Saskatchewan Health Authority

University of Saskatchewan

## COVID-19 Evidence Support Team
# RAPID REVIEW REPORT

Long COVID: What does it mean for the healthcare system and programs to deal with it?


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**Version:** 2 **Review History:** EOC021901 RR : March 15, 2021

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Full author statement available at the end of report.

**Note: latest updates will appear in red.**

## Updated Key Findings

October 29, 2021

- In October, WHO released a consensus definition of post COVID-19 condition that includes 12 domains. This development should lead to better standardization of reporting and contribute to more precise prevalence estimates and better understanding of associated risk factors.
- The effects of Variants of Concern (VoC) and COVID vaccination on progression of Long COVID symptoms remains unclear.
- Risk factors for developing Long COVID symptoms were similar but limited evidence suggests that pre-pandemic psychological distress and poor general health were associated with developing persistent symptoms. Evidence is too limited to determine whether vaccination reduces the risk of developing Long COVID among persons with breakthrough infections.
- Given the protean manifestations of Long COVID symptoms, the underlying causes are likely multifactorial; however, strong evidence to substantiate the theories of causation remains limited.
- Research related to longer-term consequences of SARS CoV-2 infections in pediatric populations is growing but remains limited.

## Key Findings

March 15, 2021

- There is a lack of consensus around the clinical definition of Long COVID which in turn causes challenges with understanding the incidence and prevalence as well as the potential impact for the health care system
- Information about the natural history of Long COVID is incomplete but limited evidence suggests that the immune response trajectories differ for those with few or no symptoms compared to those with severe disease. Individuals with severe disease are more likely to exhibit immunological marker abnormalities but anyone can experience functional limitations.
- The mechanisms underlying the development of persistent symptoms in Long COVID remain an enigma. Despite multiple theories, there is little empirical evidence for specific immunological and or biochemical abnormalities in samples of individuals with symptoms consistent with Long COVID.
- Risk factors for Long COVID include female gender, older age, higher body mass index, pre-existing asthma and the number of symptoms.
- Few studies explored the short-term impact of Long COVID on health care utilization patterns and found a higher impact for those with severe disease compared with mild disease.

## Limitations

- Several studies were published as pre-print and have not been peer reviewed.
- Few studies followed patients for longer than six months post onset of illness/diagnosis hence it is not possible to determine the duration of chronic symptoms.
- Only two studies involved children and included small samples small samples.
- Variation exists across studies with regard to use of validated instruments to capture information.

## Strength of Evidence

☐ Mature evidence
☒ Emerging Supportive evidence
☐ Mixed evidence
☐ Weak evidence

## Quality of Evidence Assessment

1. **Adequacy of primary studies**: The overwhelming majority of studies included systematic reviews, rapid evidence syntheses and cohort studies. There were a few case control studies and case reports. Most studies had been peer reviewed with fewer pre-prints.

2. **Methodological limitations**: Although there are many more systematic reviews, meta-analyses are uncommon because of the marked heterogeneity across studies in population characteristics, sample size, duration of follow up, methods of symptom assessment and approaches to data collection. Further, there is limited reporting of confounding factors such as comorbid conditions. Among cohort studies, few have access to pre-pandemic information and

incorporate control groups for comparisons. The duration of follow up is relatively short for most studies (i.e. less than 3 months) limiting the examination of symptoms over a longer period that is more consistent with the new definition. Some risk factors are less explored such as socioeconomic factors that may also be important. Literature reviews focused on exploring pathophysiology and underlying causes of Long COVID included scant information about the methods.

3. **Relevance to review question**: Studies were generally relevant to the review questions although seldom addressed the implications of COVID variants of concern and vaccination.

4. **Generalizability of findings**: The findings are generalizable to adult populations in developed contexts and more studies are occurring in outpatient contexts than in the prior review. However, studies are also increasingly system/organ focused (e.g. cardiovascular, respiratory, neuropsychological) making it difficult to get a comprehensive picture of this complex condition.

## Background/Context

**1. Clinical Context**

Estimates of the incidence and prevalence of Long COVID are variable; however, even the most conservative estimates suggest that a potentially large group of individuals may be affected by functional impairment and chronic care needs. Consequently, health care systems need a better understanding of the longer-term consequences of SARS CoV-2 infections to plan and respond appropriately. A burgeoning body of research continues to be published and it is necessary to stay abreast of key developments in the field. An update to a prior review was requested to determine if more mature evidence was available about the clinical spectrum, risk factors for developing Long COVID and the underlying pathophysiology of the condition.

