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National COVID-19 Health and Research Advisory Committee*

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Advice 12: Evidence for long-term consequences/sequelae of COVID-19

Contents

* NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Summary

- There is evidence about the long-term sequelae of COVID-19. However, this evidence is limited.
- The proportion of people with COVID-19 reporting persistence of at least one symptom following recovery from the acute disease varies greatly across studies.
- While there is some limited evidence that the presence of long-term sequelae of COVID-19 may be related to severity of the initial COVID-19 disease, persistent symptoms have also been reported in those with initially mild disease.
- The long-term post-acute symptoms with the highest reported incidence following COVID-19 infection are fatigue, breathlessness or shortness of breath, loss of or impaired sense of smell and/or taste, chest pain and sleep disorders.
- The full spectrum of long-term sequelae of COVID-19 is emerging, and some long-term sequelae may not yet have manifested as symptoms.
- The long-term sequelae of COVID-19 affect the health of individuals and the population. However, current evidence is insufficient to quantify the level of disease burden for individuals and the population, and for health systems.
- Long-term sequelae documented in survivors of SARS and MERS may predict potential long-term sequelae in COVID-19 survivors.
- Emerging issues related to long-term sequelae of COVID-19 include:
  - the need for collection of data from a broader patient set that is representative of the wider community, including children, adolescents and young adults, and people whose initial presentation of COVID-19 may be mild or asymptomatic
  - the long-term detrimental effects of the COVID-19 pandemic itself, including containment measures, on mental health and wellbeing
  - the impacts of the pandemic on health care workers
  - the preparedness of the health system for the care and management of people experiencing long-term sequelae of COVID-19.
- Ongoing research is essential to obtain evidence about the long-term sequelae of COVID-19.

Focus

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was requested to provide advice to the Chief Medical Officer on the evidence for long-term consequences/sequelae of COVID-19.

The focus of this advice paper is the long-term consequence/sequelae (hereafter referred to as sequelae) arising from the direct effects of infection with SARS-CoV-2. Long-term sequelae for both people remaining in the community and those hospitalised with COVID-19 were considered. For the purposes of this document, 'long-term' is defined as follows:

- For community cases: after the post-infectious period; that is, approximately 10–14 days after infection with SARS-CoV-2.[1]
- For hospitalised cases: post-acute hospitalisation.

All sequelae were considered, both physical (respiratory and non-respiratory) and mental health sequelae, with the focus on key areas as supported by the literature. Broader social and economic impacts on people were out of scope for this advice paper, but are important and related considerations (see 'Other considerations').

Notes

This advice paper has been developed at a point in time and may require review as further evidence becomes available. NCHRAC's conclusions are outlined below. The conclusions represent the expert interpretation of relevant evidence as at 16 November 2020.

Limitations

- the lack of high quality evidence about the long-term sequelae of COVID-19 because of the relatively short time since the emergence of the disease
- the inconsistent evidence arising from highly variable study settings, population samples, outcomes measures and available resources (e.g. the availability of COVID-19 testing for affected people).

This advice paper was developed by an NCHRAC working group (see membership at **Attachment 1**).

Introduction

As at 15 November 2020, 53,766,728 confirmed cases of COVID-19, including 1,308,975 deaths, were reported to the World Health Organization (WHO).[2] COVID-19 is a complex multisystem disease that is not restricted to the respiratory system. Other organ systems that may be affected include the cardiovascular, neurological, renal, gastrointestinal, musculoskeletal and haematological systems.[3] In addition to the acute effects from the SARS-CoV-2 virus, evidence is emerging about long-term sequelae that may be experienced following recovery from acute COVID-19 infection.[4,5,6,7]

Long-term sequelae of COVID-19 may arise from the pathogenic effects of the SAR-CoV-2 virus on multiple body systems.[8] Treatments and interventions during the acute care for

people with COVID-19 (e.g. medications, intubation, ventilation, emergency procedures) and from the experience of having a severe disease and/or being in an intensive care unit may also play a role. However, the long-term sequelae arising from these factors may not be unique to COVID-19 and are not the focus of this advice paper.

Method

The development of this advice paper was informed by an evidence review, expert advice and other literature.

Evidence review

The aim of the evidence review was to identify a body of high quality evidence reporting the post-acute (long-term) sequelae of COVID-19. The evidence search sought to identify reliable and relevant systematic reviews and cohort studies.

Given the relatively short time-frame of the COVID-19 pandemic with the disease emerging in December 2019 and the potential for limited evidence about long-term sequelae, pre-print articles were considered as well as peer-reviewed articles. As pre-prints are shared before peer review, these articles are clearly identified in the reference list and should be interpreted with caution. Because prospective studies require time to follow patients, and to analyse and report results, it was expected that the evidence included in any systematic reviews identified would be observational and retrospective.

Further information about the evidence search is provided in **Attachment 2**.

A summary of the outcomes from the evidence search for long-term sequelae of COVID-19 is provided in **Attachment 3**. Each article should be interpreted in the context of the stated objective of each study. In summary:

- 1,705 papers were identified following the evidence search.
- 30 papers meet the criteria for inclusion. Of these:
  - five were systematic reviews (four of these were pre-prints)
  - 19 were cohort studies (10 of these were pre-prints)
  - six were cross-sectional studies (five of these were preprints).
- Two of the systematic reviews provided results for SARS/MERS sequelae.

Expert advice

The development of this advice paper was also informed by expert advice, including consultation with external experts invited to present to working group meetings (see **Attachment 1**).

Other literature

Grey literature, including expert consensus and position statements and guidance documents published by other groups and institutions, was also considered.

Evidence for long-term consequences/sequelae of COVID-19 is continually emerging and constantly being updated. If this advice paper is updated, the 'living evidence' approach

should be taken using continuous evidence surveillance and rapid response pathways to incorporate new relevant evidence into recommendations as soon as it becomes available.[9]

Conclusions

This section of the paper consists of three parts:

1. Conclusions based on current evidence and expert advice. The primary approach adopted for presentation of the evidence is patient-centric, based on symptoms reported by those affected.
2. Emerging themes or areas of concern where future consideration and research is recommended.
3. Current studies and studies under development that aim to provide evidence for long-term sequelae of COVID-19.

Part 1: Evidence and expert advice

NCHRAC conclusion 1: There is evidence about the long-term sequelae of COVID-19. However, this evidence is limited.

The experience of patients with long-term sequelae of COVID-19 (often described as 'long COVID' or 'post-acute COVID-19') has been reported in the literature and the general and scientific media.[10,11,12,13,14] However, high quality evidence about the long-term sequelae of COVID-19 is limited, primarily because of the short time interval since emergence of the disease. In addition, the majority of evidence that is available about the long-term sequelae of COVID-19 is based on adult patients who have been hospitalised. As most people with COVID-19 are not sufficiently ill to require hospitalisation[15], and hospitalised patients are more likely to have severe illness or existing co-morbidities, the available evidence may not be representative of the wider population experience. Additional limitations of the available evidence are outlined in **Attachment 3** and include small sample sizes, variation in study outcome measures, and samples that may not be representative of the populations of interest.

In the absence of evidence of long-term sequelae arising from COVID-19, inferences were drawn from other coronavirus infections, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), where possible and appropriate.

The reported incidence of long-term sequelae is summarised in **Attachment 4**. This summary is presented as:

A. symptoms reported by patients
B. sequelae related to organ systems/specific disorders.

1.1 Symptoms

NCHRAC conclusion 2: The proportion of people with COVID-19 reporting persistence of at least one symptom following recovery from the acute disease varies greatly across studies.

The range of the reported incidence of at least one persistent symptom following recovery from acute COVID-19 is reflective of the variation and limitations of the evidence base and indicates the need for more extensive studies. Nevertheless, the evidence does support the existence of persistent symptoms in a proportion of people infected with SARS-CoV-2.

Most current reports about the persistence of at least one symptom following recovery from acute COVID-19 are based on cohort studies of hospitalised patients, with symptoms assessed between 1–3 months following onset of initial symptoms, COVID-19 diagnosis, or discharge from hospital.

Two studies suggest that the persistence of at least one symptom in COVID-19 positive people was significantly higher compared to COVID-19 negative people and the general population:[15,16]

- In a population study involving 21,359 respondents (comprising 233 COVID-19 positive cases, 3,652 COVID-19-negative controls, and 17,474 non-tested individuals), where only 3.4% of the COVID-19 positive cases reported having been hospitalised, 24.1% of COVID-19 positive participants reported at least one symptom 90 days after initial onset of symptoms. This compares to 13.3% for those with negative tests. In contrast, only 6.0% of participants from the general untested population developed new symptoms lasting longer than 90 days due to any illness during the same study period.[15] (**Attachment 5, Figure 1**)
- A study of 538 adult hospitalised patients reported persistence of at least one symptom in 49% of patients three months after discharge, compared to 12% in the comparison group (COVID-negative volunteers).[16]

Several other studies report the incidence of the persistence of at least one symptom in 44.3%–87.4% of hospitalised and non-hospitalised COVID-19 patients.[15,17,18,19,20] A study of 111 hospitalised COVID-19 patients reported persistence of at least one symptom in 74% of patients 8–12 weeks after onset of symptoms or discharge from hospital.[17] Furthermore, even in patients who did not require oxygen in hospital and are therefore similar to many symptomatic individuals who may have self-cared or been managed by primary care, 59% had ongoing symptoms.[17] In contrast, a study of 131 hospitalised patients reported that only 9.2% of patients had one or more symptoms in the fourth week after discharge from hospital.[21]

NCHRAC conclusion 3: While there is some limited evidence that the presence of long-term sequelae of COVID-19 may be related to severity of the initial COVID-19 disease, persistent symptoms have also been reported in those with initially mild disease.

The incidence of long-term symptoms following recovery from acute COVID-19 as reported in some cohort and cross-sectional studies appears to be higher in those with more severe

initial illness.[3,15,17,19,21,22] However, the persistence of at least one symptom is reported even in those with mild initial illness:

- In a cohort study of 110 patients post-hospitalisation[17], ongoing symptoms were reported in 59% (16/27) patients in the mild COVID-19 group compared to 75% (49/65) and 89% (16/18) in the moderate and severe groups respectively.
- A higher incidence of persistent symptoms was reported in COVID-19 cases who were initially more ill (>five initial symptoms) (59.4% at 30 days and 40.6% at 90 days). However, even for mild (<five initial symptoms) and initially asymptomatic cases, 14.3% had complications that persisted for 30 days or longer.[15]

NCHRAC conclusion 4: The long-term post-acute symptoms with the highest reported incidence following COVID-19 infection are fatigue, breathlessness or shortness of breath, loss of or impaired sense of smell and/or taste, chest pain and sleep disorders.

NCHRAC conclusion 5: The full spectrum of long-term sequelae of COVID-19 is emerging, and some long-term sequelae may not yet have manifested as symptoms.

NCHRAC conclusion 6: The long-term sequelae of COVID-19 affect the health of individuals and the population. However, current evidence is insufficient to quantify the level of disease burden for individuals and the population, and for health systems.

The outcomes of the evidence search show the most commonly reported symptoms that persist after recovery from acute COVID-19 are fatigue, breathlessness or shortness of breath, loss of or impaired sense of smell and/or taste, chest pain and sleep disorders. Several studies compared persistent symptoms following recovery from acute COVID-19 to symptoms during the acute phase of COVID-19[17] or on admission to hospital.[18] (**Attachment 5, Figures 2 and 3**).

1.1.1 Fatigue

The reported incidence of fatigue following recovery from acute COVID-19 ranged from 10%–72%.[16,17,18,19,22,23,24,25,26,27]

All studies reporting persistent fatigue were cohort studies involving hospitalised COVID-19 patients, assessed between 4–12 weeks after initial onset of symptoms or discharge from hospital. Evidence of the relationship between persistent fatigue and the severity of the initial disease varied, with some studies reporting no relationship.[17,19,26] Higher incidence of persistent fatigue was reported in patients admitted to the intensive care unit (ICU) or subject to mechanical ventilation (13.5% compared to 10.8% in patients with non-severe illness[25]; 72% in patients admitted to ICU compared to 60.3% in patients managed in the hospital ward without needing ICU care[22]). An association with the length of hospital stay was also reported.[16]

Female gender[16,26] and those with a pre-existing diagnosis of depression/anxiety[26] were over-represented in those with fatigue. The level of persistent fatigue in health care workers was reported to be 27% at 10.4 weeks following onset of symptoms.[24]

It has been suggested that persistent fatigue experienced by people following recovery from acute COVID-19 shares similar features to conditions such as Chronic Fatigue Syndrome (CFS).[27]

1.1.2 Breathlessness

While breathlessness, shortness of breath or dyspnoea is a commonly reported persistent symptom following recovery from acute COVID-19, the reported incidence is variable. Several cohort studies reported the persistence of this symptom in 14.8%–74.3% of hospitalised and community cases of COVID-19, assessed between 4–12 weeks after discharge from hospital or onset of symptoms.[15,17,18,20,22,24,25,28] However, some studies outline a lower incidence of dyspnoea in hospitalised COVID-19 patients following discharge from hospital. For example, in one study dyspnoea was reported in only 2.9% of patients with severe COVID-19 (1.5% of total moderate and severe cases) four weeks following discharge.[21] A report of dyspnoea in only 4% of hospitalised patients (50 days after diagnosis) was attributed to 'dyspnoea' not being specifically included in the protracted symptoms checklist used in the study.[19]

Expert advice provided to the working group suggests that the underlying cause of breathlessness following recovery from acute COVID-19 was not clear. This symptom could be related to physiological changes such as damage to the lungs or heart.

1.1.3 Loss/impairment of smell and taste

Loss or impaired sense of smell and/or taste are frequent initial symptoms of COVID-19. They are also reported as persistent symptoms following recovery from the acute disease in both community and hospitalised cases, between 4 weeks and 119 days after symptom onset, diagnosis of COVID-19 or discharge from hospital.[15,19,20,25,27,29,30,31]

The reported incidence of persistent loss (anosmia) or impaired sense of smell (hyposmia) varied, ranging from 1.4%–25% and 4.5%–44.7% respectively.[19,20,25,29,29,29,31] The reported incidence of persistent loss (ageusia) or impaired sense of taste (hypogeusia) ranged from 4.1%–11.5% and 5.6%–27.6% respectively.[19,20,29,31]

Disorders of smell and taste were described as being most prevalent at the earliest stages of the disease, with the incidence of at least one disorder reported to be 84.8% at baseline (within four days of onset of symptoms), and the incidence of mild hypogeusia (3.6%) and mild hyposmia (15.2%) at 60 days after the onset of COVID-19 symptoms reportedly similar to that normally found in the healthy population.[31] However, early results from a 12-month prospective cohort study involving 490 hospitalised COVID-19 patients indicated that impairment of sense of smell increased between the 1st and 4th week of follow-up after hospital discharge (3% to 4.5% in non-severe cases; and 1.9% to 5.77% in severe cases) with further results to be reported over time.[25]

Reports vary about the factors that influence recovery of the sense of smell and taste. A cohort study examining the early recovery patterns of olfactory disorders in 96 people with COVID-19 (hospitalised and non-hospitalised)[29] outlined that recovery of the sense of smell at 4 weeks post-COVID-19 diagnosis was affected by:

- gender: recovery more likely in females (recovery in 71.9% of females compared to 28.1% of males)
- initial severity: more rapid recovery within a few weeks in COVID-19 patients with hyposmia compared to than those with anosmia
- age: more rapid recovery in people aged 31–40 years (46.9% recovery, compared to 6.3% in people aged <20 years, 31.3% recovery in people aged 21–30 years, 12.5% recovery in people aged >50 years)
- co-morbidities: recovery rate worse in people with diabetes mellitus, hypertension, allergic rhinitis and history of smoking.[29]

Variable incidence of hyposmia related to severity of initial COVID-19 symptoms was also reported at 4 weeks following discharge from hospital (4.5% in non-severe cases; 5.8% in severe cases).[25]

This contrasts with the findings from a cohort study involving 138 people with COVID-19 (hospitalised and non-hospitalised) that reported no association between gender, age, need for hospitalisation, cardiovascular and pulmonary co-morbidities, diabetes and obesity, and the persistence of disorders of smell or taste at 60 days post COVID-19 diagnosis.[31]

1.1.4 Chest discomfort/pain

Chest discomfort and chest pain have been reported as a common long-term symptom following recovery from acute COVID-19. However, the reported incidence is variable.

