5	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Cardiovascular disease (dysrhythmia, ischaemic heart disease); Stroke
Xu 2022 [54] United States Department of Veterans Health Administration	Mar 2020 to Jan 2021	Prospective cohort *N* = 5,815,067	Cov: Median (IQR) – 408 (378–500) days Con: Median (IQR) – 348 (318–441) days	Mixed	0–65+ 10%	10.8 3.4	Concurrent No confirmed/ suspected SARS-CoV-2 infection	Mental disorders (anxiety disorders, major depressive disorders, psychotic disorders, stress/adjustment disorders); Neurological conditions (Alzheimer's disease, memory problems)
Zarifkar 2022 [55] Denmark Electronic health records from Capital Region and Region Zealand	Feb 2020 to Nov 2021	Prospective cohort *N* = 238,699	NR Maximum of 12 mos	Mixed	18–80+ Inpatients: 51% female Outpatients:40% females	18.5 NR	Concurrent >90% had test negative	Neurological conditions (Alzheimer's disease, Guillain-Barre syndrome, multiple sclerosis, myasthenia gravis, Parkinson's disease); Stroke

Con: control group; Cov: SARS-CoV-2 infected group; FU: follow-up; ICU: intensive care unit; IQR: interquartile range; mos: months; NA: not applicable; NR: not reported; SD: standard deviation.

Table 2. Risk of bias assessment according to JBI's Cohort Studies tool.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Overall
Abel 2021	Y	N	U	Y	Y	Y	Y	U	U	U	Y	Moderate
Ayoubkhani 2021	N	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	High
Bohlken 2022	Y	N	N	Y	Y	Y	Y	Y	Y	NA	Y	High
Chevinsky 2021	U	U	Y	Y	Y	Y	Y	N	U	U	U	Moderate
Cohen 2022	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Moderate
Daugherty 2021	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Donnachie 2022	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	High
Jacob 2022	Y	N	Y	Y	U	Y	Y	U	U	Y	U	Moderate
Kompaniyets 2022	Y	N	Y	Y	U	Y	Y	Y	U	Y	Y	Moderate
Park 2021	Y	N	U	Y	Y	Y	Y	Y	Y	NA	Y	Moderate
Pietropaolo 2022	Y	N	Y	Y	Y	Y	U	Y	U	U	Y	Moderate
Qureshi 2022	Y	Y	Y	Y	Y	Y	Y	Y	U	U	U	Moderate
Rao 2022	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Low
Rezel-Potts 2022	Y	N	U	Y	Y	Y	Y	Y	Y	NA	Y	Moderate
Roessler 2022	Y	N	U	Y	Y	Y	U	Y	U	Y	U	Moderate
Taquet 2022	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y	Moderate
Taquet 2021	Y	N	U	Y	Y	Y	Y	N	U	U	Y	High
Tartof 2022	Y	Y	U	Y	Y	U	Y	Y	Y	NA	Y	Low
Wang 2022a	Y	N	Y	Y	Y	Y	Y	Y	U	U	Y	Moderate
Wang 2022b	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Low
Westman 2022	Y	N	Y	Y	Y	Y	Y	U	Y	NA	Y	Moderate
Xie 2022a	Y	N	Y	Y	Y	Y	Y	U	Y	NA	Y	Moderate
Xie 2022b	Y	N	Y	Y	Y	Y	Y	U	U	U	Y	Moderate
Xu 2022	Y	N	Y	Y	Y	Y	Y	U	U	U	Y	Moderate
Zarifkar 2022	Y	Y	Y	Y	U	U	Y	Y	U	U	U	Moderate

N: no; NA: not applicable; U: unsure; Y: yes.

Questions:

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?*
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the condition/diagnosis of interest at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons for loss to follow up described and explored
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

*Most studies got "No" for this question because they relied on the *absence* of a positive SARS-CoV-2 test/diagnosis to identify the control group (i.e. the control group was not tested and we considered this differential ascertainment in exposure).

ndition categories and individual conditions for which we had moderate or high certainty were limited to the outpatient/mixed care group and are outlined below.