**2. Purpose**

This rapid review was conducted to support health decision makers' response to the COVID pandemic. This review seeks to identify, appraise, and summarize emerging research evidence to support evidence-informed decision-making.

**3. Review Question(s)**

- What symptom profiles occur most frequently among those who develop Long COVID?
- Who is at risk of developing Long COVID symptoms? How does this risk change with infection from variants of concern or post COVID vaccination?
- What are the potential underlying causes of Long COVID symptoms?

## Method

For each Rapid Review, the initial question is posed by a decision-maker in the health care system seeking the evidence base for a specific policy decision. According to the subject of the question, the COVID Evidence Support Team (CEST) Intake Committee allocates the question to the appropriate Working Group. Each Working Group may be comprised of a librarian, researcher, 1-2 clinicians, 1-2 subject matter experts, and a group leader. A reference interview is conducted to establish the parameters of the question to ensure it is articulated in a clear, searchable manner. The librarians assigned to the team then conduct a thorough search of the indexed literature, grey literature,

news sources, or other sources as agreed upon. Some reference lists for especially pertinent articles are also reviewed. An Evidence Search Report is thereby created. See Appendix for more details on the search strategy. A Rapid Review of the identified literature is then performed by the researcher using the approach of a systematic review, but without a double review, formal assessment of quality of reported study, or meta-analysis. Importantly, the review is completed in a time-sensitive manner. Relevant evidence is summarized in both tabular and narrative form, key findings and limitations articulated, and the quality of the body of evidence evaluated using a four-point grading system that assesses the methodologies, adequacy of the included studies, the direct relevance to the question and the generalizability of the findings related to the question. The draft Rapid Review Report is reviewed and edited by the Working Group clinicians, experts, and leader. Once revisions are complete, the Rapid Review is submitted to the requesting decision-maker and placed in the COVID-19 repository and database. For certain topics with rapidly changing evidence, after a period of time an updated evidence search is performed, the review process repeated, and an updated Rapid Review released.

## Summary of Evidence

This review is based on 23 studies with just over half comprising systematic or rapid reviews of existing studies (n=13). Most of the studies focused on the epidemiology of Long COVID including prevalence and frequency of symptoms as well as risk factors. Study settings often included developed contexts with majority of adults who had been previously hospitalized. Only three studies pertained to children. Many studies followed participants for a period less than 3 months post disease onset now considered the minimum duration for symptoms. Few studies reported the duration of symptoms.

The recent release of a consensus definition of post COVID-19 condition is a welcome development in this field.[1] According to the WHO:

> *Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis.*[1]

Based on expert consensus, post COVID-19 condition remains a diagnosis of exclusion; however, it does not rely on laboratory confirmation of SARS CoV-2 infection given the limited availability of testing earlier in the pandemic. It usually occurs three months after symptom onset and lasts for at least 2 months. Although common symptoms are mentioned, there is no minimum number of symptoms to satisfy the criteria and may be new, persistent, fluctuating or relapse over time. It is anticipated that there will be greater standardization of reporting symptoms in the future and better estimation of prevalence and risk of the disorder.