- Several cohort studies report an incidence of 12.3%–25.9% in hospitalised and non-hospitalised COVID-19 patients, 10-12 weeks after onset of symptoms or discharge from hospital.[16,20,24]
- The results from a longitudinal questionnaire involving 21,359 respondents from the general population (233 reported a positive COVID-19 test; 3,652 a negative test, and 17,474 were not tested) reported that in COVID-19 positive people, chest pain was a persistent common symptom at 30 days, but was not present at 60 days.[15]
- Lower incidences of chest discomfort/pain were reported in two studies: a cross-sectional study of 284 hospitalised COVID-19 patients reported chest pain in 3% of people at a mean of 50 days following COVID-19 diagnosis[19], and a cohort study of 131 hospitalised COVID-19 patients reported chest tightness in only 0.76% of people four weeks after discharge for hospital.[21]

1.1.5 Sleep disorders

Sleep disorders including insomnia, occurring 1–3 months following discharge from hospital, diagnosis of COVID-19 or onset of symptoms, were reported in 1.9%–38.8% of hospitalised and non-hospitalised people with COVID-19.[16,17,19,20, 20,25,27,32]

In a study based on the electronic health records of 69 million patients, a first diagnosis of insomnia was reported in 1.9% (95% CI: 1.6–2.2) of a cohort of 44,779 people with COVID-19 during the 90 days following COVID-19 diagnosis, and insomnia was diagnosed more frequently than other control health events.[32] A comparison between COVID-19 patients three months following discharge from hospital to COVID-19 free patients demonstrated a

significant difference in the incidence of insomnia (17.7% compared to 4.9%).[16] The incidence of insomnia was reportedly related to the severity of the disease in hospitalised patients (5.3% in non-severe, and 7.7% in severe cases), with the incidence increasing from the first to the fourth week following discharge from hospital.[25]

1.1.6 Quality of life and patient experiences

Current evidence supports a decrease in quality of life measures (health, physical and mental components) in patients hospitalised with COVID-19, when assessed between 15 days and 12 weeks after discharge from hospital or onset of symptoms.[17,22,28,33,34] Reported incidence of lower quality of life scores is 39.1% for mental components, and 44.1%–80% for physical components.[33,34]

Lower physical function in people recovered from COVID-19 appeared to be associated with more severe initial illness (the need for oxygen supplementation or ICU admission).[34]

As previously highlighted, high quality evidence about the long-term sequelae of COVID-19 is limited, and the majority of current evidence relates to COVID-19 patients who have been hospitalised. Narratives about the often life-changing experiences of COVID-19 patients are published in the media and other informal fora (e.g. social media) ahead of formal documentation in the academic literature. Accounts include those of patients with ongoing and often debilitating symptoms that may not be recognised as long-term sequelae of COVID-19 because they were not tested for COVID-19 during the acute phase, and people who experienced mild or no symptoms initially with symptoms becoming more severe over time.[3,35]

The accounts of the types of persistent symptoms following recovery from acute COVID-19 also vary widely. In addition, there are reports of patients describing long-term symptoms that abate and relapse, and 'move around their body'.[3,35]

1.1.7 Additional long-term symptoms

Additional long-term symptoms and their reported incidence in the literature include the following:

Consequence/sequelae	Reported Incidence %	Reference #
Chills	4.6%–3.7%	16, 20
Concentration poor	1.9%–15%	15, 19, 20
Confusion/altered mental state	Not stated	15, 27
Cough	2%–25.9%	15, 16, 19, 20, 21, 25
Cough (productive)	3%	16
Diarrhoea	1.9%	20
Dizziness	2.6%-7%	16, 19, 27

Consequence/sequelae	Reported Incidence %	Reference #
Facial pain	Not stated	27
Feeling sad	6.4%	20
Fever	3.7%	20
Flushing	4.8%	16
Hair loss	2.8%–28.6%	16, 20
Headache	3.9%–17%	15, 19, 20, 27, 30
Joint pain	7.6%–27.3	16, 18
Joint/muscle pain	2.8	20
Muscle pain	4.5%–22%	16, 19
Memory loss	1.9	15, 20
Palpitations	14%–22.2%	15, 20, 24
Skin numbness/tingling	6%	19
Sweating	23.6%	16
Throat pain	0.76%–3.2%	16, 21
Weakness	44.9%	20
Weight loss	7.6-11.5%	25

1.2 Specific organ systems/disorders

COVID-19 is a multisystem disease affecting other organ systems as well as the respiratory system, including the cardiovascular, neurological, gastrointestinal, musculoskeletal and haematological systems.[3] This section outlines long-term sequelae related to specific organ systems and disorders. Although these sequelae have been divided by organ systems/disorders, a holistic approach to the management of long-term COVID-19 sequelae has been recommended.[36]

1.2.1 Respiratory

Expert advice provided to the working group suggests that information is still emerging about the long-term respiratory sequelae that are specific to COVID-19. Compared to other viral diseases, COVID-19 has a different underlying pathophysiology and an unusual time course where it may initially present as a mild disease, which can progress to pneumonitis and then serious illness. It was also noted that, as all ventilated patients have structural lung damage on follow up, many long-term respiratory effects may not be unique to COVID-19.

Recent guidance and review articles suggest that potential long-term respiratory problems associated with COVID-19 may include chronic cough, fibrotic lung disease, bronchiectasis, and pulmonary vascular disease.[37,38]

Current evidence about the long-term respiratory sequelae of COVID-19 at 8–12 weeks includes:

- persistent respiratory sequelae in 39% of hospitalised COVID-19 patients, three months after discharge from hospital, contrasted with 6.0% in the comparison group[16]; for example, increased respiratory rate following activity and at rest in 21.4% and 4.7% respectively of patients, compared to 5.4% and 0% of the comparison group
- abnormalities in chest radiographs in 10.1% of hospitalised and non-hospitalised COVID-19 cases[20] and 13.6% of hospitalised COVID-19 patients[17]
- abnormalities in chest computerised tomography (CT) in 37% of COVID-19 patients (hospitalised and non-hospitalised)[20]
- abnormal lung function tests in 10% of hospitalised COVID-19 patients[17]
- requirement for home oxygen after hospital discharge in 35.1% of patients who required at least 6 litres of oxygen at any point during hospitalisation and previously had no pre-COVID-19 oxygen requirements, with 13.5% continuing to need oxygen 30–43 days post hospital discharge.[28]

1.2.2 Cardiovascular

Expert advice provided to the working group suggests that, while COVID-19 is associated with a high incidence of acute cardiac injury, evidence is emerging about the long-term cardiovascular sequelae. Some long-term sequelae may relate to peripheral artery disease associated with COVID-19. Expert advice also highlights emerging evidence of the high incidence of thromboembolic disease in people with COVID-19 (reported incidence of venous thromboembolic events ranging from 29%–39% in ICU patients), which may lead to long-term sequelae in multiple organ systems.[39]

While the pathophysiology of SARS-CoV-2 differs from other viruses, long-term studies in patients with viral-induced cardiovascular disease may be relevant to COVID-19. A recent review[40] outlines that myocarditis from other viral pathogens can evolve into overt or subclinical myocardial dysfunction. Sudden death has been described in the convalescent phase of viral myocarditis. Patients with ostensibly recovered cardiac function may still be at risk of cardiomyopathy and cardiac arrhythmias. As up to 20%–30% of patients hospitalised with COVID-19 have evidence of myocardial involvement, this raises concerns for patients recovering from COVID-19. In addition, there are no data on how acute treatment of COVID-19 may affect the convalescent phase or long-term cardiac recovery and function.

Current evidence suggests that the long-term cardiovascular sequelae include:

- persistent cardiovascular sequelae in 13% of 538 adult COVID-19 patients three months after discharge from hospital, contrasted with 0.5% in the comparison group[16]; for example, newly diagnosed hypertension, an increased heart rate at rest and limb

oedema were detected in 1.3%, 11.2% and 2.6% of COVID-19 patients respectively, compared to 0% for these findings in the comparison group.

- myocarditis/myocardial fibrosis, with reported incidence ranging from 9% (non-hospitalised college athletes, 52 days after confirmation of COVID-19)[41] to 60% (hospitalised COVID-19 patients, a minimum of two weeks after diagnosis).[42] In health-care workers (hospitalised and non-hospitalised), the reported incidence of myocarditis, pericarditis and myopericarditis was 26%, 3% and 11% respectively (10.4 weeks after onset of symptoms), even in patients who were asymptomatic at the time of assessment.[24] Abnormal cardiac findings on magnetic resonance imaging (MRI) were reported in 78% of hospitalised COVID-19 patients a minimum of two weeks after diagnosis[42], and in 30% of hospitalised patients 102.52 ± 20.56 days after discharge.[43]

Myocardial inflammation and abnormal cardiac MRI findings were reported to be independent of pre-existing conditions, severity and overall course of the acute illness, and time from the original diagnosis.[42]

1.2.3 Neurological

A systematic review of the neurological manifestations of coronavirus infections[23] proposed that human coronaviruses, particularly SARS-CoV-1 and SARS-CoV-2, share similar neurological symptomatology and complications. At least five classes of neurological complications were identified: (1) Cerebrovascular disorders including ischaemic stroke and macro/micro-haemorrhages (2) encephalopathies, likely caused by combined effects of sepsis, hypoxia and immune hyperstimulation (3) para-/post-infectious immune-mediated complications such as Guillain–Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) (4) meningo-encephalitis, potentially with concomitant seizures and (5) neuropsychiatric complications such as mood disorders or psychosis. However:

- The majority of current evidence reporting on the incidence of stroke in COVID-19 patients refers to the acute presentation. Nevertheless, this complication is likely to be associated with long-term sequelae.
- While para-/post-infectious immune-mediated complications such as GBS are suggested following COVID-19[23,27,44], a causal link between COVID-19 infection and GBS is not supported by a study comparing the incidence of GBS during 2016–2019 to 2020.[45]

Neurocognitive impairment (including memory, speech, executive function) is reported in COVID-19 patients when assessed two months following discharge from hospital.[33]

1.2.4 Renal

Expert advice provided to the working group suggests that approximately 20-30% of COVID-19 patients that are admitted to ICU have acute kidney injury (AKI) that is sufficiently severe to require dialysis.[46] It is also hypothesised that a small proportion of these patients will not recover kidney function and will develop chronic kidney disease in the long term. AKI associated with COVID-19 in people with diabetes could contribute to an increase in the incidence of end-stage kidney disease in these patients. Because of the short timeframe since emergence of the SARS-CoV-2 virus, there is little evidence related to these

complications arising from COVID-19, which are expected to increase within the next few years.

1.2.5 Diabetes

Diabetes is a multi-system disorder and affects many key organs and body systems including heart and peripheral vasculature, kidneys, liver, brain, immune and haematological systems. The long-term effects of diabetes are potential complications of COVID-19 if the manifestation of pre-exiting diabetes worsens in a patient during the course of the infection, or if a COVID-19 patient develops new onset diabetes. Expert advice provided to the working group included the reported emergence of new onset Type 1 diabetes in COVID-19 patients, in both adults and paediatric patients,[47,48] and that many patients admitted to ICU are hyperglycaemic. The potential diabetogenic effect of COVID-19, beyond the well-recognised stress response associated with severe illness, has been described.[47] However, whether the alterations of glucose metabolism that occur with a sudden onset of diabetes in severe COVID-19 persist or remit when the infection resolves is unclear.

1.2.6 Mental health

Any severe illness like COVID-19, and the impact of the COVID-19 pandemic itself, can have long-term indirect effects not related to infection with SARS-CoV-2. In addition to the long-term socio-economic impacts, individuals can be predisposed to the development of new mental health issues such as anxiety and depression during or after the acute phase of the disease, or the disease can amplify existing mental health issues (see also Part 2).[49]

While the focus of this advice paper is the direct effect of infection with SARS-CoV-2, it is difficult to separate the direct and indirect mental health consequences of COVID-19.

Current evidence suggests a high incidence of anxiety and depression, post-traumatic stress disorder (PTSD) and lower scores for the mental component of quality of life measures in patients who have recovered from acute COVID-19, in both hospitalised patients and patients with mild illness, assessed between one to three months following discharge from hospital or diagnosis of COVID-19.[16,19,20,22,28,32,33,49] In patients with no prior psychiatric history, COVID-19 was associated with an increased incidence of psychiatric diagnoses in the three months after infection compared to the incidence of several other health events (influenza, other respiratory tract infections, skin infection, cholelithiasis, urolithiasis, fracture of a large bone) (**Attachment 5, Figure 4**).[32]

Long-term mental health issues in COVID-19 survivors, including suicidal ideation, psychosis, anxiety, depression, have been identified.[27]

Expert advice provided to the working group included the potential neuro-invasion of SARS-CoV-2, suggested by the presence of antibodies produced in the central nervous system during SARS-CoV-2 infection, with unknown consequences.[50,51]

1.3 Specific population groups

1.3.1 Paediatric

There is little evidence about the specific long-term sequelae of COVID-19 in children and adolescents. However, expert advice provided to the working group suggests that there is the potential for legacy effects from COVID-19 in this group, with potentially large public health impacts. Such effects include cardiovascular, respiratory and metabolic effects, mental health issues, diabetes, obesity and eating disorders.

PIMS-TS (Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2) is a hyper-inflammatory condition with severe multisystem involvement that has been reported in children and adolescents in the UK, Europe and the USA.[52,53] The heterogeneous clinical presentation of PIMS-TS includes myocardial injury, coronary artery damage including aneurysms and acute renal injury, which may be associated with long-term sequelae.[52,53] Despite frequent intensive care interventions, the mortality rate is reportedly low and short-term outcome is favourable. Long-term follow-up of possible chronic complications is crucial.[53] Expert advice provided to the working group indicated that there have been a number of confirmed cases of PIMS-TS in Australia and long-term follow-up will be crucial.[54,55]

1.3.2 Pregnant women

Analysis of the long-term sequelae of COVID-19 in pregnant women is complex. Complicating factors include a lack of reporting on pregnancy outcomes and gestational age at delivery, unclear reporting on the timing of COVID-19 infection and birth, the often very short follow up period of reporting for perinatal outcomes, and the intersection of the effect of COVID-19 infection and environmental stress from the pandemic on the pregnancy and outcomes.

There have been over 80 systematic reviews of COVID-19 in pregnancy and a further 94 registered in PROSPERO but most are of poor quality.[56] The most robust systematic review[56] is a 'living review' that will be updated as new evidence emerges. However, this review does not cover all maternal and perinatal outcomes. Other systematic reviews identified in the evidence search have also been considered, and their results should be interpreted with reference to their limitations (refer to **Attachment 3**).