For ≥65 year-olds, we have high certainty that SARS-CoV-2 infection is associated with a small-to-moderate increase of any cardiovascular disorder, acute coronary disease, arrhythmias/dysrhythmias, and heart failure. For 18–64 year-olds, we have high certainty of a large increase in cardiomyopathy and of a small-to-moderate increase of heart failure. For all age groups (<18 y, 18–64 y, ≥ 65 y), we have high certainty of little-to-no difference in anxiety/anxiety disorders.

For individuals <18 years old, we have moderate certainty of a small-to-moderate increase in trauma and stress disorders, chronic fatigue syndrome, and stroke; and moderate certainty of little-to-no difference in arrhythmias/dysrhythmias, chronic kidney disease, type 2 diabetes, and asthma.

For 18–64 year-olds, we have moderate certainty of a large increase in encephalopathy, interstitial lung disease, and respiratory failure; moderate certainty of a small-to-moderate increase of any cardiovascular disorder, acute coronary disease, arrhythmias/dysrhythmias, hypertension, chronic kidney disease, myoneural junction/muscle disease, dementia/mild cognitive disorder, and haemorrhagic stroke; and moderate certainty of little-to-no difference for depression/mood disorders.

Among individuals ≥65 years old, we have moderate certainty of a large increase of encephalopathy, interstitial lung disease, and respiratory failure; moderate certainty of a small-to-moderate increase of cardiomyopathy, hypertension, any diabetes, type 2 diabetes, any mental disorder, psychosis/psychotic disorders, myoneural junction/muscle disease, communication and motor disorders, dementia/mild cognitive disorder, epilepsy, haemorrhagic stroke, and transient ischaemic attack; and, moderate certainty of little-to-no difference for depression/mood disorders.

Two studies reported on how associations varied across time since infection or by variant of concern (Table 4). Change in risk over time since SARS-CoV-2 infection likely differs between conditions; however, there is not enough evidence to draw condition-specific conclusions at this time. One study reported on differing risks across variants of concern which suggested that risks may differ across variants, but these differences may also be confounded by

Table 3. Summary of Findings for new diagnoses of chronic conditions after SARS-CoV-2 infection.

Outcome	Subgroup Number of Studies	Relative findings HR (95% CI)	Conclusion Certainty for relative findings	Excess cases per 1000 people over 6 monthss (95% CI)
Cardiovascular disorders				
1. Any cardiovascular disorder	Inpatients, 18–64 y 1 study	4.30 (1.93–9.57)*	Small-to-moderate increase Low[a,b]	11.87 (3.35–30.82)
	Inpatients, ≥ 65 y 1 study	2.90 (2.26–3.72)	Large increase Low[a,b]	45.79 (30.36–65.55)
	Outpatients/mixed, < 18y 2 studies	1.16 (1.12–1.20)	Little-to-no difference Low [b,c,1]	NE
	Outpatients/mixed, 18–64 y 4 studies	1.62 (1.21–2.17)	Small-to-moderate increase Moderate [d]	1.29 (0.44–2.43)
	Outpatients/mixed, ≥ 65 y 3 studies	1.82 (1.57–2.13)	Small-to-moderate increase High	12.41 (8.62–17.1)
2. Acute coronary disease	Outpatients/mixed, < 18y 1 study	3.32 (0.42–26.23)	Very Low [b,D]	NE
	Outpatients/mixed, 18–64 y 4 studies	1.54 (1.16–2.06)	Small-to-moderate increase Moderate [d]	0.53 (0.16–1.04)
	Outpatients/mixed, ≥ 65 y 3 studies	1.79 (1.52–2.10)	Small-to-moderate increase High	6.23 (4.1–8.67)
3. Arrhythmias/ dysrhythmias	Outpatients/mixed, < 18y 2 studies	1.21 (1.02–1.44)	Little-to-no difference Moderate [d]	NE
	Outpatients/mixed, 18–64 y 4 studies	1.69 (1.46–1.96)	Small-to-moderate increase Moderate [b]	3.88 (2.59–5.4)
	Outpatients/mixed, ≥ 65 y 3 studies	1.83 (1.65–2.02)	Small-to-moderate increase High	12.56 (9.84–15.43)
4. Cardiomyopathy	Outpatients/mixed, 18–64 y 2 studies	2.81 (2.31–3.42)	Large increase High	1.26 (0.91–1.69)
	Outpatients/mixed, ≥ 65 y 2 studies	1.90 (1.16–3.13)	Small-to-moderate increase Moderate [d]	6.19 (1.1–14.65)
5. Heart failure	Outpatients/mixed, < 18y 1 study	0.56 (0.08–3.92)	Very Low [b,D]	NE
	Outpatients/mixed, 18–64 y 3 studies	2.07 (1.71–2.52)*	Small-to-moderate increase High	0.92 (0.61–1.3)
	Outpatients/mixed, ≥ 65 y 2 studies	2.01 (1.77–2.27)*	Small-to-moderate increase High	12.77 (9.73–16.05)
6. Hypertension	Outpatients/mixed, 18–64 y 1 study	1.70 (1.55–1.87)	Small-to-moderate increase Moderate [b]	6.45 (5.07–8.02)
	Outpatients/mixed, ≥ 65 y 1 study	1.70 (1.36–2.13)	Small-to-moderate increase Moderate [b]	3.6 (1.85–5.81)
Chronic kidney disease				
7. Any chronic kidney disease	Inpatients, 18–64 y 1 study	3.50 (2.65–4.63)	Large increase Low [a,b]	5.22 (3.44–7.57)
	Inpatients, ≥ 65 y 1 study	2.04 (1.00–4.13)	Very low [a,b,d]	NE
	Outpatients/mixed, < 18 y 1 study	1.07 (0.94–1.21)	Little-to-no difference Moderate [b]	NE
	Outpatients/mixed, 18–64 y 1 study	1.60 (1.29–1.98)	Small-to-moderate increase Moderate [b]	1.33 (0.64–2.17)