**Epidemiology**

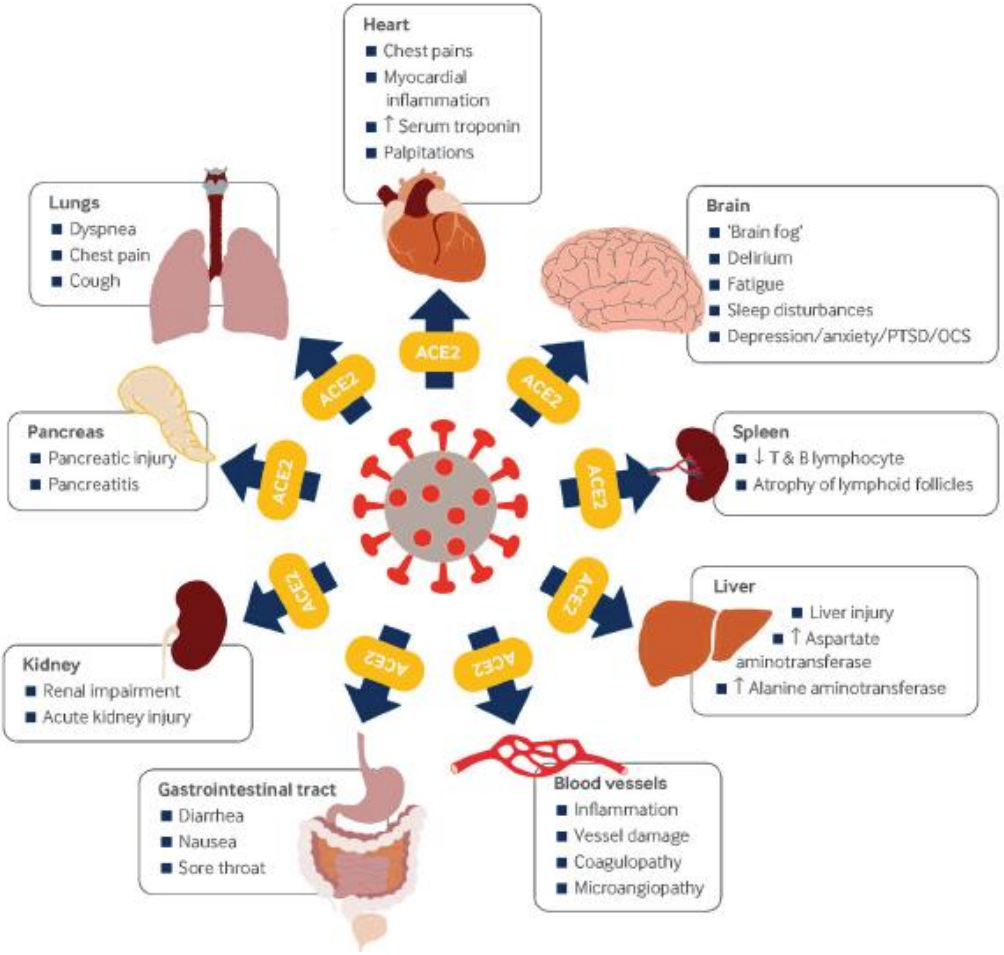
The growing body of research has established that Long COVID can occur following mild, severe or even asymptomatic SARS CoV-2 infections.[1,2] It can also occur in pediatric populations although thought to be less common.[3-6] In general, those patients with more severe acute disease were more expected to experience significant longer-term consequences.[7] The natural history of Long COVID symptoms is unclear but most individuals appear to get better with time.[7]

**Clinical manifestations**

It has been challenging to establish the exact prevalence of Long COVID symptoms because of variations in timing of assessment, symptoms and methods of assessment and populations studied.[8,9] Common symptoms in studies with the longest follow up include fatigue and asthenia as well as cognitive

manifestations such as memory and concentration difficulties.[8,10-13] Other symptoms that have often been reported include breathlessness, myalgia, headache, anosmia/ageusia and palpitations.[9,10,14-16]

Figure 1 shows the various symptoms that may occur in persons experiencing Long COVID[2]




Little is known about the effects of COVID Variants of Concern (VoC) on the development of persistent symptoms.[8,9] Further, few studies have explored the effects of COVID vaccination on progression of Long COVID symptoms.[8,17] One rapid review based on limited evidence suggested that more adverse effects occur peri-immunization with improvement in LC symptoms over time.[8] Another recent study among 620 French adults with prior probable or confirmed SARS CoV-2 infection reported variation of LC symptoms following COVID vaccination.[17] In this study the impact of SARS-CoV-2 vaccination on Long COVID symptoms was not different depending the vaccine used (p=0.60). A worsening of symptom severity was reported by 117 patients (31% of vaccinated patients) and were mostly represented by fever/chills (74%), gastro-intestinal symptoms (70%), paresthesia (64%) and arthralgia (63%). Conversely, symptom improvement was reported by 83 (21.8%) and included anosmia (62%) and brain fog (51%). Vaccine impact on LC symptoms lasted more than 2 weeks in 67.8% of patients. It was noted that the most frequently reported worsening symptoms were similar to those reported by the general population.[17]