It has been reported that, from the limited available literature, maternal and foetal/neonatal survival was excellent (98% and 99%) and that foetal/neonatal infection was rare.[57]

Foetal outcomes

Reported foetal outcomes, where there is evidence of maternal COVID-19 infection, include foetal distress *in utero*.[58,59] Reported miscarriage rates were 16.1% (5/31) among women who acquired COVID-19 in the first trimester and 3.6% (2/55) among those who acquired it in the second trimester. All women who had a miscarriage exhibited mild COVID-19 disease.[59]

Preterm birth

Overall, the rates of preterm birth in pregnant women with COVID-19 was 17%.[56] In a matched cohort, comparison between pregnant women with and without COVID-19 showed a higher rate of preterm birth (15.9% in COVID-19 positive; 6.1% in COVID-19 negative women) and higher odds of any preterm birth (3.01, 95% confidence interval 1.16 to 7.85; -2 studies; 339 women).[56]

Mode of birth

There was no difference in caesarean section rates in COVID-19 and non-COVID-19 deliveries.[56]

Vertical transmission of SARS-CoV-2

Further research is needed about the possibility of vertical transmission as there have been conflicting reports to date and varying levels of neonatal testing for SARS-CoV-2.[57,58] Of 405 newborns tested for COVID-19 via naso- and oropharyngeal swabs between 16 and 48 hours of life, 8 (2%) were positive.[59] Of those eight cases, only one was asymptomatic and the other seven were admitted to the neonatal intensive care unit (NICU) with signs of chest infection.[59]

Perinatal outcomes

A quarter of all neonates born to mothers with COVID-19 were admitted to the neonatal unit (25%) and were at increased risk of admission (odds ratio 3.13, 95% confidence interval 2.05 to 4.78, I2=not estimable; one study, 1121 neonates) than those born to mothers without COVID-19.[56]

Stillbirth and neonatal death rates were low in women with suspected or confirmed COVID-19[56,59], and do not appear to be higher than the background rates.[56]

Many studies have reported asymptomatic neonates and promising results of neonatal outcomes, with conservative treatment and regular monitoring leading to the babies recovering well.[58]

The potential effect of SARS-CoV-2 on development during the prenatal period is unknown.

Due to inconsistent data regarding the impact of COVID-19 on the newborn, further investigation and monitoring of possible infection in the babies born to COVID-19-infected mothers, and long-term sequelae in the child due to potential impact of infection on development, should be undertaken.

1.3.3 People with risk factors for long-term sequelae of COVID-19

The evidence search provided some information about risk factors including the impact of co-morbidities on the development of long-term sequelae of COVID-19 (**Table 1**). However, as these factors were not the subject of the evidence search, information on this aspect of long-term sequelae of COVID-19 may not fully represent the current evidence on this topic.

Table 1: Risk factors for developing long-term symptoms reported in one or more publications.

Factor	Risk
Age	Increased risk for any long-term symptom (Patients <65 years old)[20]
Gender	Female – increased risk for: • decreased physical function[34] • psychiatric morbidity[33] • fatigue[26] • PTSD symptom severity and hence protracted symptoms (see below)[19]
	Not a risk factor for any long-term symptom[15]
Body mass index (BMI)	Not a risk factor for any long-term symptom[15]
Health-care workers	Increased risk for any long-term symptom[20]
Large number of initial symptoms	Increased risk for: • Any long-term symptom[15] • Depression, anxiety, PTSD[49]
Pre-existing diabetes	Not a risk for any long-term symptom[15]
Pre-existing chronic lung disease	Not a risk for any long-term symptom[15]
Pre-existing comorbidities	Increased risk for lower physical function[34]
	Not a risk factor for cardiac involvement and myocardial inflammation[42]
Dyspnoea:	Increased risk for: 1. Any long-term symptom[15] 2. Physical decline/fatigue[16]
Delirium	Increased risk for developing neurocognitive impairment[33]
Autoimmune/ rheumatologic disorders	Nominal association with increased risk for long-term symptoms[15]
Neurocognitive impairment	Increased risk for psychiatric morbidity[33]
Smoking status	Increased risk for decreased physical function[34]
Stress-related symptoms	Increased risk for developing neurocognitive impairment[33]
Anxiety disorder	Nominal association with increased risk for long-term symptoms[15]
Pre-existing diagnosis of depression/anxiety	Increased risk for fatigue[26]

Factor	Risk
Moderate to severe PTSD (IES-R score)	Increased risk for any long-term symptom (sole predictor)[19] Predictors of increased severity of PTSD symptoms: • female gender • past traumatic events • protracted symptoms • perceived stigmatization • a personal view that the COVID-19 outbreak was a serious threat.

1.4 Relevance of evidence from SARS and MERS

NCHRAC conclusion 7: Long-term sequelae documented in survivors of SARS and MERS may predict potential long-term sequelae in COVID-19 survivors.

Experiences from the global outbreaks of two coronavirus infections, SARS and MERS, may be used to anticipate the long-term sequelae of COVID-19.

Studies that have examined the long-term sequelae in survivors of SARS and MERS indicate that respiratory complications may be important sequelae of COVID-19. Between 20% and 60% of survivors of these global outbreaks experienced persistent physiological impairment and abnormal radiology consistent with pulmonary fibrosis.[39] A systematic review and meta-analysis of long-term clinical outcomes in survivors of SARS and MERS reports lung function abnormalities and reduced exercise capacity were common in SARS and MERS survivors.[60] This is consistent with the current evidence of long-term sequelae of COVID-19 at 8-12 weeks (see Part 1.2.1), and so longer term respiratory impacts can be anticipated.

Previous coronavirus epidemics were associated with long-term mental health sequelae, such as depression, anxiety, PTSD, insomnia, memory impairment and impaired concentration[60,61], which have also been found in COVID-19 (see Parts 1.1.7 and 1.2.6). Other sequelae that have been identified in SARS and MERS survivors, such as euphoria, pressured speech, irritability, emotional lability and traumatic memories, are possible in the long-term survivors of COVID-19.[61]

While medium-term (up to 12 weeks) evidence is currently available for quality of life in COVID-19 survivors, longer-term data is not yet available. A systematic review and meta-analysis of long-term clinical outcomes in survivors of SARS and MERS reports that quality of life measures were considerably reduced in survivors at six months post-infection, showed only slight improvement beyond six months, and remained below that of the normal population and of those with chronic conditions (**Attachment 5, Figure 5**).[60] A similar outcome was shown in another systematic review, where health-related quality of life was reported to be lower in SARS and MERS survivors than the general population.[61] It is anticipated that quality of life may continue to be lower in the longer term for COVID-19 survivors.

Part 2: Emerging issues

NCHRAC conclusion 8: Emerging issues related to long-term sequelae of COVID-19 include:

- the need for collection of data from a broader patient set that is representative of the wider community including children, adolescents and young adults, and people whose initial presentation of COVID-19 may be mild or asymptomatic
- the long-term detrimental effects of the COVID-19 pandemic itself, including containment measures, on mental health and wellbeing
- the impacts of the pandemic on health care workers
- the preparedness of the health system for the care and management of people experiencing long-term sequelae of COVID-19.

During the preparation of this advice paper, the following emerging issues were identified that require further consideration and research.

- Most of the reported follow-up of people with COVID-19 has involved patients who have been hospitalised or who have more severe illness. These studies are more likely to involve patients who are older or who have co-morbidities. To improve our understanding of the long-term sequelae of COVID-19, there is a need for the collection of data in the medium- and long-term from more representative samples of people infected with COVID-19. Cohorts should include younger as well as older people, a range of severity of COVID-19 (from severe illness to asymptomatic), and various levels of medical care/intervention (community care, hospitalisation, admission to ICU). Long-term cohort studies are needed to identify legacy effects from COVID-19 in children and adolescents. Longitudinal studies of exacerbation of existing vascular disease due to COVID-19 should also be considered. Future data needs encompass clinical pathology/laboratory results that are part of the clinical investigations of COVID-19 including haematology, biochemistry, cerebrospinal fluid analysis, serology, immunology, genetics and biomarkers. Information about current studies is provided in **Part 3**.

- There is emerging evidence about the long-term detrimental effects of the COVID-19 pandemic itself, including public health responses to the pandemic such as lockdown and impacts on businesses and employment, on mental health and wellbeing more generally that are not directly related to infection with SARS-CoV-2.[3,62,63] Separation of the direct and indirect consequences of COVID-19 may be difficult. Expert advice provided to the working group suggests that indirect long-term consequences of the pandemic may include an increase in eating disorders, weight gain, anxiety, depression, insomnia, self-harm and suicide. Data from the Commonwealth Department of Health indicates a significant increase in mental health services delivered nationally since 16 March 2020, with Victorian state data showing a 33% increase in child and youth contacts in community mental health services for eating disorders.[64]

- Focus on the impacts of the pandemic, both direct results of infection and indirect effects, on health care workers has been identified as a key area of importance.[36]

- Concerns have been raised about the preparedness of the health system for the care and management of patients with long-term sequelae of COVID-19. Issues that need to be addressed include access to care (including equity and timeliness), service delivery and models of care, and ongoing provision of information and guidance for general practitioners, allied health, nursing, psychologists, physiotherapists and other primary health care providers.[65,66,67,68,69] NCHRAC is aware of work being undertaken by the Commonwealth Department of Health analysing the potential demand for health services, the current health care services and recommendations to address potential gaps. Guidance on the care and management of patients with post-COVID-19 conditions, such as those recently issued by the Royal Australian College of General Practitioners[70], may require frequent updating as new evidence emerges. NHMRC is soon to release the *Australian guidelines for the clinical care of people with COVID-19.* While these guidelines currently focus on diagnosis and management of acute infection, the need to address long-term sequelae is recognised, based on evidence where possible and consensus guidelines where necessary.

Part 3: Current and developing studies

NCHRAC conclusion 9: Ongoing research is essential to obtain evidence about the long-term sequelae of COVID-19.

Given the paucity and limitations of current evidence about the long-term sequelae of COVID-19, there is a need for ongoing research to inform the care and management of affected patients. A summary of relevant current and future studies is provided in **Attachment 6**. These studies aim to yield information in the short, medium and longer term.

Large-scale national standardised data collection is vital. Mechanisms for collaboration between Australian researchers and international efforts to understand the long-term impact of COVID-19, and to ensure Australia has access, and can contribute, to international data sets, should be considered.

Other considerations (Out of scope)

In the course of developing this advice paper, NCHRAC identified the following considerations that were out of scope, but are important and related considerations:

- Treatments and interventions during the acute care for people with COVID-19 (e.g. medications, intubation, ventilation, emergency procedures) and the experience of having a severe disease and/or being in an intensive care unit, that may lead to long-term sequelae and may not be unique to COVID-19.
- Patients with pre-existing health conditions who may require immediate or longer-term changes to the management of those conditions as a result of their COVID-19 episode.
- Patients with pre-existing health conditions who have not received the necessary health care due to lack of access, resources and opportunity. Examples include reduction in availability of organs for transplantation from deceased donors, suspension of surgical

waiting lists, reduced access to specific care, reduced capacity for provision of health care due to number of people with COVID-19, fear of contracting COVID-19.

Attachments

Attachment 1: NCHRAC working group members and consulted experts

Attachment 2: Evidence search: Summary

Attachment 3: Evidence search: Characteristics of studies included

Attachment 4: Long-term sequelae of COVID-19: Reported incidence

Attachment 5: Figures

Attachment 6: Current studies

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Note: Research papers shared before peer review are identified as pre-prints in this reference list. Accordingly, they should be interpreted with caution.

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About the Committee and the Working Group

About the National COVID-19 Health and Research Advisory Committee

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was established in April 2020 to provide advice to the Commonwealth Chief Medical Officer advice on Australia's health response to the COVID-19 pandemic. NCHRAC provides rapid and evidence-based advice (or expert advice in the absence of evidence) on Australia's health response to the COVID-19 pandemic with the aim of preventing new cases, optimising the treatment of current cases, and assisting in optimising overall health system readiness to deal with the pandemic as it progresses.

Further information on the terms of reference and membership of the Committee is available at: www.nhmrc.gov.au/nchrac. NHMRC is providing secretariat and project support for the Committee. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Working Group Membership

NCHRAC convenes working groups of its members and external experts to deliver its reports. The following NCHRAC members and external experts were involved in the development of this advice:

NCHRAC Members

- Professor Alison Venn (Chair)
- Professor Alex Brown
- Professor Frances Baum AO
- Dr Michael Freelander
- Ms Christine Morgan
- Professor Ingrid Scheffer AO

Additional experts

- Professor Greg Dore, Program Head, Viral Hepatitis Clinical Research Program, Kirby Institute; Infectious Diseases Physician, St Vincent's Hospital, Sydney
- Ms Sally Hall, Research Manager, Rural Clinical School ANU and PhD Scholar, ANU Medical School
- Professor Maree Teesson, Director, The Matilda Centre for Research in Mental Health and Substance Use, The University of Sydney; National Mental Health Commissioner

Experts consulted

During the development of this advice, the working group consulted with the following experts who provided information to working group meetings and/or comment on the draft advice paper during its finalisation:

- Dr Anne-Maree Boxall, Chief Allied Health Officer
- Professor Bruce Brew AM, Consultant Physician and Neurologist; Professor of Medicine (Neurology), University of New South Wales; Head Neurosciences Program and Peter Duncan Neurosciences Unit, St Vincent's Centre for Applied Medical Research; President of the International Society for Neurovirology
- Professor David Burgner, paediatric infectious diseases clinician scientist, Murdoch Children's Research Institute
- Professor Mark Cooper AO, Head of Department of Diabetes, Monash University
- A/Professor Nigel Crawford, Director of SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community), a vaccine safety and clinical immunisation research, Murdoch Children's Research Institute
- Professor Geoff Donnan, Professor of Neurology, The University of Melbourne
- Professor David Isaacs, Clinical Professor, Paediatrics and Child Health, Children's Hospital, Westmead
- Professor Leonard Kritharides, Senior Staff Specialist & Head of Department of Cardiology, Concord Repatriation General Hospital; Conjoint Professor of Medicine, University of Sydney; Chair Heart Research Institute
- A/Professor Jo-Anne Manski-Nankervis, Department of General Practice, University of Melbourne
- Professor Guy Marks, Head, Respiratory and Environmental Epidemiology Group, Woolcock Institute of Medical Research
- Professor Danielle Mazza, Head, Department of General Practice, School of Primary Health Care, Monash University
- Professor Stephen McDonald, The University of Adelaide, Director of Dialysis and Senior Staff Nephrologist, Royal Adelaide Hospital
- Professor Bruce Neal, Executive Director, The George Institute for Global Health, Australia
- Professor Lena Sanci, Chair of General Practice, Medicine Dentistry and Health Sciences Division, University of Melbourne
- Professor Paul Torzillo, Senior Respiratory Physician and Intensive Care Physician, Royal Prince Alfred Hospital
- Professor Paul Zimmet AO, Professor of Diabetes at Monash University and formerly Director Emeritus, Baker IDI Heart and Diabetes Institute

Evidence Review: Summary of search for studies reporting long term (post-acute) sequelae of COVID-19