(*Continued*)

Table 3. Continued.

Outcome	Subgroup Number of Studies	Relative findings HR (95% CI)	Conclusion Certainty for relative findings	Excess cases per 1000 people over 6 monthss (95% CI)
	Outpatients/mixed, ≥ 65 y 1 study	1.36 (1.21–1.53)	Small-to-moderate increase Low [b,d]	6.96 (4.06–10.25)
Diabetes				
8. Any diabetes	Inpatients, 18–64 y 1 study	1.70 (1.60–1.81)	Small-to-moderate increase Low [a,b]	14.18 (12.15–16.4)
	Inpatients, ≥ 65 y 1 study	1.46 (1.12–1.89)	Very low [a,b,d]	NE
	Outpatients/mixed, < 18y 3 studies	1.05 (0.78–1.40)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 4 studies	1.27 (1.07–1.52)	Small-to-moderate increase Low [b,d]	3.1 (0.8–5.97)
	Outpatients/mixed, ≥ 65 y 2 studies	1.65 (1.21–2.24)	Small-to-moderate increase Moderate [d]	14.43 (4.66–27.53)
9. Type 1	Outpatients/mixed, < 18y 2 studies	1.23 (1.13–1.33)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 1 study	0.54 (0.32–0.89)	Very Low [b,c,2,d]	NE
10. Type 2	Outpatients/mixed, < 18y 2 studies	1.17 (1.11–1.23)	Little-to-no difference Moderate [b]	NE
	Outpatients/mixed, 18–64 y 2 studies	1.34 (0.72–2.47)	Small-to-moderate increase Low [b,d]	0.92 (−0.75–3.96)
	Outpatients/mixed, ≥ 65 y 1 study	1.96 (1.60–2.40)	Small-to-moderate increase Moderate [b]	5.9 (3.69–8.61)
Mental disorders				
11. Any mental disorder	Outpatients/mixed, < 18y 6 studies	1.06 (0.88–1.28)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 7 studies	1.35 (1.22–1.49)	Small-to-moderate increase Low [b,d]	9.04 (5.68–12.66)
	Outpatients/mixed, ≥ 65 y 7 studies	1.54 (1.34–1.76)	Small-to-moderate increase Moderate [b]	21.12 (13.3–29.73)
12. Anxiety/anxiety disorders	Outpatients/mixed, < 18y 4 studies	0.95 (0.83–1.09)	Little-to-no difference High	NE
	Outpatients/mixed, 18–64 y 3 studies	1.08 (0.94–1.25)	Little-to-no difference High	NE
	Outpatients/mixed, ≥ 65 y 2 studies	1.04 (0.87–1.26)	Little-to-no difference High	NE
13. Depression/mood disorders	Outpatients/mixed, < 18y 3 studies	1.02 (0.78–1.32)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 3 studies	1.06 (0.98–1.15)	Little-to-no difference Moderate [b]	NE
	Outpatients/mixed, ≥ 65 y 2 studies	1.17 (1.12–1.22)	Little-to-no difference Moderate [d]	NE
14. Psychosis/psychotic disorders	Outpatients/mixed, < 18y 2 studies	0.65 (0.07–6.56)	Very Low [B,d]	NE
	Outpatients/mixed, 18–64 y 1 study	1.18 (1.08–1.29)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, ≥ 65 y 2 studies	1.89 (0.97–3.66)	Small-to-moderate increase Moderate [d]	1.27 (−0.04–3.79)