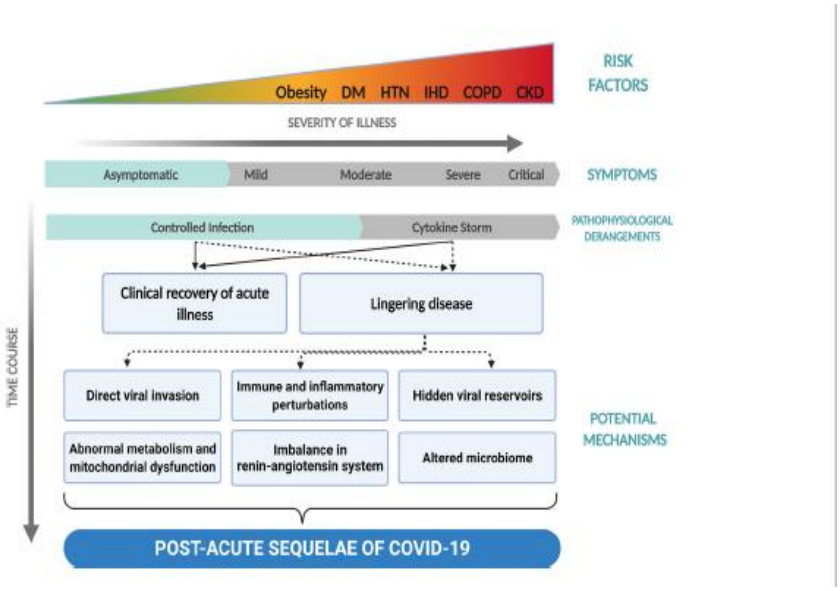
**Risk factors**

It is not completely understood who is more likely to develop persistent symptoms after SARS CoV-2 infections. However, the following risk factors have been identified in several studies: age, gender, number of comorbidities, and reported symptoms.[8,11,12, 18-20] A UK study based on several large longitudinal cohorts also reported that poor pre-pandemic mental health (OR=1.46 [1.17-1.83), poor general health (OR=1.62 [1.25-2.09]) as well as having asthma (OR=1.32 [1.07-1.62]) or being overweight/obese (OR=1.25 [1.01-1.55]) was associated with high risk of symptoms.[18] It might also be that specific symptoms or clusters are associated with different risk factors. A recent review found inconsistent results for the relationship between disease severity, persistent fatigue, respiratory symptoms, pulmonary function, functional capacity, and health related quality of life.[21]

**Pathophysiology of Long COVID**

Although the post COVID-19 condition is increasingly being recognized, the exact mechanisms still remain a mystery. The causes of persisting symptoms is likely to be multifactorial.[22] There are several mechanisms that have been proposed to explain long COVID symptoms; however, aberrant cellular or humoral immunity responses are believed to be the main contributors to pathogenesis.[20,23] Figure 2 shows several of the potential mechanisms that have some supporting evidence. These pathways include: a)residual viral tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs, b) delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue repair, c) cross reactivity of SARS-CoV-2-specific antibodies with host proteins resulting in autoimmunity, d) mitochondrial dysfunction and impaired immunometabolism, e) alterations in microbiome, and f) imbalance in renin-angiotensin system.

Figure 2: Development of Long COVID symptoms and putative mechanisms[23]




*Viral reservoirs*

Evidence to support the presence of viral reservoirs has come from intestinal biopsies and post-mortem studies that show viral particles in multiple organs. It is thought that viral reservoirs may also occur in immune-privileged sites such as the brain and lead to chronic infection.[22,23] The viral reservoir theory is consistent with evidence of long term viral shedding from the respiratory and gastrointestinal tracts in some COVID-19 patients that extended over three months.[22,23] A more recent study has discovered SARS-

CoV-2 nucleic acids and proteins in the small intestines of 50% of asymptomatic COVID-19 cases at 4-month post-disease onset. These observations suggest that SARS persistence is possible and might be inducing immune activation and contributing to Long COVID symptoms.[23]

*Autoimmunity*

Viral induced autoimmunity is another mechanism that has been proposed as SARS-CoV-2-specific antibodies can cross-react with mammalian host proteins.[20] Anti-neuronal autoreactive antibodies have been detected in COVID-19 patients with neurological symptoms indicating the likelihood for the development of autoimmune neurological sequelae, such as autoimmune encephalitis.[20,22] Autoantibodies such as antiphospholipid antibody and other antibodies against interferons, neutrophils, connective tissues, cyclic citrullinated peptides, and cell nucleus have been identified in serum of COVID patients.[20,22] While it isn't know if the autoantibodies are long lasting; autoantibodies have been linked to chronic autoimmune conditions such systemic lupus erythematosus and rheumatoid arthritis that bear some symptomatic resemblance to Long COVID.[22,23]Additionally, thyroid dysfunction has been detected in 15–20% of patients with COVID-19. As the thyroid is closely linked to T-cell-mediated autoimmunity, thyroid dysfunction may play a role in the autoimmunity pathophysiology of long COVID.[23]