Database/platform	Searching for	Search string applied	Date search conducted	Result/Notes
General searches				
PubMed	Published Systematic reviews and meta-analyses of COVID-19	"COVID-19"[Supplementary Concept] AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR ("systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]))	4 September 2020	435
Europe PMC	Preprints of Systematic reviews of COVID-19	((("2019-nCoV" OR "2019nCoV" OR "COVID-19" OR "SARS-CoV-2" OR "COVID19" OR "COVID" OR "SARS-nCoV" OR ("wuhan" AND "coronavirus") OR "Coronavirus" OR "Corona virus" OR "corona-virus" OR "corona viruses" OR "coronaviruses" OR "SARS-CoV" OR "Orthocoronavirinae" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "Middle East Respiratory Syndrome" OR ("SARS" AND "virus") OR "soluble ACE2" OR ("ACE2" AND "virus") OR ("ARDS" AND "virus") or ("angiotensin-converting enzyme 2" AND "virus")) AND (SRC:PPR)) and ("systematic review")) and (("long term") or ("consequence") or ("sequelae") or ("follow up"))	4 September 2020	115
Europe PMC	Preprints of cohort studies of COVID-19 reporting long term data	(("2019-nCoV" OR "2019nCoV" OR "COVID-19" OR "SARS-CoV-2" OR "COVID19" OR "COVID" OR "SARS-nCoV" OR ("wuhan" AND "coronavirus") OR "Coronavirus" OR "Corona virus" OR "corona-virus" OR "corona viruses" OR "coronaviruses" OR "SARS-CoV" OR "Orthocoronavirinae" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "Middle East Respiratory Syndrome" OR ("SARS" AND "virus") OR "soluble ACE2" OR ("ACE2" AND "virus") OR ("ARDS" AND "virus") or ("angiotensin-converting enzyme 2" AND "virus")) and ("sequelae" or "rehabilitation")) AND (SRC:PPR)	8 September 2020	162
medRxiv	Preprints of COVID-19 reporting long term data	“covid-19 sequelae study”	14 September 2020	144
medRxiv	Preprints of COVID-19 reporting long term data	“covid-19 rehabilitation study”	14 September 2020	216

Database/platform	Searching for	Search string applied	Date search conducted	Result/Notes
medRxiv	Preprints of COVID-19 reporting cohort studies	"covid-19 cohort study"	16 September 2020	2952. Conducted to provide baseline number of cohort studies of COVID-19 on medRxiv
PubMed	Published cohort studies of covid-19	("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND "Epidemiologic Studies"[MeSH Terms]	16 September 2020	2,320. Conducted to provide baseline number of cohort studies of COVID-19 on PubMed.
PubMed	Published cohort studies of covid-19 after 1 August 2020	("long-term"[All Fields] OR "long-haul"[All Fields] OR "post-acute"[All Fields] OR ("recoveries"[All Fields] OR "recovery"[All Fields]) OR ("rehabilitant"[All Fields] OR "rehabilitants"[All Fields] OR "rehabilitate"[All Fields] OR "rehabilitated"[All Fields] OR "rehabilitates"[All Fields] OR "rehabilitating"[All Fields] OR "Rehabilitation"[MeSH Terms] OR "Rehabilitation"[All Fields] OR "rehabilitations"[All Fields] OR "rehabilitative"[All Fields] OR "Rehabilitation"[MeSH Subheading] OR "rehabilitation s"[All Fields] OR "rehabilitational"[All Fields] OR "rehabilitator"[All Fields] OR "rehabilitators"[All Fields]) OR ("Rehabilitation"[MeSH Subheading] OR "Rehabilitation"[MeSH Terms])) AND ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("Cohort Studies"[MeSH Terms] OR "cohort"[Title/Abstract]) AND 2020/08/01:3000/12/31[Date - Publication]	8 October 2020	177

Database/platform	Searching for	Search string applied	Date search conducted	Result/Notes
PubMed	Published cohort studies of covid-19 after 1 August 2020, including 'survivors' and excluding the previous search results from PubMed on 8 Oct	((("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("Cohort Studies"[MeSH Terms] OR "cohort"[Title/Abstract]) AND ("survivor s"[All Fields] OR "survivors"[MeSH Terms] OR "survivors"[All Fields] OR "survivor"[All Fields])) NOT (("long-term"[All Fields] OR "long-haul"[All Fields] OR "post-acute"[All Fields] OR ("recoveries"[All Fields] OR "recovery"[All Fields]) OR ("rehabilitant"[All Fields] OR "rehabilitants"[All Fields] OR "rehabilitate"[All Fields] OR "rehabilitated"[All Fields] OR "rehabilitates"[All Fields] OR "rehabilitating"[All Fields] OR "Rehabilitation"[MeSH Terms] OR "Rehabilitation"[All Fields] OR "rehabilitations"[All Fields] OR "rehabilitative"[All Fields] OR "Rehabilitation"[MeSH Subheading] OR "rehabilitation s"[All Fields] OR "rehabilitational"[All Fields] OR "rehabilitator"[All Fields] OR "rehabilitators"[All Fields]) OR ("Rehabilitation"[MeSH Subheading] OR "Rehabilitation"[MeSH Terms])) AND ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("Cohort Studies"[MeSH Terms] OR "cohort"[Title/Abstract]))) AND 2020/08/01:3000/12/31[Date - Publication]	12 October 2020	46
MedRxiv	Preprints of COVID-19 reporting long term data	"covid 19 sequelae study"	12 October 2020	159

Database/platform	Searching for	Search string applied	Date search conducted	Result/Notes
Specific searches				
Cardiovascular				
PubMed	Epidemiologic studies in covid-19 and cardiovascular disease	("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND "Epidemiologic Studies"[MeSH Terms] AND ("Cardiovascular System"[MeSH Terms] OR "Cardiovascular Diseases"[MeSH Terms])	8 September 2020	242
PubMed	Systematic reviews in covid-19 and cardiovascular disease	("systematic review"[Publication Type] OR "meta-analysis"[Publication Type]) OR ("systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]) AND covid-19 NOT "COVID-19"[Supplementary Concept] AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR ("systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract])) AND cardio	8 September 2020	51
medRxiv	Cohort studies in covid-19 and cardiovascular disease	"covid-19 cohort study" and Subject Area = "Cardiovascular Medicine"	8 September 2020	43
Respiratory				
medRxiv	Cohort studies in covid-19 and respiratory medicine	"covid-19 cohort study" and Subject Area = "Respiratory Medicine"	11 September 2020	“respiratory medicine” filter unhelpful. Search abandoned.
Paediatrics				
MedRxiv	Systematic reviews in COVID-19 and paediatric medicine	“covid-19 systematic review" and Subject Area = “Paediatrics”	15 September 2020	22

Database/platform	Searching for	Search string applied	Date search conducted	Result/Notes
MedRxiv	Cohort studies in COVID-19 and paediatric medicine	"covid-19 cohort study" and Subject Area = “Paediatrics”	15 September 2020	31
Endocrinology				
MedRxiv	Systematic reviews in COVID-19 and endocrinology	“covid-19 systematic review" and Subject Area = “endocrinology (including diabetes mellitus and metabolic disease)”	25 September 2020	12
MedRxiv	Cohort studies in COVID-19 and endocrinology	"covid-19 cohort study" and Subject Area = “endocrinology (including diabetes mellitus and metabolic disease)”	25 September 2020	15
Neurology				
MedRxiv	Systematic reviews in COVID-19 and neurology	“covid-19 systematic review" and Subject Area = “neurology”	25 September 2020	32
MedRxiv	Cohort studies in COVID-19 and neurology	"covid-19 cohort study" and Subject Area = “neurology”	25 September 2020	36
Nephrology				
MedRxiv	Systematic reviews in COVID-19 and nephrology	“covid-19 systematic review" and Subject Area = “nephrology”	25 September 2020	11
MedRxiv	Cohort studies in COVID-19 and nephrology	"covid-19 cohort study" and Subject Area = “nephrology”	25 September 2020	20
Mental health				
MedRxiv	Systematic reviews in COVID-19 and mental health	“covid-19 systematic review" and Subject Area = “psychiatry and clinical psychology”	25 September 2020	69
MedRxiv	Cohort studies in COVID-19 and mental health	"covid-19 cohort study" and Subject Area = “endocrinology (including diabetes mellitus and metabolic disease)”	25 September 2020	53

Evidence search – Characteristics of articles included

A total of 1,705 articles were identified and assessed following the evidence search (comprising 19 separate searches).

Inclusion criteria:

- Studies that related to long-term sequelae arising from the direct effects of infection with SARS-CoV-2.
- Systematic reviews, cohort studies (prospective and retrospective, including data linkage studies), randomised controlled trials, nested case-control studies, and case-control studies.

Exclusion criteria:

- Studies that related to acute presentation of infection with SARS-CoV-2, or the effects from the pandemic itself.
- Studies exploring risk factors for particular outcomes.
- Case reports and case studies.
- Studies where only an abstract was available (i.e. no full article), studies that were protocols for systematic reviews (i.e. did not include results), and duplicate records.

Of the articles that met the inclusion criteria:

- five were systematic reviews, four of which were preprints
- 19 were cohort studies, 10 of which were preprints
- six were cross-sectional studies, five of which were preprints.

Five additional systematic reviews that did not meet the inclusion criteria of relating to long-term sequelae, but examined specific population groups (paediatrics, pregnant women) were characterised separately.

Systematic reviews: Characteristics

First author and title	Aim	A priori methods (protocol)	COVID-19 confirmed[1]	Country or city	Search (end) date	Types of study eligible	Risk of bias - assessed[2] - tool	Duplication - Study selection - Data extraction	Types of studies included	Population			Sample (size)
										Context[3]	Life stage[4]	Other (including co-morbidities)	
Ahmad Guillain-Barré syndrome in COVID-19:A scoping review [preprint]	To summarize the demographic features, clinical presentation, diagnostics workup, and management strategies of COVID-19 associated GBS reported in literature.	No		Italy USA Iran Spain Germany China France, Switzerland Morocco.	18 May 2020	All	- No - NA	- Yes - Unclear	Letters to editor Case reports Case series	Hospitalised	23–84 years old (adult, elderly)	18/24 patients were male.	24 cases of Guillain-Barré Syndrome in COVID-19
Ahmed Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis	To determine the long-term clinical outcomes in survivors of SARS and MERS coronavirus infections after hospitalisation or intensive care unit admission	Yes	PCR Antibody Clinical	Beijing Hong Kong, Guangzhou, Singapore Taiwan Korea Canada	31 March 2020	Primary research studies	- Yes - OCEBM	- Yes - Yes	28 studies in systematic review - 15 prospective cohort studies with good follow-up - 8 prospective cohort with follow-up or retrospective cohort studies - 2 non-consecutive cohort studies - 3 case series.	Hospitalised	Adults	26 studies reported findings from the SARS outbreak and 2 studies reported findings from the MERS outbreak.	Total sample number not stated. The sample size ranged from a case series of 4 patients to a cohort study of 406 patients.

[1] Options for this column (*COVID-19 confirmed*): RT-PCR, Antibody, Clinical, Not stated.
[2] Risk of bias assessed of studies included in review. OCEBM= Oxford Centre for Evidence-Based Medicine; NOS= Newcastle-Ottawa scale
[3] Options for this column (*Context*): Hospitalised, Hospitalised with ICU, Non-hospitalised (community), Other (include details), Not stated.
[4] Options for this column (*Life stage*): Embyro/neonate, infants, children, adolescent, adults, pregnant women, elderly.

First author and title	Aim	A priori methods (protocol)	COVID-19 confirmed[1]	Country or city	Search (end) date	Types of study eligible	Risk of bias - assessed[2] - tool	Duplication - Study selection - Data extraction	Types of studies included	Population			Sample (size)
										Context[3]	Life stage[4]	Other (including co-morbidities)	
[review article]									23 studies in meta-analysis				
Almqvist Neurological manifestations of coronavirus infections: a systematic review [preprint]	To systematically summarize neurological and neuroimaging manifestations of all known human coronaviruses (HCoVs) in order to provide possibilities to predict short- and long-term neurological complications of COVID-19	Yes	NA	SARS-CoV-2 patients from 35 different countries.	26 July 2020	Original studies Abstracts	- Yes - NOS Didn't assess publication bias.	- Yes - Yes	327 studies included for SARS-CoV-2, including: Case series Case reports Case-control Cohort Survey	Both	Adults Children	NA	17549 patients in total (including 14418 SARS-CoV-2 patients).
Rogers Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic [article]	To assess the psychiatric and neuropsychiatric presentations of SARS, MERS, and COVID-19	No	Variable for each paper. Information captured in Table 2.	China Hong Kong South Korea Canada Saudi Arabia France Japan Singapore UK USA	18 March 2020 (publications) and 10 April 2020 (preprints)	All studies and preprints	- Yes - NOS	- Yes - Yes	Randomised controlled trials Cohort studies Case-control studies Cross-sectional studies Case series Case reports Qualitative studies Preprints and letters	Almost all patients were hospitalised	Age ranged from 12.2–68.0 years old (Children, adolescents adults, elderly)	Follow-up time for the post-illness studies varied between 60 days and 12 years	65 peer-reviewed studies and seven preprints. 3559 coronavirus cases. No data on the post-acute phase of COVID-19.
Wildwing The Neurological Symptoms of Long COVID-19: A Comparison with other Neurological Conditions and Implications for Healthcare Services [preprint]	To inform future service provision for those who develop long-term neurological symptoms due to COVID-19; as well as exploring the effect of COVID-19 on health professionals' perceptions towards those with symptoms of Functional Neurological Disorder.	No	Suspected or confirmed infection included	31 different countries, including: China Italy South Korea Spain UK USA	1 September 2020	Systematic reviews	- Yes - CASP	- Yes - Not reported	Systematic reviews	Patients with COVID-19	Not stated	NA	29 systematic reviews included, covering 417 studies. More than 43, 166 participants overall.