(*Continued*)

Table 3. Continued.

Outcome	Subgroup Number of Studies	Relative findings HR (95% CI)	Conclusion Certainty for relative findings	Excess cases per 1000 people over 6 monthss (95% CI)
15. Trauma and stress disorders	Outpatients/mixed, < 18y 1 study	1.71 (1.42–2.06)	Small-to-moderate increase Moderate [b]	54.67 (32.34–81.62)
	Outpatients/mixed, 18–64 y 1 study	1.42 (1.09–1.85)	Small-to-moderate increase Low [b,d]	0.61 (0.13–1.23)
Musculoskeletal disorders				
16. Any musculoskeletal disorder	Outpatients/mixed, < 18y 2 studies	1.28 (0.65–2.55)	Very low [b,c,3,d]	NE
17. Myoneural junction/muscle disease	Outpatients/mixed, < 18y 1 study	1.90 (1.19–3.03)	Small-to-moderate increase Low [b,d]	0.13 (0.03–0.29)
	Outpatients/mixed, 18–64 y 1 study	1.88 (1.71–2.07)	Small-to-moderate increase Moderate [b]	0.7 (0.57–0.86)
	Outpatients/mixed, ≥ 65 y 1 study	1.82 (1.61–2.05)	Small-to-moderate increase Moderate [b]	1.72 (1.28–2.21)
Neurological disorders				
18. Any neurological disorder	Outpatients/mixed, < 18y 6 studies	1.29 (1.01–1.65)	Small-to-moderate increase Low [b,d]	11.27 (8.38–14.43)
	Outpatients/mixed, 18–64 y 7 studies	1.55 (0.85–2.84)	Small-to-moderate increase Low [b,d]	4.83 (−1.32–16.16)
	Outpatients/mixed, ≥ 65 y 9 studies	1.40 (1.22–1.62)	Very low [b,c,4,d]	NE
19. Chronic fatigue syndrome	Outpatients/mixed, < 18y 2 studies	2.46 (1.89–3.19)*	Small-to-moderate increase Moderate [b]	0.63 (0.38–0.95)
	Outpatients/mixed, 18–64 y 1 study	2.03 (1.34–3.06)*	Small-to-moderate increase Low [a,b]	1.94 (0.64–3.88)
	Outpatients/mixed, ≥ 65 y 1 study	1.12 (1.01–1.24)	Little-to-no difference Low [a,b]	NE
20. Communication and motor disorders	Outpatients/mixed, < 18y 3 studies	1.19 (1.08–1.30)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 3 studies	1.13 (0.73–1.75)	Very low [b,D]	NE
	Outpatients/mixed, ≥ 65 y 3 studies	1.28 (1.14–1.43)	Small-to-moderate increase Moderate [d]	0.15 (0.07–0.23)
21. Dementia/mild cognitive disorder	Inpatients, 18–64 y 1 study	0.98 (0.69–1.39)	Very low [b,D]	NE
	Inpatients, ≥ 65 y 1 study	6.17 (0.14–279.99)	Very low [b,D]	NE
	Outpatients/mixed, 18–64 y 6 studies	2.55 (1.27–5.13)*	Small-to-moderate increase Moderate [b]	0.61 (0.11–1.61)
	Outpatients/mixed, ≥ 65 y 8 studies	1.58 (1.37–1.82)	Small-to-moderate increase Moderate [b]	2.11 (1.34–2.98)
22. Encephalopathy	Outpatients/mixed, 18–64 y 1 study	6.26 (4.02–9.75)	Large increase Moderate [b]	1.83 (1.05–3.05)
	Outpatients/mixed, ≥ 65 y 1 study	3.36 (2.87–3.93)	Large increase Moderate [b]	19.9 (15.77–24.71)
23. Epilepsy	Outpatients/mixed, < 18y 2 studies	1.09 (0.61–1.93)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, 18–64 y 3 studies	0.97 (0.70–1.36)	Little-to-no difference Low [b,d]	NE

(*Continued*)

Table 3. Continued.