*Immune exhaustion*

Chronic viral infections can also lead to immune exhaustion due to prolonged antigen stimulation. Notably, a marked decrease in the absolute number and functional exhaustion of anti-viral cytotoxic lymphocytes, including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, were reported in patients with SARS-CoV-2 infection, particularly in those with severe disease. The main features of T cell exhaustion include reduced cytokine production, lack of clonal expansion, upregulation of co-inhibitory receptors, altered metabolism, impaired proliferation and memory cell response.[23]

*Gut dysbiosis*

The disruption of gut microbiome has been observed in some COVID patients.[22,23]When detected, gut dysbiosis also correlated with increased COVID-19 severity and inflammatory biomarkers and prolonged SARS-CoV-2 faecal shedding. It has also been reviewed that the gut microbiome modulates the neurotransmitter circuitries in the gut and brain *via* the microbiota-gut-brain axis. Hence, persistent gut dysbiosis may also contribute to the gastrointestinal and neurological symptoms of long COVID.[22,23]

*Abnormal immunometabolism and mitochondrial dysfunction*

SARS CoV-2 has been shown to modulate mitochondrial function. In turn, ACE2 regulation of mitochondria and other proteins could lead to viral replication and evasion of host immunity. Compromised mitochondrial function and energy insufficiency in COVID-19 patients may lead to metabolic reprograming in the infected cells and a metabolic switch to glycolysis.[23]A similar mechanism could be responsible for the chronic fatigue observed in patients with long COVID-19.

In addition, the elevated cytokine levels induced by SARS-CoV-2 may facilitate pancreatic beta cell hyperstimulation and insulin resistance leading to exhaustion and subsequent onset of metabolic alterations. Recently, abnormalities in beta cell function, insulin resistance and glycometabolic control were documented in a cohort of hospitalized COVID-19 patients. The patients did not have a prior history of diabetes and changes persisted for at least 2 months post disease onset suggesting that it could play a role in post COVID-19 condition.[23]

*Imbalance of the Renin-Angiotensin System (RAS)*
SARS-CoV-2 has a special affinity for angiotensin-converting enzyme-2 (ACE-2) receptors found in abundance in organs such as lungs, liver, kidneys, and blood vessels.[23] The virus attaches and penetrates the host cell, and starts damaging the organ. It erodes into the capillary endothelium, causing endothelitis and leads to the formation of microthrombi. The virus also stimulates the inflammatory cascade, causing significant release of cytokines and chemokines leading to cytokine storm in severe cases. The resultant organ damage caused by such excessive inflammatory response takes much longer to recover and is responsible for the symptoms of Long-COVID-19.[23] Researchers have reported the immune dysregulation behind the prothrombotic state and its related conditions in COVID-19 patients.

## Conclusions

The body of research related to Long COVID is rapidly growing. However, lack of a standardized definition and tools for symptom assessment has limited our understanding of clinical manifestations and associated risk factors. There remains uncertainty about the causal mechanisms and their relationship to condition risk factors. More studies with longer follow up of non-hospitalized cohorts that also include pediatric populations and controls for comparison are needed. A better understanding of the role of variants and vaccination is also needed.

## Table 1: Summary of Evidence

Consult the Summary of Evidence table using the following link:

- https://covid19evidencereviews.saskhealthauthority.ca/en/permalink/coviddoc397

This link provides access to the database where it is possible to view the spreadsheet for review.