Cohort and cross-sectional studies: Characteristics

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
Amer. Early recovery patterns of olfactory disorders in COVID-19 patients; a clinical cohort study.	To delineate the different patterns of olfactory disorders recovery in patients with COVID-19	Hospitalised Non-hospitalised	Adult Age: ≥18		Single centre – Tanta University hospital, Egypt. Sample size: 96	RT-PCR on nasopharyngeal sample	Egypt	Olfactory dysfunction	Yes Age, sex, family history of anosmia, history of nasal disease, smoking.	Regular medical visits on a weekly basis for 4 successive visits	Described as "cross-sectional cohort study"
Arnold. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Preprint	To assess the prevalence of complications from COVID-19 within these patients to inform appropriate follow up in secondary or primary care.	Hospitalised	Adult Age: ≥18		Unclear if this is a subset of DISCOVER, or all recruited to 3rd June. Consecutive patients hospitalised with COVID-19 were prospectively recruited. 163 patients	RT-PCR or clinic-radiological diagnosis	United Kingdom	Symptoms (fever, cough, breathlessness, anosmia, fatigue, myalgia, headache, chest pain, arthralgia, diarrhoea, abdominal pain, nausea, insomnia at 12 weeks follow-up. Chest radiograph, spirometry, sit to stand test, health status questionnaire (SF36)	Diabetes Heart disease Chronic lung disease Severe liver disease Severe kidney disease Hypertension HIV No adjustment for confounders.	28 days after admission (remote), 8-12 weeks (face-to-face)	Patients recruited via DISCOVER study, "a single centre prospective study recruiting consecutive patients admitted with COVID-19" http://www.bristol.ac.uk/news/2020/august/discover-study-findings.html. This paper appears to be reporting preliminary results.
Brandao Neto. Chemosensory Dysfunction in COVID-19: Prevalences, recovery rates, and clinical associations on a large Brazilian sample.	To better understand how SARS-CoV-2 affects the perception of smell and taste To evaluate the percentage of reported olfactory or tastes loss, severity, duration and recovery time.	Hospitalised Not stated	Adult Age: 18-65		2 groups: - Hospitalised (not ICU) and consented. Unclear if consecutive. - Responders to notices placed in social media. Sample size: Hospitalised = 110; Social media = 545	RT-PCR of nasopharyngeal or oropharyngeal swab	Brazil	Olfactory or taste disturbance; self-reported	Regression adjusted for known confounders	One author interviewed 143 patients with history of covid-19 olfactory or taste loss only, between 36 and 119 days of symptom onset. It was not reported which group these individuals were from or how they were selected.	The "social media" group are a self-selected group who were younger and more likely to be female, white and hold a bachelor degree or higher. This is not a reliable study and therefore, the results have not extracted for the advice paper.
Carfi Persistent symptoms in patients after acute COVID-19	To assess persistent symptoms in patients who were discharged from hospital after recovery from COVID-19	Patients meeting WHO criteria for discontinuation of quarantine, testing RT-PCR negative at time of enrolment into study.	Not stated		Single centre (post-acute outpatient service) in Rome, Italy. All patients were asked to retrospectively recount the presence or absence of symptoms during the acute phase, and whether symptoms persisted at time of enrolment. Sample size: 179 potentially eligible, 143 included.	Not stated	Italy	Comprehensive medical assessment with detailed history and physical examination. Data on specific symptoms potentially correlated with COVID-19 were obtained using a standardized questionnaire administered at enrolment. Standardized questionnaire administered at enrolment. Patients were asked to recount retrospectively the presence or absence of symptoms during the acute phase of COVID-19, and whether each symptom persisted at the time of the visit. The EuroQol visual analog scale was use for quality of life.	No	Patients assessed a mean of 60.3 days after onset of the first COVID-19 symptom	Published as letter.
Cirulli. Long-term COVID-19 symptoms in a large unselected population. Preprint	To characterize the frequency, duration, and other properties of long-term COVID-19 symptoms by reporting the results of a prospective research study of the general population represented by participants in the Helix	Non-hospitalised (community)	Adult (18-89+)		Participants in the Helix DNA Discovery Project and Healthy Nevada Project who consented to research involving their electronic medical records were sent the online questionnaire. Sample size 21,359	Self reported in survey (antibody test, molecular or PCR test, rapid or antigen test, unsure)	United States of America	Self reported through answering an online questionnaire.	Comorbidities were collected and included in the regression analysis	Surveys were administered at intervals of 4-6 weeks from April to September 2020. Participants could respond more than once, but in that case their data was summarised across surveys and included in analysis once.	Administered periodic longitudinal questionnaires to collect self-reported phenotypes to capture the occurrence and duration of COVID-19 symptoms, COVID-19infection status, and other long-term outcomes in the general population, regardless of history of COVID-19 infection or test.

[5] Options for this column (*COVID-19 confirmed*): RT-PCR, Antibody, Clinical, Not stated
[6] Options for this column (*Context*): Hospitalised, Hospitalised with ICU, Non-hospitalised (community), Other (include details), Not stated.
[7] Options for this column (*Life stage*): Embyro/neonate, infants, children, adolescent, adults, pregnant women, elderly.

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
	DNA Discovery Project and the Healthy Nevada Project.									Participants were asked about symptoms they had experienced for more than 30 days.	21,359 respondents, 233 reported a positive COVID-19 test, 3,652 a negative test, and 17,474 were not tested
Clark. COVID-19 Myocardial Pathology Evaluated Through screening Cardiac Magnetic Resonance (COMPETE CMR). Preprint	To use comprehensive cardiac magnetic resonance (CMR) to assess the prevalence and extent of cardiovascular sequelae in collegiate athletes that had recently recovered at home from COVID-19 infection.	Non-hospitalised (community)	Adults	Athletes	Retrospective cohort analysis. All athletes at the university were screened twice weekly for COVID-19. The positive cases were detected during this screening. Healthy controls were used from a cohort of healthy adult subjects over 18 years old who had previously consented for non-contrasted CMR imaging. Additional athletic controls were selected from a cohort of tactical athletes referred to the centre over the previous 12 months for cardiac symptomatology found to have normal cardiac function without pathology.	RT-PCR nasal swab	United States of America	Clinical demographics, laboratory, electrocardiographic, and CMR results	Age, weight, height, body surface area, race, ethnicity, gender.	The median time from SARS-CoV-2 infection to CMR was 52 days	
Eiros. Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers. Preprint	To address the prevalence of myocardial damage suggestive of myocarditis and to address the prevalence of pericarditis in health care workers		Adults		Cross-sectional study. HCW from a single centre (University Hospital of Salamanca, Spain) Sample size: 142 (registry); 139 (reported)	(i) RT-PCR assay of a specimen collected on a nasopharyngeal swab followed by a second negative RT-PCR and at least 14 days from this negative RT-PCR. (ii) Presence of IgM antibodies and negative RT-PCR after the antibody assessment. (iii) Presence of neutralizing IgG antibodies and absence of IgM.	Spain	Myocarditis Pericarditis Atrial fibrillation Ischaemic heart disease Dilatation of right heart chambers Valvular heart disease Rhythm disorders	Sex HCW category Comorbidities Daily physical activity COVID-19 symptoms COVID-19 pneumonia Cardiovascular chronic drug therapy COVID-19 treatment Additional drug therapy at examination	Examined (10.4 [9.3–11.0] weeks after infection like Symptoms	Registered: NCT04413071 Unclear how many were invited. Prevalence measures unlikely to be generalizable.
Halpin. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation.	To inform service development, our multidisciplinary rehabilitation team examined the impact of COVID-19 on survivors discharged from hospital.	Hospitalised	Adult Age: ≥18		Leeds Teaching Hospitals NHS Trust (LTHT). Patients treated for COVID-19 were followed up by telephone 4 weeks or more since discharge. "Participants who had received ward-based care were then selected randomly from the list and we continued to recruit participants until a total of 100 participants had been successfully followed up." Sample size: 191 on central list (33 ineligible, 56 not contactable, 2 declined) = 100 consenting	PCR nasopharyngeal sample	United Kingdom	Fatigue Breathlessness Neuropsychological Speech and swallow Nutrition Continence Quality of life (EQ-5D-5L) Perceived health Health service contact Vocation change	ICU v ward-based care	Participants were between 29 and 71 days post discharge (mean 48 days and SD 10.3 days). Telephone follow-up using developed screening tool.	"Those who required intubation had largely not been discharged for long enough to be included in this study".
Ismael. Post-infection depression, anxiety and PTSD: a retrospective cohort study with mild COVID-19 patients. Preprint	Investigate the association between COVID-19 symptoms and post-infection depression, anxiety and post-traumatic stress disorder (PTSD) among a sample of patients diagnosed with mild COVID-19 in Brazil.	Non-hospitalised (community)	Adults		Retrospective cohort study. All patients in a local government area that tested SARS-CoV-2 positive were invited to participate in the cohort. Sample size: 895.	RT-PCR nasal swab	Brazil	Total number of COVID-19 symptoms, GAD-7 scale for anxiety, PHQ-9 scale for depression, PCL-C scale for PTSD.	Lifetime diagnosis of psychiatric disorder (yes vs. no), current psychiatric treatment (yes vs. no), age (continuous: 18-88 years), gender (male vs. female), education (up to high school vs. more than high school), civil status (married vs. single, which included previously married), income level (as defined by the Brazilian Institute of Geography and Statistics: up to three times	The questionnaire was administered between 10 and 120 days of recovery from COVID-19. Patients were followed up to 14 days from completion of their initial questionnaire.	

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
									the typical salary for a minimum wage job vs. more), current health treatment for any acute or chronic medical condition (yes vs. no) and time between the treatment intake and mental assessment (continuous: 6-116 days), were assessed as potential confounders.		
Keddie. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Preprint	To characterise a cohort of UK cases of COVID-19 associated GBS to explore any difference from non-COVID-19 GBS	Not stated	Adults		Reports of Guillain-Barre Syndrome (GBS) were submitted by members of the British Peripheral Nerve Society, who cover 81 different UK sites. Members were emailed on a weekly basis to collect information on hospital presentations of GBS from the 1st March to the 31st May, 2020. Sample size 47.	Guillain-Barre Syndrome (GBS) cases were stratified into three groups: definite COVID-19, probable COVID-19 and non-COVID-19. Definite cases had positive RT-PCR or antibody results. Probable cases were based on clinical signs.	United Kingdom	Anonymised clinical data of demographics and medical history, COVID-19 infection, symptoms and management were collected. Precipitating illness, clinical features of GBS, investigation findings including cerebrospinal fluid (CSF) and electrophysiology, management and outcomes were also collated.	Unclear	Unclear	
Mendez. Short-term neuropsychiatric and quality of life in COVID-19 survivors. Preprint	To assess the neuropsychiatric and quality of life (QoL) consequences 2 months after hospital discharge	Hospitalised	Adults Age: 18 - 85		Cross sectional analysis of a prospective cohort study in a large tertiary care hospital in Valencia, Spain. Survivors were referred to the COVID-19 outpatient clinic in the Pneumology Department for clinical control where they were invited to participate in the study. 229 followed in outpatient clinic, 197 contacted by phone, 179 completed test battery	RT-PCR of nasopharyngeal swab or sputum samples.	Spain	Neurocognitive function (immediate verbal memory / learning, delayed verbal memory, semantic verbal fluency, and working memory) Psychiatric morbidity (anxiety, depression, PTSD) Quality of life and functionality (SF-12: physical component and mental component	Age, sex, education, smoking, comorbidities, covid-19 severity and treatment, respiratory support, outcomes and complications (including length of stay, admission t intensive care unit)	All recruited patients were contacted by telephone 2 (±1) months from the date of hospital discharge	
Mohamed-Hussein. Post-COVID-19 functional status: Relation to age, smoking, hospitalization and comorbidities. Preprint	To assess the Post COVID-19 functional status in Egypt by the PCFS (Post Covid-19 Functional Status) scale and to evaluate if age, gender, comorbidities have any effect on functional limitations	Hospitalised Non-hospitalised (community)	Adults		Patients from a registry run by the Ministry of Health and Population in Egypt (75.7% in the sample had been admitted to hospital). Cross sectional study Contacted and ask to complete online forms. **Note**: it is unclear how many were invited or what the response rate was. Target sample size was 425 (allowing 10% drop-out) Sample size: 444	Positive or indeterminate COVID-19 PCR test, or presumed presence of Covid-19 based on clinical & radiological criteria		Post COVID-19 functional status	Gender Residence (urban v rural) Quarantine status Oxygen supplementation ICU admission Seasonal influenza vaccination Smoking status Presence of any comorbidity	The mean duration since the onset of symptoms was 35.31±18.75 days	A potential problem with this data is that it is possible that it a biased sample is responding. Very few report moderate or severe limitations but this could be because most were young (mean age 33), urban (71%) non-smokers (78%).
Pizzini. Impact of vitamin D deficiency on COVID-19 – a prospective analysis from the CovILD registry.	To investigate associations of Vitamin D status to disease presentation within the CovILD registry.	Hospitalised patients and outpatients with persistent symptoms	Adults		Prospective, multicentre, observational study Sample size: 22 outward and 87 hospitalised patients (of which 18 in ICU)	Confirmed diagnosis of COVID-19 based on typical clinical presentation and a positive RT-PCR test	Austria	Various laboratory parameters including Vitamin D and parathyroid hormone concentration	Yes Age, sex, BMI, comorbidities	Various tests 8 weeks after confirmed diagnosis	This is a sub-study of the CovILD registry [8]
Poncet-Megemont. High prevalence of headaches during COVID-19 infection: a retrospective cohort study.	To document the prevalence of new headaches during the acute phase of COVID-19 infection and assess their evolution 1 month after recovery.	Hospitalised Non-hospitalised (community)	Age not mentioned		All patents with laboratory or CT confirmed COVID-19, diagnosed in the dedicated laboratory of the Clermont-Ferrand University hospital. Convenience sample of 139	Positive PCR or chest CT	France	New headaches.	Yes. Results presented by age, sex, hospitalisation, other symptoms.	Outpatients and discharged inpatients were followed by phone call twice a week until recovery. Last call made 1 month after disappearance of fever and dyspnoea.	Retrospective cohort

[8] "Development of Interstitial Lung Disease (ILD) in Patients With Severe SARS-CoV-2 Infection (COVID-19) (CovILD)" is a cohort study registered on Clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT04416100. The primary outcome (not yet reported) is pulmonary function at 1, 3 and 6 months.

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
Poyraz. Psychiatric morbidity and protracted symptoms in recovered COVID-19 patients. Preprint	To examine the extent of the psychiatric symptomatology (symptoms of PTSD, anxiety and depression, sleep impairment, and suicidality) in recovered COVID-19 patients.		Adults		Patients who received care at the tertiary hospital of Cerrahpaşa Medical Faculty, Istanbul. 1200 met WHO criteria for discontinuation of quarantine (identified from hospital records), contacted via WhatsApp® and short message service (SMS) messages and invited to participate in online survey. Also enrolled volunteering post-acute COVID-19 outpatients followed by the infectious disease department. 239 responses / 1200 invited (20% response rate) + 79 outpatients. 284 completed surveys available.	Not stated	Turkey	PTSD symptoms, symptoms of anxiety and depression, sleep impairment, suicidality, and protracted symptoms.	Age, sex, education, occupation, marital status, income, household size Covid-19 severity, oxygen, hospital or outpatient setting	Unclear. Patients receiving care between 15 March 2020 and 15 May 2020were invited, and the survey was conducted between June 1 and July 1.	Very poor response rate, length of follow-up not reported.
Puntmann. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease (COVID-19)	To better understand the prevalence, extent, and type of cardiovascular sequelae following COVID-19 infection.	Not stated	Adults		Participants were identified from the University Hospital Frankfurt COVID-19 Registry via the Department of Infectious Diseases and the Institute for Experimental and Translational Cardiovascular Imaging. Sample size 100 Comparisons were made with age-matched and sex-matched control groups of normotensive adults who were taking no cardiac medications, had normal cardiac volumes and function, and had no evidence of scar. Sample size =50	RT-PCR	Germany	Cardiovascular magnetic resonance imaging on clinical 3-T scanners. A minimum of 2 weeks from the original diagnosis if they had resolution of respiratory symptoms and negative results on a swab test at the end of the isolation period.	Comparisons were made with risk factor–matched patients (n = 57) for age, sex, hypertension, diabetes, smoking, known coronary artery disease, or comorbidities, sourced from the International T1 Multicenter Outcome Study	A minimum of 2 weeks from the original diagnosis if they had resolution of respiratory symptoms and negative results on a swab test at the end of the isolation period.	Prospective observational cohort
Sami. A one-year hospital-based prospective COVID-19 open-cohort in the Eastern Mediterranean region: The Khorsid COVID Cohort (KCC) study. Preprint	To analyse the following signs and symptoms findings in patients with COVID-19 pneumonia for temporal changes and establish the incidence of psychological disorders and related prevalent symptoms after discharge from the hospital.	Hospitalised	Adults		Patients admitted for COVID-19 from February 2020 until September 2020 in the Khorshid Hospital in Isfahan. Sample size = 600	RT-PCR Clinical	Iran	Outcomes are impaired pulmonary function, later signs and symptoms, psychotic disorders, sleep disorders, and sustained end-organ failure. Week 1 and 4 are telephone questionnaires. Week 12 and one year are in hospital visits and examinations include spirometry, Patient Health Questionnaire-9 (PHQ-9), Depression and Anxiety Stress Scales (DASS-21)	Comorbidities reported in baseline table	Week 1, 4, 12 and one year	Prospective cohort
Taquet. Bidirectional associations between COVID-19 and psychiatric disorder: a study of 62,354 COVID-19 cases. Preprint	To assess the psychiatric sequelae and antecedents of COVID-19 using electronic health record data.	Hospitalised Hospitalised with ICU Non-hospitalised (community)	Adolescent Adults Elderly People aged over 10		Used data from TriNetX Analytics Network (www.trinetx.com), a global federated research network capturing anonymized data from EHR in 54 healthcare organizations in the USA, totalling 69·8 million patients. Sample size: 44,779 Five cohorts were used for comparison.	Used ICD-10 codes for COVID-19.	United States of America	The primary outcome was the incidence of a first psychiatric diagnosis (F20-F48) over a period from 14 days to 90 days after a diagnosis of COVID-19. Other outcomes were dementia, insomnia and dementia in patients over 65 years.	Cohorts were matched for confounding variables using the built-in propensity score matching capability in TriNetX. They also tested three alternative hypotheses, which could explain differences in outcomes between cohorts.	Data from 14-90 days following COVID-19 diagnosis.	Retrospective cohort
Townsend. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. Preprint	To establish whether patients recovering from SARS-CoV-2 infection remained fatigued after their physical recovery, and to investigate whether there was a relationship between severe fatigue and a variety of clinic-pathological parameters.	Hospitalised Non-hospitalised (community)	Not recorded		Patients attending the post-COVID-19 outpatient clinic at St James's Hospital, Dublin, Ireland 128/223 offered an outpatient appointment and consecutively enrolled	Positive SARS-CoV-2 nasopharyngeal swab PCR	Ireland	Fatigue Routine laboratory parameters	Dates of COVID-19 symptoms, inpatient admission, treatment with supplemental oxygen and admission to the critical care/Intensive Care Unit (ICU) Regular medications Comorbidities (including depression, anxiety and frailty)	Participation in the study had to occur at least 6 weeks after either: (i) date of last acute COVID-19 symptoms (for outpatients) and (ii) date of discharge for those who were admitted during their	