Outcome	Subgroup Number of Studies	Relative findings HR (95% CI)	Conclusion Certainty for relative findings	Excess cases per 1000 people over 6 monthss (95% CI)
	Outpatients/mixed, ≥ 65 y 3 studies	1.40 (1.11–1.77)	Small-to-moderate increase Moderate [d]	1.2 (0.33–2.31)
24. Guillian-Barre syndrome	Outpatients/mixed, < 18y 1 study	2.20 (0.88–5.50)*	Small-to-moderate increase Low [b,d]	0.05 (0–0.17)
	Outpatients/mixed, 18–64 y 3 studies	1.09 (0.91–1.32)	Little-to-no difference Low [b,d]	NE
	Outpatients/mixed, ≥ 65 y 3 studies	1.13 (0.90–1.43)	Little-to-no difference Low [b,d]	NE
25. Migraine	Outpatients/mixed, 18–64 y 1 study	1.29 (1.12–1.48)	Small-to-moderate increase Low [b,d]	1.53 (0.63–2.54)
	Outpatients/mixed, ≥ 65 y 1 study	1.26 (1.03–1.55)	Small-to-moderate increase Low [b,d]	1.92 (0.22–4.06)
26. Multiple sclerosis	Outpatients/mixed, 18–64 y 1 study	0.76 (0.35–1.65)	Very low [b,D]	NE
	Outpatients/mixed, ≥ 65 y 1 study	2.36 (0.88–6.31)*	Small-to-moderate increase Low [b,d]	0.13 (−0.01–0.51)
27. Nerve disorders	Outpatients/mixed, < 18y 2 studies	1.15 (0.50–2.63)	Very low [b,c,5,d]	NE
	Outpatients/mixed, 18–64 y 3 studies	1.32 (0.95–1.83)	Very low [b,c,5,d]	NE
	Outpatients/mixed, ≥ 65 y 3 studies	1.10 (0.77–1.56)	Very low [b,c,5,d]	NE
Respiratory disorders				
28. Any respiratory disorder	Inpatients, 18–64 y 1 study	10.50 (9.65–11.43)	Large increase Low [a,b]	168.04 (153.01–184.49)
	Inpatients, ≥ 65 y 1 study	6.86 (3.06–15.39)	Large increase Low [a,b]	385.92 (135.66–947.68)
	Outpatients/mixed, < 18y 2 studies	1.25 (0.68–2.29)	Small-to-moderate increase Low [D]	NE (no control rate data available)
	Outpatients/mixed, 18–64 y 1 study	8.94 (5.42–14.73)	Large increase Low [b,c,6]	2.82 (1.57–4.88)
	Outpatients/mixed, ≥ 65 y 1 study	3.65 (2.95–4.51)	Large increase Low [b,c,6]	10.84 (7.98–14.36)
29. Asthma	Outpatients/mixed, < 18y 1 study	1.00 (0.99–1.01)	Little-to-no difference Moderate [b]	NE
30. Interstitial lung disease	Outpatients/mixed, 18–64 y 1 study	7.71 (4.94–12.04)	Large increase Moderate [b]	2.38 (1.4–3.92)
	Outpatients/mixed, ≥ 65 y 1 study	3.07 (2.44–3.87)	Large increase Moderate [b]	8.47 (5.89–11.74)
31. Respiratory failure	Outpatients/mixed, 18–64 y 1 study	12.85 (6.39–25.84)	Large increase Moderate [b]	1.74 (0.79–3.66)
	Outpatients/mixed, ≥ 65 y 1 study	4.53 (3.50–5.87)	Large increase Moderate [b]	10.52 (7.45–14.51)
Stroke				
32. Any stroke	Outpatients/mixed, < 18y 4 studies	1.31 (0.95–1.81)	Small-to-moderate increase Moderate [d]	0.03 (0–0.08)
	Outpatients/mixed, 18–64 y 7 studies	1.19 (1.01–1.40)	Little-to-no difference Low [b,d]	NE

(*Continued*)

Table 3. Continued.