## Reference List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## Appendix 1: Evidence Search Details

**Note:** To view full search strategy details, please consult the associated Evidence Search Report.

| | |
|---|---|
| **Filters, Limits & Exclusions:** | English only<br>February 24, 2021 – Current |
| **Sources Searched:** | • CADTH<br>• CanCOVID<br>• CEBM (UK)<br>• COVID Evidence Alerts McMaster<br>• COVID-END<br>• COVID-19 Best Evidence Front Door<br>• COVID-19 Rapid Evidence Link<br>• Embase<br>• Evidence Synthesis Network (Ontario)<br>• Evidence Check Australia<br>• Google/Google Scholar<br>• HSE Ireland<br>• L-OVE<br>• McMaster Forum<br>• MEDLINE<br>• medRxiv<br>• National Collaborating Centre for Methods and Tools<br>• Norwegian Institute of Public Health<br>• Public Health Ontario<br>• Veteran's Affairs Database<br>• WHO Global Research Database |
| **Librarian(s):** | Michelle Dalidowicz, Clinical Librarian, Saskatchewan Health Authority<br>Mark Mueller, Clinical Librarian, Saskatchewan Health Authority |

## Appendix 2: Evidence Search Strategies

*Copied from the most current ESR.*

**MEDLINE**

**Ovid MEDLINE(R) ALL <1946 to October 18, 2021>**

| # | Searches | Results |
|---|---|---|
| 1 | COVID-19/ or SARS-CoV-2/ | 113419 |
| 2 | (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/) | 40070 |
| 3 | (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2 or coronavirus*).ti,ab,kf,nm,ox,rx,px. | 195866 |
| 4 | ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf. | 54463 |
| 5 | ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf. | 9933 |

| | | |
|---|---|---|
| 6 | ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf. | 369 |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 | 200400 |
| 8 | limit 7 to (english language and yr="2021 -Current") | 107185 |
| 9 | Long Term Adverse Effects/ or Recurrence/ or Symptom Flare Up/ or Symptom Assessment/ | 199081 |
| 10 | ((long-term or long term or long-tail or long tail or longitudinal* or chronic* or persist* or permanent or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) adj2 (condition? or symptom* or complicat* or consequence* or outcome* or effect* or aftereffect? or after-effect? or after effect? or manifest*)).ti,ab,kf. | 378783 |
| 11 | (sequela* or long-COVID* or long COVID* or chronic-COVID or chronic COVID or long-hauler? or long hauler?).ti,ab,kf,kw. | 74669 |
| 12 | 9 or 10 or 11 | 632358 |
| 13 | (post-acute or postacute or post-hospital* or posthospital* or post-discharg* or postdischarg*).ti,ab,kw,kf. or ((post or after or follow*) adj2 (discharge? or release? or hospital*)).ti,ab,kf. | 114495 |
| 14 | (postcovid* or post-covid* or postcoronavirus* or post-coronavirus*).ti,ab,kw,kf. | 2231 |
| 15 | 13 or 14 | 116542 |
| 16 | 8 and 12 and 15 | 668 |
| 17 | (sequela* or long-COVID* or long COVID* or chronic-COVID* or chronic COVID* or post-acute COVID* or post acute COVID*).ti. | 12474 |
| 18 | 8 and 17 | 459 |
| 19 | Longitudinal Studies/ or Follow-Up Studies/ or exp Randomized Controlled Trials as Topic/ or Randomized Controlled Trial/ or Random Allocation/ | 1517666 |
| 20 | (((study or studies) adj1 (follow-up or followup or follow up or longitudinal)) or (random* or clinical trial? or RCT?)).ti,ab. or "clinical trial".pt. or tu.fs. | 3888191 |
| 21 | 19 or 20 | 4531545 |
| 22 | 8 and 12 and 21 | 581 |
| 23 | 8 and 17 and 21 | 55 |
| 24 | 16 or 18 or 22 or 23 | 1371 |
| 25 | remove duplicates from 24 | 1362 |
| 26 | limit 25 to dt=20210224-20211231 | 1099 |
| 27 | Systematic Review/ or systematic reviews as topic/ or exp Review/ or exp Review Literature as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ | 3026899 |
| 28 | (meta-analys?s or meta anals?s or systematic review? or meta-regression* or metaregression*).ti,ab,kw,kf. or ((systematic* or rapid or methodologic* or quantitative or integrative or scoping or literature or collaborative or research or evidence or data or umbrella or comprehensive or state-of-the-art or "state of the art" or up-to-date or "up to date") adj3 (review* or overview* or synthes*)).ti,ab,kf. or (pool adj2 analy*).ti,ab. | 811859 |

| | | |
|---|---|---|
| 29 | (systematic review or meta-analysis).pt. | 242288 |
| 30 | 27 or 28 or 29 | 3287983 |
| 31 | 26 and 30 | 239 |