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
	To examine persistence of markers of disease beyond clinical resolution of infection.									acute COVID-19 illness. The median interval between study assessment and discharge from hospital or a time-point 14 days following diagnosis if managed as an outpatient was 72 days (IQR: 62-87).	
Vaira. Smell and taste recovery in coronavirus disease 2019 patients: a 60 day objective and prospective study.	To understand the longer-term recovery rate of chemosensitive functions	Hospitalised Non-hospitalised (community)	Adults Over 18		Patients with a diagnosis of severe SARS-CoV-2. Presenting within 4 days of symptom onset. Sample size: 150. Follow up available for 138.	RT-PCR	Italy	Olfactory score Gustatory score Home quarantined patients: self-administered olfactory and gustatory psychophysical tests. Hospitalised patients: Connecticut Chemosensory Clinical Research Centre orthonasal olfaction test.	Regression adjusted for known confounders: age, sex, need for hospitalisation, co-morbidities	Olfactory and gustatory dysfunction assessed for all patients within 4 days of clinical onset, then every 10 days for 60 days.	Conclude that chemosensitive disorders are most prevalent at the earliest stages of disease
Valiente-De Santis. Clinical and immunological status 12 weeks after infection with COVID-19: prospective observational study. Preprint	To undertake a multidisciplinary follow-up at 12 weeks after an acute episode of COVID-19 to assess the functional status, persistence of symptoms and immunoserological situation.	Hospitalised Non-hospitalised (community)	Adults Elderly		First patients seen at the outpatient office. Followed up with phone call 12 weeks post infection and invited to clinic visit. Sample size = 108	RT-PCR Clinical	Spain	Symptoms, blood tests, clinical assessment, chest radiograph.	Not stated	12 weeks after acute illness	Prospective, observational, single-centre cohort
Wang H. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiac magnetic resonance imaging. Preprint	To evaluate mid-term cardiac sequelae in recovered COVID-19 patients by cardiac magnetic resonance imaging (CMRI).	Hospitalised	Adults		Single centre: 1 hospital in Beijing, China. Sample size 44, control 31	Not stated	China	Cardiac function. Measured by cardiac MRI at clinic visit. The average duration from discharge from the hospital to CMR examination was 102.52 ± 20.56 days.	Age- and sex-matched healthy controls, who underwent the cardiac MRI exams in our hospital previously, were selected from a health screening database.	12 weeks after discharge from the hospital.	Prospective single centre cohort
Wang X. Clinical features and outcomes of discharged coronavirus disease 2019 patients: a prospective cohort study.	To investigate clinical outcomes, distribution of quarantine locations and the infection status of contacts of COVID-19 patients after discharge.	Hospitalised	Adults Elderly		Single centre: 1 hospital in Wuhan, China. Confirmed COVID-19 cases discharged 3rd February to 21st February. Sample size: 131/147 consented+	Not stated	China	Symptoms: no symptoms, fever, cough, fatigue, expectoration, chest tightness, dyspnoea, chest pain, dizziness, palpitation, pharyngeal pain, nausea, loss of appetite, vomiting, headache, diarrhoea, myalgia, rhinorrhoea Laboratory tests and chest CT	No	Patients followed up every 7 days up to 4 weeks after discharge.	Prospective cohort
Weerhandi. Post-discharge health status and symptoms in patients with severe COVID-19. Preprint	To characterise overall health status and the physical and mental health of patients discharged home after severe COVID-19.	Hospitalised	Adults	Required at least 6 litres of oxygen during admission	We used the electronic health record to identify consecutive discharges within the prior 30-40 days. Trained study personnel manually reviewed each patient's chart to verify eligibility. Eligible patients were then called to solicit interest in the study. Sample size: 152	Not stated	United States of America	Outcomes were elicited through validated survey instruments: the PROMIS Dyspnea Characteristics and PROMIS Global Health-10. The study survey was either conducted by study personnel with the patient over the phone or independently online by the patient, per the patient's preference. Participants completed surveys at a median of 37 days (range 30-43) after hospital discharge (equivalent to a median of 55 days (range 38-95) after hospital admission).	Comorbidities reported in baseline table.	One month after discharge	Prospective single health system observational cohort

First author and title	Aim	Population			Recruitment	COVID-19 confirmed[5]	Country	Outcomes - Name - How measured - When measured	Confounders - Identified - Adjusted for	Follow-up	Comments
		Context[6]	Life stage[7]	Other (including comorbidities)							
Xiong. Clinical sequelae of COVID-19 in survivors in Wuhan, China:" a single-centre longitudinal study.	To describe the prevalence, nature and risk factors for the main clinical sequelae in COVID-19 survivors who have been discharged from hospital for more than 3 months	Hospitalised	Age: 20-80 years		Single centre: 1 hospital in Wuhan, China. 891 potentially eligible, 538 for whom telephone follow-up was achieved. 184 (of 215 included) in comparison group. Comparison group: Cohort of volunteers with similar demographic characteristics, were free of COVID-19; lived in the urban area of Wuhan during the outbreak, had been completely grounded at home for more than three months and had not done much physical work during the outbreak.	WHO interim guidance	China	General symptoms, respiratory symptoms, cardiovascular symptoms, psychosocial symptoms, specific symptoms.	Multivariate logistic regression to explore risk factors	Telephone follow-up. 3+ months following discharge.	Single centre longitudinal cohort

Systematic reviews about specific population groups: Characteristics

First author and title	Aim	A priori methods (protocol)	COVID-19 confirmed	Country or city	Search (end) date	Types of study eligible	Risk of bias - assessed[9] - tool	Duplication - Study selection - Data extraction	Types of studies included	Population			Sample (size)
										Context	Life stage	Other (including co-morbidities)	
Akhtar. COVID-19 (SARS-CoV-2) Infection in Pregnancy: A Systematic Review	To review published studies related to the association of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections with pregnancy, foetal, and neonatal outcomes during coronavirus disease 2019 (COVID-19) pandemic in a systematic manner.	No	Not stated	Not stated	May 22, 2020	Inclusion: Articles that reported on outcomes of COVID-19 during pregnancy. Exclusion: Studies where no cohort outcomes were observed, consensus documents, editorials, commentaries, narrative reviews.	- Yes - NOS	- Yes - Yes	22 studies. Not stated what type	Not stated	Neonate Adult (maternal ages ranged from 22 to 42 years)		156 pregnant women with COVID-19 and 108 neonatal outcomes
Allotey. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis	To determine the clinical manifestations of covid-19 in pregnant and recently pregnant women, identify the risk factors for complications, and quantify maternal and perinatal outcomes.	Yes Registered CRD42020178076	"We defined women as having confirmed covid-19 if they had laboratory confirmation of covid-19 infection irrespective of clinical signs and symptoms. Women with a diagnosis based only on clinical or radiological findings were defined as having suspected covid-19." "All (77 included) studies tested respiratory samples using RT-PCR to confirm the presence of SARS-CoV-2; 23 studies additionally diagnosed covid-19 based on clinical suspicion."	USA, China, Italy, Spain, UK, France, Belgium, Brazil, Denmark, Israel, Japan, Mexico, the Netherlands, Portugal.	26th June 2020	All studies	Cohort studies: NOS. Randomised control trails (RCTs): RoB 2 tool. Diagnostic accuracy studies: QUADAS-2. Prevalence studies: Hoy et al.	- Yes - Yes	Primary case reports, case series, observational studies or randomised-controlled trials. 77 cohort studies (55 comparative, 22 non-comparative) were included in the systematic review	Not stated	Neonate Adults	Figures 3 and 4 Acute symptoms • Aguesia • Cough • Diarrohea • Dyspnoea • Fever • Mylagia	11,432 pregnant women. There are many systematic reviews of COVID-19 in pregnancy. However, this systematic review is of high quality and is recent.

[9] Risk of bias assessed of studies included in review. OCEBM= Oxford Centre for Evidence-Based Medicine; NOS= Newcastle-Ottawa scale

First author and title	Aim	A priori methods (protocol)	COVID-19 confirmed	Country or city	Search (end) date	Types of study eligible	Risk of bias - assessed[9] - tool	Duplication - Study selection - Data extraction	Types of studies included	Population			Sample (size)
										Context	Life stage	Other (including co-morbidities)	
Hoste Multisystem inflammatory syndrome in children related to COVID-19: A systematic review [preprint]	How is the novel paediatric multisystem inflammatory condition associated with coronavirus disease 2019 (COVID-19) characterized?	Yes PROSPERO CRD42020189248	Not stated	Mainly France, USA, UK. Reports from non-Western countries were rare	June 30th, 2020	RCT, observational studies, case-control studies, cross-sectional studies, case reports and case series	- Yes - NOS	- Yes - Yes	40 studies. Observational data from single case reports or case series (2-186 cases per publication). All studies were non-controlled, although two publications used historical cohorts as a reference population.	Hospitalised Hospitalised with ICU	Infants and children (median age 9 [IQR 6.0-12.3], range 0-19)		687 patients
Pastick. A Systematic Review of Treatment and Outcomes of Pregnant Women With COVID-19—A Call for Clinical Trials	To highlight the heterogeneity of treatment and outcome data for pregnant persons with COVID-19 and summarize the literature related to COVID-19 in pregnancy.	No	Not stated for mothers "Neonatal testing for SARS-CoV-2 varied widely"	Not stated	June 29th, 2020	All publications	- Not stated	- Yes - Unclear	52 case reports, 44 case series, 25 prospective/retrospective cohort studies, 3 governmental or national reports, 2 case-control studies	Not stated	Neonate Adults		11,308 women
Turan. Clinical characteristics, prognostic factors, and maternal and neonatal outcomes of SARS-CoV-2 infection among hospitalized pregnant women: A systematic review	To evaluate clinical characteristics and maternal, fetal, and neonatal outcomes among pregnant women admitted to hospital with laboratory-confirmed SARS-CoV-2 infection by conducting a large global comprehensive review of data from various epicenters.	No	Either quantitative real-time polymerase chain reaction (RT-PCR) or dual fluorescence PCR assessment	Not stated	May 29th, 2020	Case reports and case series	- Yes - National Institutes of Health. Quality Assessment Tools for Observational Studies.	- Yes - Unclear	28 case series, 31 case reports, 4 retrospective cohort studies	Hospitalised	Neonate Adults	Recorded for 359 women, including overweight / obesity, asthma, hypertension, and type II diabetes mellitus	637 pregnant women

Long-term sequelae of COVID-19: Reported incidence

This attachment outlines the reported incidence of long-term sequelae of COVID-19. The information is presented in two tables:

- Attachment 4A: Symptoms as reported by patients
- Attachment 4B: Sequelae related to organ systems or specific disorders.

Method:

SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms; Australian extension)[1] was used to standardise the description of sequelae described in relevant articles, and to allow grouping of sequelae wherever possible.

Each sequela was then categorised as a 'symptom' or a 'sequelae related to a body-system or disorder' based, in part, on the classifications used in SNOMED-CT:

- Sequelae classified in SNOMED-CT as a 'finding' were normally categorised as a 'symptom' and included in Attachment 4A.
- Sequelae classified in SNOMED-CT as a 'disorder' were normally categorised as a 'sequelae related to organ systems or specific disorders' and included in Attachment 4B.
- If the classification in SNOMED-CT was not clearly delineated, a 'common sense approach' was taken to assess whether the reported sequela was something the patient would say to their doctor; for example, 'I am feeling…..' or 'My legs are swollen'. If so, the sequela was normally categorised as a 'symptom' and included in Attachment 4A.

Reported incidence:

The reported incidence of each sequelae in Attachments 4A and 4B is listed under the relevant article. Information about the articles and the characteristics of the studies is provided in **Attachment 3**.