Outcome	Subgroup Number of Studies	Relative findings HR (95% CI)	Conclusion Certainty for relative findings	Excess cases per 1000 people over 6 monthss (95% CI)
	Outpatients/mixed, ≥ 65 y 5 studies	1.23 (1.00–1.51)	Little-to-no difference Low [b,d]	NE
33. Haemorrhagic stroke	Outpatients/mixed, 18–64 y 1 study	2.59 (1.41–4.75)*	Small-to-moderate increase Moderate [b]	0.38 (0.1–0.9)
	Outpatients/mixed, ≥ 65 y 1 study	2.04 (1.68–2.47)*	Small-to-moderate increase Moderate [b]	6.83 (4.46–9.65)
34. Ischaemic stroke	Outpatients/mixed, < 18y 1 study	1.89 (1.15–3.10)	Small-to-moderate increase Low [b,d]	0.22 (0.04–0.53)
	Outpatients/mixed, 18–64 y 3 studies	0.84 (0.51–1.37)	Very low [b,D]	NE
	Outpatients/mixed, ≥ 65 y 3 studies	0.98 (0.65–1.49)	Very low [b,D]	NE
35. Transient ischaemic attack	Outpatients/mixed, 18–64 y 1 study	1.45 (1.19–1.76)	Small-to-moderate increase Low [b,d]	NE (no control rate data available)
	Outpatients/mixed, ≥ 65 y 1 study	1.63 (1.39–1.91)	Small-to-moderate increase Moderate [b]	NE (no control rate data available)

CI: confidence interval; HR: hazard ratio; NE: not estimated.

GRADE legend: *Rated as Small-to-moderate effect for greater certainty due to less concern around lack of precision in the effect estimate; A = ROB, B = lack of consistency (including >80% contribution to estimate from 1 study), C = Indirectness (reasons in footnotes), D = imprecision

Lowercase and capital letters represent downrating that domain for one or two steps, respectively. Conclusions are reported only for outcomes with at least Low certainty.

Footnotes:

1 Largest contribution to estimate (>99%) from Kompaniyets, which has only one outcome in this category (cardiac dysrhythmias)

2 Concerns about indirectness because of age (i.e. Type 1 DM is very rare in individuals >30 years)

3 one of two studies reporting any MSK outcome only reported on a single condition (Myoneural junction/muscle disease)

4 three out of nine studies (35.6% weight) contributing to this outcome report only on dementia

5 "nerve disorders" were rarely well defined by included studies

6 Composite composed only of chronic respiratory failure and interstitial lung disease, therefore may not be generalizable to other respiratory disorders (E.g. COPD).

Note**:** Chevinksy 2021 reported on 31 different conditions across 7 categories, but did not stratify results for adults (≥18 y; ∼15% of sample was ≥65 y), and reported broad results for children (<18 y) stating "Children with COVID-19 were not more likely to experience new diagnoses than children without COVID-19." Since no effect size or variance was reported for children, this study was not included in the meta-analysis. Despite attempts to contact the authors, we were unable to obtain more detailed paediatric results.

Table 4. Summary of time-varying effects and subgroup analyses by variant in a systematic review of new diagnoses of chronic conditions after SARS-CoV-2 infection.