**Embase**

**Embase <1974 to 2021 October 20>**

| # | Searches | Results |
|---|---|---|
| 1 | exp coronavirus disease 2019/ or exp severe acute respiratory syndrome coronavirus 2/ | 164967 |
| 2 | (exp Coronavirinae/ or exp betacoronavirus/ or exp Coronavirus infection/) and (disease outbreaks/ or exp epidemic/ or pandemic/) | 78919 |
| 3 | (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2 or coronavirus*).ti,ab,kw,px. | 198131 |
| 4 | ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kw. | 51811 |
| 5 | ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kw. | 11583 |
| 6 | ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kw. | 413 |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 | 214664 |
| 8 | limit 7 to (abstracts and english language and yr="2021 -Current") | 85730 |
| 9 | exp disease course/ or recurrent disease/ or symptom assessment/ | 3741258 |
| 10 | ((long-term or long term or long-tail or long tail or longitudinal* or chronic* or persist* or permanent or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) adj2 (condition? or symptom* or complicat* or consequence* or outcome* or effect* or aftereffect? or after-effect? or after effect? or manifest*)).ti,ab,kf. | 540888 |
| 11 | (sequela* or long-COVID* or long COVID* or chronic-COVID or chronic COVID or long-hauler? or long hauler?).ti,ab,kf,kw. | 93389 |
| 12 | 9 or 10 or 11 | 4195893 |
| 13 | (post-acute or postacute or post-hospital* or posthospital* or post-discharg* or postdischarg*).ti,ab,kw,kf. or ((post or after or follow*) adj2 (discharge? or release? or hospital*)).ti,ab,kf. | 182054 |
| 14 | (postcovid* or post-covid* or postcoronavirus* or post-coronavirus*).ti,ab,kw,kf. | 2483 |
| 15 | 13 or 14 | 184291 |
| 16 | 8 and 12 and 15 | 1334 |
| 17 | (sequela* or long-COVID* or long COVID* or chronic-COVID* or chronic COVID* or post-acute COVID* or post acute COVID*).ti. | 10520 |
| 18 | 8 and 17 | 299 |

| | | |
|---|---|---|
| 19 | longitudinal study/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trial/ or randomization/ | 1115419 |
| 20 | (((study or studies) adj1 (follow-up or followup or follow up or longitudinal)) or (random* or clinical trial? or RCT?)).ti,ab. or "clinical trial".pt. or tu.fs. | 2294784 |
| 21 | 19 or 20 | 2576400 |
| 22 | 8 and 12 and 21 | 1641 |
| 23 | 8 and 17 and 21 | 35 |
| 24 | 16 or 18 or 22 or 23 | 2953 |
| 25 | remove duplicates from 24 | 2920 |
| 26 | limit 25 to conference abstract status | 608 |
| 27 | 25 not 26 | 2312 |
| 28 | limit 27 to dd=20210224-20211231 | 500 |
| 29 | exp "systematic review"/ or exp "review"/ or exp "systematic review (topic)"/ or exp meta analysis/ or exp "meta analysis (topic)"/ | 2960605 |
| 30 | (meta-analys?s or meta anals?s or systematic review? or meta-regression* or meta regression*).ti,ab,kw,kf. or ((systematic* or rapid or methodologic* or quantitative or integrative or scoping or literature or collaborative or research or evidence or data or umbrella or comprehensive or state-of-the-art or "state of the art" or up-to-date or "up to date") adj3 (review* or overview* or synthes*)).ti,ab,kf. or (pool adj2 analy*).ti,ab,kf. | 997673 |
| 31 | 29 or 30 | 3379154 |
| 32 | 28 and 31 | 116 |

**Keywords Used in Other Resources:**

- COVID or Coronavirus or SARS-2 or nCOV
- "long covid" or "COVID sequelae" or "post acute covid" or "post covid syndrome" or "long haulers" or “post acute covid syndrome” or “chronic covid” or “long hauler” or PACS"
- Chronic symptoms or long-term effects or long-term symptoms or post-acute or sequelae or persistent symptoms or post-covid syndrome or after care or rehabilitation or post-discharge or follow-up

Review or overview or meta analysis or meta-analysis or synthesis

## Appendix 3: Review History

List in reverse chronological order (newest first)

| Previous Review Date | Review Code |
|---|---|
| March 15, 2021 | EOC021901 RR |
| | |

## Authorship & Contact


| | |
|---|---|
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The authors declare they have no conflicts of interest to report.