[1] https://browser.ihtsdotools.org/?perspective=full&conceptId1=404684003&edition=MAIN/SNOMEDCT-AU/2019-07-31&release=&languages=en

Reported incidence of long-term sequelae: Symptoms

Attachment 4A

Sequelae	Almqvist	Amer	Arnold	Carfi	Cirulli	Eiros	Halpin	Poncet-Megemont	Poyraz	Sami	Taquet	Townsend	Vaira	Valiente-De Santis	Wang, X	Weerahandi	Wildwing	Xiong
Breathing painful					Not stated													
Breathlessness/ shortness of breath			39%	43.4%	Not stated	26%	42.6%-65.6%		4%	14.75-19.23%				55.6%	1.53%	74.3%		
Chest discomfort															0.76%			
Chest pain				21.7%	Not stated	19%			3%					25.9%				
Chills														3.7%				4.6%
Confusion					Not stated												Not stated	
Cough					Not stated				2%	15.38-18.25%				25.9%	5.34%			7.1%
Cough (productive)																		3%
Diarrhoea														1.9%				
Dizziness									7%								Not stated	2.6%
Facial pain																	Not stated	
Fatigue	53%		39%	53.1%		27%	60.3%-72%		40%	10.75-13.46%		52.3%					Not stated	28.3%
Feeling sad														6.4%				
Fever														3.7%				
Flushing																		4.8%
Hair loss														2.8%				28.6%
Headache								3.6%	17%					9.3%			Not stated	
Joint pain				27.3%														7.6%
Joint/muscle pain														2.8%				
Limb oedema																		2.6%
Memory loss														1.9%				
Muscle pain									22%									4.5%
Overall: At least one symptom			74%	87.4%	24.1%				44.3%					75.9%	9.16%			49.6%
Overall: Cardiovascular-related symptoms																		13%
Overall: Respiratory symptoms																		39%
Palpitations						14%								22.2%				
Poor concentration					Not stated				15%					1.9%				
Poor sleep			24%							5.25-7.69%	Probability 1.9% (1.6–2.2)			1.9%			Not stated	17.7%
Seizure																	Not stated	
Sense of smell impaired									17%	4.5-5.77%								
Sense of smell lost		25%			Not stated			14.4%						9.3%				
Sense of smell lost or impaired													5.8%					
Sense of taste impaired									18%					5.6%				
Sense of taste lost					Not stated			11.5%					4.3%					
Sense of smell or taste impaired																	Not stated	
Skin numbness/tingling									6%									
Sweating																		23.6%
Throat pain															0.76%			3.2%
Weakness														44.9%				
Weight loss										7.75-11.54%								

Reported incidence of long-term sequelae: Organ systems/disorders

Attachment 4B

Sequelae	Ahmad	Almqvist	Arnold	Clark	Eiros	Halpin	Ismael	Keddie	Mendaz	Mohamed-Hussein	Pizzini	Poyraz	Puntmann	Taquet	Valiente-De Santis	Wang, H	Weerahandi	Wildwing	Xiong
Cardiovascular																			
Cardiac MRI abnormal				9%									78%			30%			
Heart rate increase (resting)																			11.2%
Hypertension																			1.3%
Myocarditis					26%								60%						
Myocarditis/fibrosis				9%															
Myopericarditis					11%														
Pericarditis					3%														
Respiratory																			
Central alveolar hypoventilation syndrome (Ondine's curse)																		Not stated	
Chest radiograph/CT abnormal			13.6%												37%				
Lung function test abnormal			10%																
Oxygen dependency																	13.5%		
Respiratory rate increase (at rest)																			4.7%
Respiratory rate increase (post-activity)																			21.4%
Neurological/neurocognitive																			
Cognitive and psychological disorders															16.7%				
Dysphagia																		Not stated	
Encephalitis																		Not stated	
Guillain-Barre Syndrome and Acute Demyelinating Encephalomyelitis		Not stated																	
Guillain-Barre syndrome	Not stated							Not stated											
Guillain-Barre syndrome (incl. Miller Fisher Syndrome)																		Not stated	
Myelitis																		Not stated	
Neuralgia/ polyneuropathy																			
Neurocognitive impairment: Cognitive impairment									58.7%										
Neurocognitive impairment: Executive function impaired									6.1%										
Neurocognitive impairment: Memory impairment									38%										
Neurocognitive impairment: Speech fluency delayed									34.6%										
Neurocognitive impairment: Verbal memory delayed									11.8%										
Sensory disturbance (including vision)																		Not stated	

Reported incidence of long-term sequelae: Organ systems/disorders

Attachment 4B

Sequelae	Ahmad	Almqvist	Arnold	Clark	Eiros	Halpin	Ismael	Keddie	Mendaz	Mohamed-Hussein	Pizzini	Poyraz	Puntmann	Taquet	Valiente-De Santis	Wang, H	Weerahandi	Wildwing	Xiong
Mental health																			
Anxiety							22.4%		29.6%			18.4%		Probability 4.7% (4.2–5.3)	6.4%				6.5%
Dementia														Probability 0.44% (0.33-0.60)					
Depression							17.3%		26.8%			18.8%		Probability 1.7% (1.4–2.1)					4.3%
Mental health disorder									39.1%					Probability: 5.8% (5.2–6.4)				Not stated	22.7%
Mood disorder														Probability 2% (1.7–2.4)					1.7%
Post Traumatic Stress Disorder						23.5%-46.9%	26.2%		25.1%			25.4%							
Psychotic disorder														Probability 0.1% (0.08-0.2)					
Musculoskeletal																			
Muscle issues (incl. myalgia, muscle injury, ataxia, spasms, dystonia)																		Not stated	
Quality of life																			
Quality of life decreased						45.6%-68.8%													
Quality of life (health) decreased			Not stated																
Quality of life (mental) decreased									39.1%								Not stated		
Quality of life (physical) decreased									44.1%	80%							Not stated		
Metabolic																			
Vitamin D deficiency											12%								
Vitamin D insufficiency											41%								

Figures

Figure 1: Frequency and duration of symptoms in study participants (Total number = 21,359; number COVID-19 positive test = 233, number COVID-19 negative test = 3,652, number not tested = 17,474).[1]

Percent of participants with at least one symptom during the study period (initial), or at least one symptom that lasted longer than 30 days, 60 days, or 90 days. For the 30, 60, and 90-day timepoints, participants are split into those who initially had 5 or fewer symptoms and those who had more (>5). Individuals whose symptoms had started less than 30, 60 or 90 days ago were excluded from the 30, 60 and 90-day panels, respectively. The study period covered any illness over a nine month period (January - September 2020), and most participants reported at least one symptom occurring during that time frame.

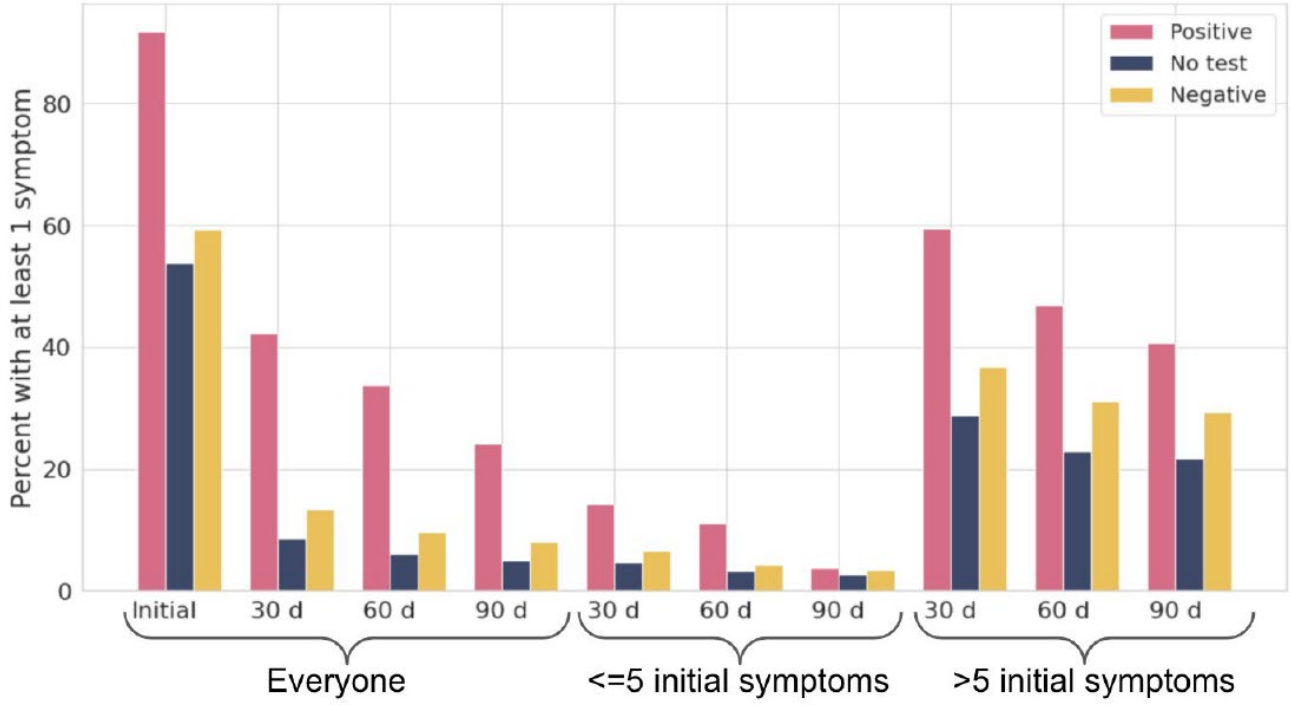


Figure 2: Frequency of symptoms reported at 12-week follow-up compared to hospital admission (n=163 participants).[2]

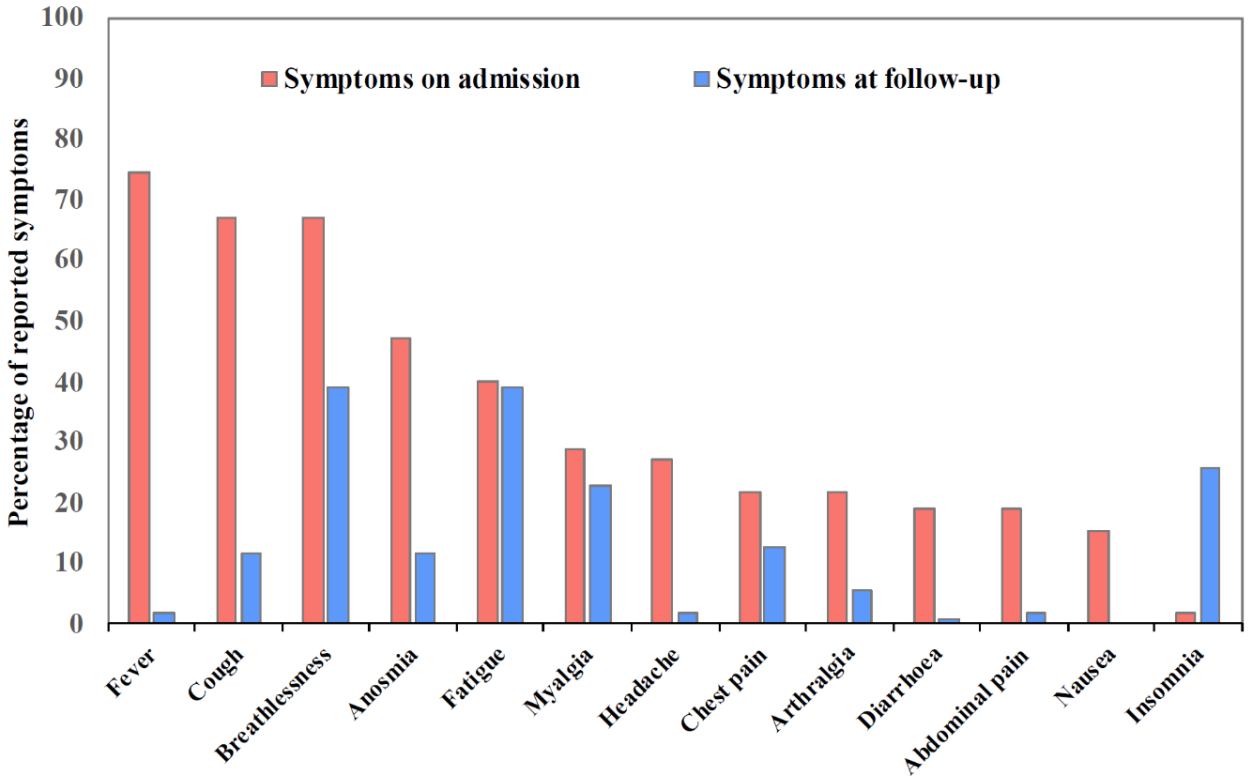


Figure 3: COVID-19–related symptoms during acute phase of the disease and at follow-up.[3]

The figure shows percentages of patients (n=139) presenting with specific coronavirus disease 2019 (COVID-19)–related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

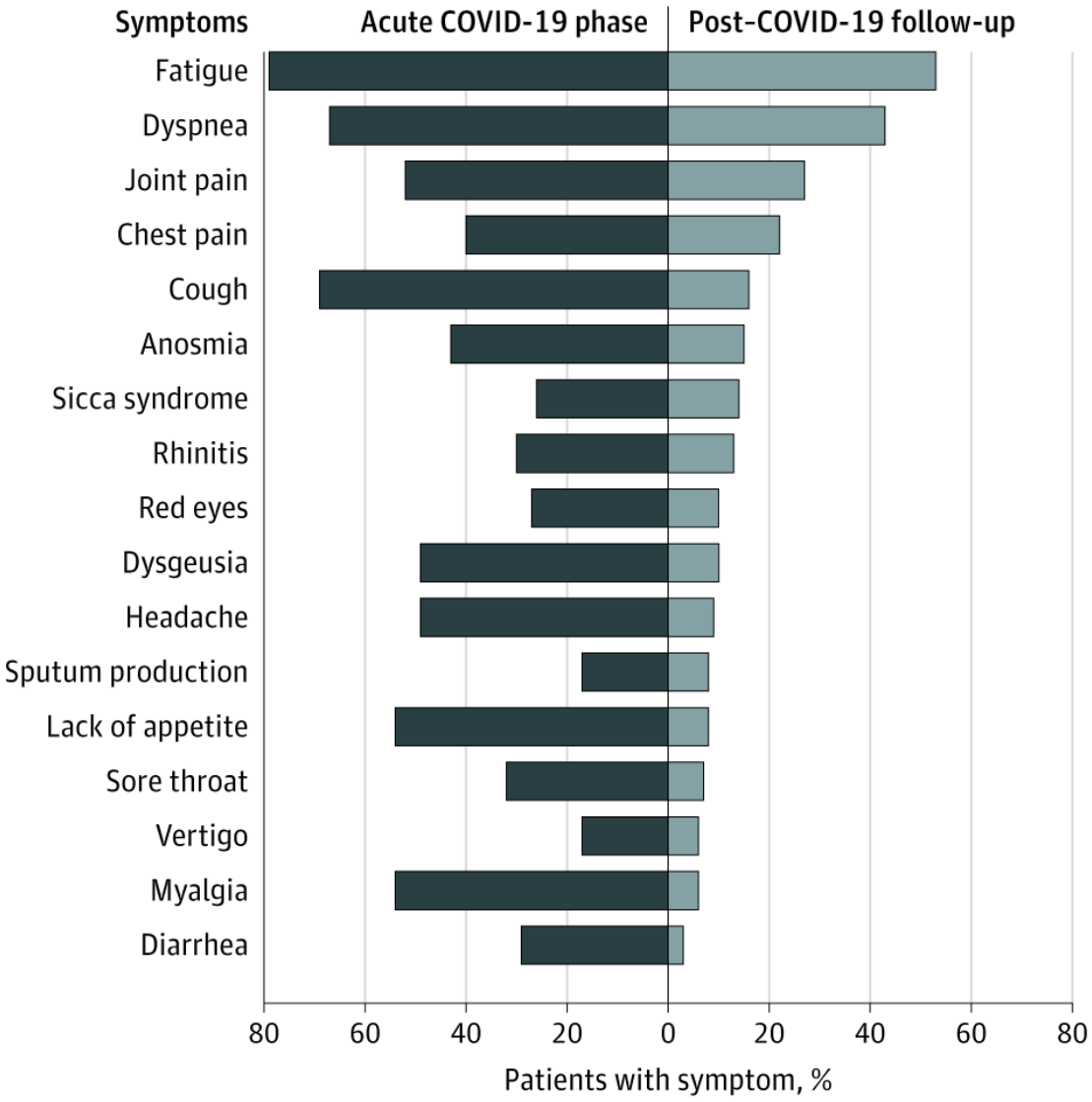


Figure 4: Kaplan-Meier curves representing the psychiatric sequelae of COVID-19 compared to influenza and other respiratory tract infections (RTI).[4]

Shaded areas represent 95% confidence intervals. The number of subjects within each cohort corresponds to all those that did not have the outcome before the follow-up period.