Study	Age group	Conditions reported	Time varying effects	Effects across Variants
Rezel-Potts 2022 [45]	18–64 y	Cardiovascular disease, diabetes	For both cardiovascular disease and diabetes, IRR was highest at 4–7 weeks, decreasing over time to IRR ~1 by 24 weeks.	Not reported
Taquet 2022 [47]	<18 y, 18–64 y, ≥ 65 y	Many	Outcomes fell into three categories: (1) within 2 years, HRs have returned to baseline (e.g. mood disorder, anxiety disorder, and ischaemic stroke) and cumulative incidence equalizes between cohorts; (2) HRs have returned to baseline within 2 years but equal cumulative incidence was not reached (i.e. myoneural junction or muscle disease); (3) HRs remained greater than 1 at the end of the follow-up period and new diagnoses are being made more frequently after COVID-19 diagnosis than after a diagnosis of another respiratory infection up to 2 years after the index event (e.g. dementia, psychotic disorders, epilepsy). These different risk trajectories were broadly similar in children, adults, and older adults.	Alpha vs. Delta vs. Omicron. Risk profiles differed across variants. Alpha: 6-month HRs did not notably change from before to after emergence of Alpha. Delta: Increased 6-month HRs of anxiety disorders, insomnia, cognitive deficit, epilepsy or seizures, and ischaemic strokes, but a lower risk of dementia, were observed in those diagnosed after the emergence of the delta variant compared to those diagnosed before. These risks were compounded by an increased risk of death. Omicron: After Omicron, patients were at an increased risk (over 140 days of follow-up) of dementia, mood disorders, and nerve, nerve root, and plexus disorders, and at a broadly similar risk of most other outcomes. All risks were largely offset by a reduced risk of death after the emergence of omicron. The authors concluded: "The decreased composite risks of death and neurological or psychiatric sequelae are reassuring for patients. However, the ongoing risk of individual outcomes indicates that health services will likely continue to face a similar rate of these post-COVID-19 diagnoses even with SARS-CoV-2 variants that lead to otherwise less severe disease."

HR: hazard ratio; IRR: incidence rate ratio.

average severity of acute disease and mortality of each variant. We did not identify any studies eligible for our review that looked at differences in risk between vaccinated vs. unvaccinated groups.

Discussion

We conducted a systematic review to identify associations between SARS-CoV-2 infection and exacerbations of pre-existing or new diagnoses of chronic conditions. We stratified analyses by age category and severity of SARS-CoV-2 infection (using hospitalization during acute phase of infection as a proxy) to enable meaningful interpretation of the findings and because these are strong predictors of severity of outcomes both in the acute [24] and recovery stages of COVID-19 [25]. After SARS-CoV-2 infection, there is probably an increased risk of new diagnoses for some, but not all chronic conditions. In general, we had the most certainty in associations between SARS-CoV-2 infection and new diagnoses of chronic conditions, especially cardiac conditions, in outpatient/mixed care samples aged ≥65 years. People in this age category are already at increased risk of many chronic conditions and are more susceptible to poor outcomes after SARS-CoV-2 infection [24,26]. We also had moderate to high certainty in associations between SARS-CoV-2 infection and at least a small increase of new diagnoses of several chronic conditions in individuals 18–64 years old and a few chronic conditions in individuals <18 years (i.e. trauma and stress disorders, chronic fatigue syndrome, and stroke). We identified only two eligible studies reporting on associations between hospitalization with SARS-CoV-2 infection and new diagnosis of chronic conditions. While it is widely recognized that severity of initial SARS-CoV-2 infection leads to poorer long-term outcomes [25], we were not able to draw conclusions in any age group regarding an association between SARS-CoV-2 infection and subsequent new diagnoses of chronic conditions among individuals hospitalized during the acute infection phase. Finally, although we did not identify any eligible studies reporting on exacerbations of pre-existing chronic conditions after SARS-CoV-2 infection, this does not preclude the existence of this relationship for some conditions.

While previous systematic reviews have reported on the incidence of newly diagnosed chronic conditions after SARS-CoV-2 infection or reported on associations with specific conditions [7–12], this is the first systematic review we are aware of that reports on associations between SARS-CoV-2 infection and new diagnoses of a wide range of chronic conditions specifically by age group. Our strict eligibility criteria, including the requirement to account for sex and relevant comorbidities, also likely reduced the number of eligible studies at high risk of bias. Overall, our findings suggest that there is probably an increased risk of diagnoses for some – but not all – chronic

conditions after SARS-CoV-2 infection. In general, cardiovascular diseases and respiratory conditions showed the most consistent effects across adult age categories and disease severities. These associations have implications for decision makers in both policy and healthcare systems at a time when healthcare systems are already under considerable strain As the number of individuals infected by SARS-CoV-2 increases, so too will the number of new diagnoses for chronic conditions, leading to increased health care utilization in the form of specialty care, follow-up with primary care providers and increasing medication and treatment costs at either the patient or system level.

One notable gap highlighted by our review is the lack of evidence around cancer diagnoses after SARS-CoV-2 infection. This is not surprising, as there has likely been insufficient time since the start of the pandemic for disease processes and diagnosis, and longitudinal studies of this association have already been proposed [27]. However, such studies will have to be conducted with careful considerations of the impacts of the pandemic apart from SARS-CoV-2 infection. Public health restrictions during the early waves of the pandemic created access barriers to cancer screening and diagnosis, creating a potential backlog of missed screenings [28]. This may have resulted in delayed diagnoses and therefore will need to be controlled for in the study design of any longitudinal studies examining cancer incidence after SARS-CoV-2 infection.

We also found very few eligible studies examining how the potential risk of being diagnosed with a new chronic condition changes over time since SARS-CoV-2 infection, as well as across different variants of concern. Based on human tissue cultures and animal models, SARS-CoV-2 variants may preferentially infect or replicate in different organ systems or tissues [29–31], and thus may result in a changing constellation of new chronic disease diagnoses after SARS-CoV-2 infection.

Limitations

As with any systematic review, our synthesis comes with some limitations. First, while we made attempts to limit study eligibility to only those reporting on conditions documented or diagnosed by a medical provider, for some conditions it was not always possible to differentiate between chronic disorders versus persistent post-COVID symptoms. Additionally, while most studies included in this review used International Classification of Diseases (ICD)-10 codes (or similar administrative coding systems) to define outcomes of interest, there was substantial variation across studies in which codes were used to define each condition. This likely contributed to the substantial heterogeneity in estimates for some conditions. Second, some of the chronic conditions of interest are much simpler to diagnose than others. For example, diagnosis of type 2 diabetes relies on empirical signs and biological markers that can be objectively measured and diagnosed by primary care providers, whereas it may take a longer time after initially seeking care to be diagnosed with conditions such as chronic fatigue syndrome or mood disorders because they are typically diagnosed by specialists that patients may or may not have access to. Third, we included studies using control groups that did not explicitly require a negative SARS-CoV-2 test; thus it is possible in these studies that some individuals may have had a SARS-CoV-2 infection, especially during later stages of the pandemic when testing patterns shifted towards at-home testing [56]. This potential contamination in some control groups may result in underestimated associations between SARS-CoV-2 infection and new chronic conditions diagnoses, including confounding the true existence of associations for which we have reported little-to-no association. Fourth, although some of the included studies attempted to control for differences in care-seeking behaviour between control and SARS-CoV-2 infected groups (e.g. by matching on index date and only including control participants with at least one health care contact after their determined index visit), we did not evaluate this potential confounder as part of our synthesis. Although we would not expect the ability to obtain a diagnosis to differ between infected and non-infected people who have sought care, there are likely differences in the number of health care contacts between the groups. Thus, some of the associations identified in our review may be the result of surveillance biases. In other words, an undiagnosed chronic condition may have been present in some individuals prior to SARS-CoV-2 infection, but seeking care for the infection (and subsequent health care contacts for follow-up) resulted in the undiagnosed condition being diagnosed when it otherwise may not have been until further on in the disease progression. Lastly, we used the event rates in non-SARS-CoV-2 infected control groups to estimate the excess incidence for conditions in which we had at least low certainty of some direction of effect, standardized to rates over six months; however, event rates were not always reported as 6-month rates. Our estimate of excess incidence assumes that the incidence of new diagnoses in the SARS-CoV-2 group is constant, e.g. that the rate is the same 2 months after infection as it is 6 months after infection, and there is no evidence that this assumption holds true.

Conclusion

After SARS-CoV-2 infection, there is probably an increased risk of diagnoses for some, but not all,

chronic conditions. However, the extent of increased risk that is directly caused by SARS-CoV-2 is uncertain due to other factors, such as increased health care contacts or monitoring in infected individuals, which are difficult to fully account for in observational study designs. Although the findings of this review likely apply well to the pandemic period, reflecting the pandemic's current impact on healthcare availability and people infected by the virus, it is uncertain whether the impact will remain stable into future years. Finally, how this risk changes over time since infection or by variant of concern is uncertain.

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Data availability statement

Data are available from the authors on reasonable request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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