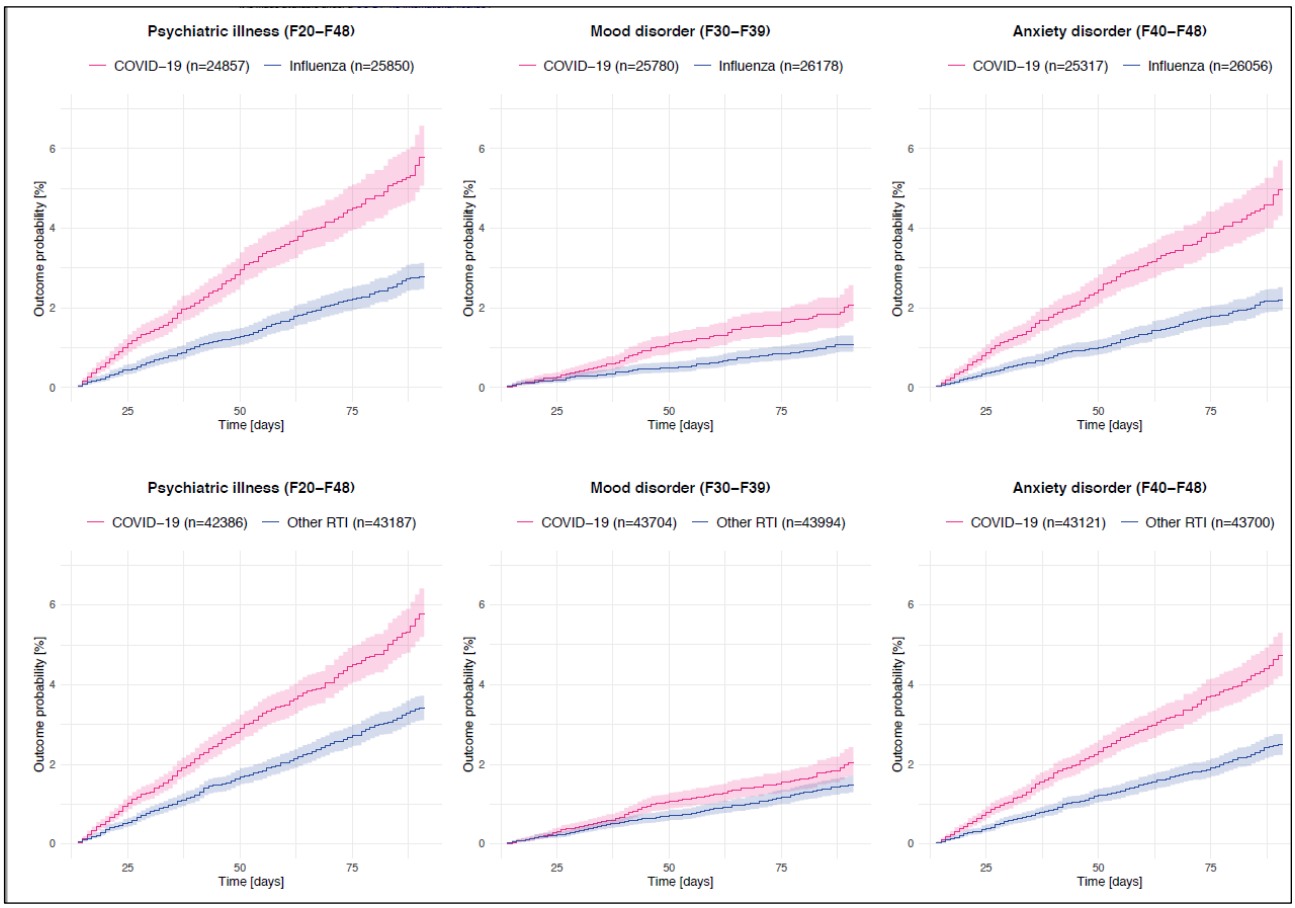
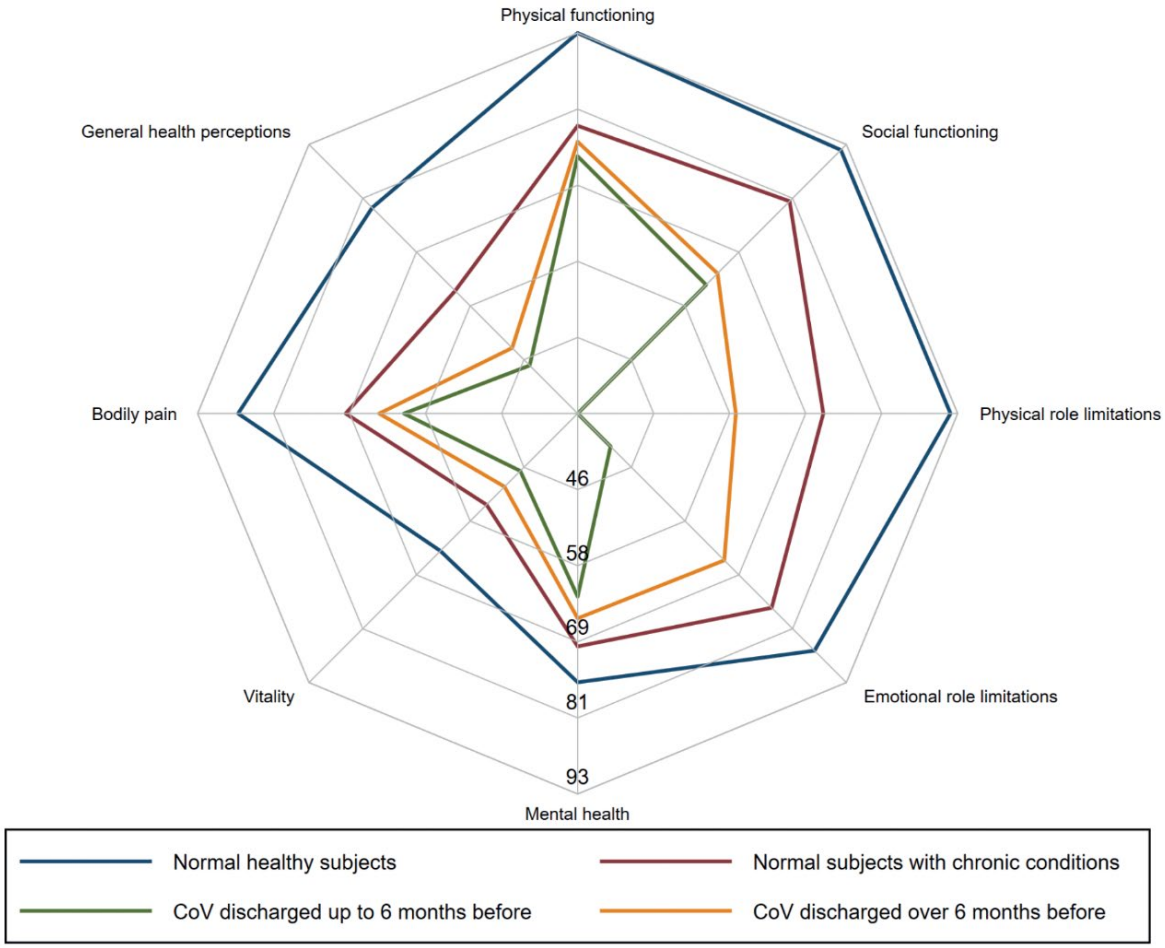


Figure 5: Radar plot showing pooled estimate of mean scores for different domains of Short Form 36 health survey (SF-36) in coronavirus survivors up to 6 months (green) and over 6 months (orange) compared to healthy individuals (blue) and subjects with chronic conditions (red).[5]

Systematic review reporting on 26 studies; sample size ranged from a case series of four patients to a cohort study of 406 patients. Countries/cities involved: Beijing, Hong Kong, Guangzhou, Singapore, Taiwan, Korea, Canada. (*Note: Related to SARS and MERS.)*



References (for Attachment 5)

[1] Cirulli E, Schiabor Barrett KM, Riffle S, Bolze A, Neveux I, et al. (2020). Long-term COVID-19 symptoms in a large unselected population. medRxiv, 2020.2010.2007.20208702. doi:10.1101/2020.10.07.20208702 **[Pre-print]**

[2] Arnold DT, Hamilton FW, Milne A, Morley A, Viner J, et al. (2020). Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. medRxiv, 2020.2008.2012.20173526. doi:10.1101/2020.08.12.20173526 **[Pre-print]**

[3] Carfì A, Bernabei R, Landi F, et al. (2020). Persistent symptoms in patients after acute COVID-19. JAMA, 324(6), 603-605. doi:10.1001/jama.2020.12603

[4] Taquet M, Luciano S, Geddes JR, & Harrison P J. (2020). Bidirectional associations between COVID-19 and psychiatric disorder: a study of 62,354 COVID-19 cases. medRxiv, 2020.2008.2014.20175190. doi:10.1101/2020.08.14.20175190 **[Pre-print]**

[5] Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, et al. (2020) Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. Journal of rehabilitation medicine, 52(2), jrm00063. Doi: 10.2340/16501977-2694

Ongoing studies known to be collecting long-term data

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
Identified by NCHRAC working group members and external experts			
Count me in	"A national research register of one million Australians involved in COVID-19 research" No further information on eligibility criteria.	Australia	UNSW and George Institute for Global Health. The aim is to establish and operate a secure technical platform to host and interrogate routinely collected health data for use by COVID-19 researchers. The register will support a broad range of COVID-19-related research projects led by UNSW Sydney and partners around the country, and will: • Link routinely collected health data to one million Australians willing to engage in research on COVID-19 • Place UNSW Sydney researchers at the heart of the COVID-19 research response • Enable large-scale recruitment of participants across Australia for COVID-19 research • Define the medium- and long-term effects of COVID-19 on our health and wellbeing.
The Murdoch Children's Research Institute (MCRI) is following children (COVID Immune) and adolescent (YoungLives) cohorts.	Not available	Australia	
The Royal Children's Hospital in Melbourne is following up families through the First Few X (FFX) project and has a cohort following up acute infections and admissions.	Not available	Australia	The overall aim of the 'First Few X' (FFX) project is to gain an early understanding of the infectiousness and severity of the initial cases of COVID-19 presenting in different countries around the world. This information helps to support international understanding of this new disease.

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
			The Australian FFX project is coordinated through the Australian Government Department of Health and APPRISE (Australian Partnership for Preparedness Research on InfectiouS disease Emergencies) in collaboration with states and territories. The Australian FFX project is based on a World Health Organization protocol and is one of many similar studies being conducted worldwide.
General practice data repositories that could be utilised for COVID-19 research to monitor long term impacts of COVID-19 include: a. Patron (University of Melbourne) https://medicine.unimelb.edu.au/school-structure/general-practice/engagement/data-for-decisions b. Outcomes Health https://www.outcomehealth.org.au/polar.aspx c. NPS Medicine Insight https://www.nps.org.au/medicine-insight d. UNSW ePBRN: https://cphce.unsw.edu.au/research/informatics-and-ehealth/electronic-practice-based-research-network e. PHN datasets (if COVID-19 related data is being extracted)	N/A	Australia	
Data linkage initiative	People with SARS-CoV-2 based on a positive nasopharyngeal swab test, with matched (age, gender, co-morbidity) swab negative controls.	Australia – NSW and Victoria	This initiative will link Covid-19 notifications to several administrative datasets including hospitalisations, Pharmaceutical Benefits Scheme and Medical Benefits Scheme. In NSW, this initiative will also include age/gender/baseline co-morbidity matching with swab negative controls.

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
COSIN (Coronavirus Outbreak Samples in NSW) https://kirby.unsw.edu.au/project/natural-history-cohort-following-sars-cov-2-infection	Patients infected with SARS-CoV-2 from several major hospitals in NSW	Australian - NSW	
Current collections of nephrology data include the national data collections of renal replacement therapy (such as ANZDATA in Australia and New Zealand), and the international society of nephrology's coronation registry	N/A	Australia and New Zealand	
Long-term outcomes in patients with COVID-19 https://clinicaltrials.gov/ct2/show/NCT04508712	900 participants This study will enrol survivors of COVID-19 aged over 18 years old who had been admitted to Leishenshan Hospital for COVID-19 patients in Wuhan, China.	China	
Long-term pulmonary outcomes after infection with SARS-CoV-2 https://clinicaltrials.gov/ct2/show/NCT04401163	180 patients Patients will be invited to follow-up visits 3 and 12 months after hospitalization with COVID19. Inclusion will take place during 2020. We expect to enrol 180 non-ICU patients and 36 ICU patients.	Denmark	The objective of this study is to assess the long-term outcomes after hospital admission with Covid-19 with respect to pulmonary function, physical capacity, imaging, quality of life and socioeconomic outcomes.
Real-time Assessment of Community Transmission (REACT) Study	100,000 randomly selected people across England	England	Antibody prevalence Unclear what long term plans are
Prevalence of Long-term Respiratory Complications of Severe SARS-CoV-2 Pneumonia NCT04376840	240 participants. 18 years and older.	France	Objective is to evaluate prevalence of long-term respiratory complications after severe SARS-CoV2 pneumonia.
Assessment of Long-term Impact Post COVID-19 for Patients and Health Care Professionals of the European Hospital (ALCOVID) NCT04525911	258 participants. Patients and medical staff having symptomatic COVID-19 infection confirmed (by RT-PCR or ELISA serology) or probable (CT criteria). 18 years and older.	France	The purpose of the study is to Assess of Long-term impact post COVID for patients and health care professionals. The patients and medical staff will be followed for 2 years in order to provide clinical and para-clinical data not yet published in the literature.

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
Sequelae of SARS-CoV-2 infections https://clinicaltrials.gov/ct2/show/NCT04442789	30 adults who have been hospitalised for COVID	Germany	Clinical evaluation and testing will start 2 months after symptom onset and the last visit is scheduled 10 months later.
Berlin prospective COVID-19 patient cohort (Pa-COVID-19) https://link.springer.com/article/10.1007/s15010-020-01464-x	All patients diagnosed with COVID-19 at Charite - Universitätsmedizin Berlin are eligible for inclusion. We will also recruit a representative cohort of outpatients with mild symptoms of COVID-19, in whom study visits and biosamplings are only performed at enrolment (V1) and at day 15 (V7) plus follow-up, provided that no hospitalization becomes necessary during the course of disease. Telephone interviews will be performed with outpatients to assess patient-reported health status between V1 and V7.	Germany	Data are collected longitudinally from patients with confirmed COVID-19 three times per week during their hospitalization and at follow-up visits. Data include epidemiological and demographic parameters, medical history and potential risk factors, documentation of standard of care procedures, and clinical course, including different patterns of organ involvement, quality of care, morbidity, and quality of life. Moreover, extensive serial high-quality bio-sampling consisting of various sample types with deep molecular, immunological, and virological phenotyping through single-cell- and bulk- multi-omics analysis is performed.
Development of Interstitial Lung Disease (ILD) in Patients With Severe SARS-CoV-2 Infection (COVID-19) (CovILD) https://clinicaltrials.gov/ct2/show/NCT04416100	130 participants COVID-19 patients discharged from hospital or outpatients referred to our Outpatient Department of Pneumology at the University Hospital of Innsbruck because of persistent respiratory symptoms in recovery phase will be followed up. Diagnosis of COVID-19 must have been ensured by nasopharyngeal and oropharyngeal swabs. **Inclusion Criteria:** • Female and male patients ≥ 18 years. • Confirmed infection with SARS-CoV-2 according to the definition of the Austrian Federal Ministry of Social Affairs, Health, Care and Consumer Protection	Innsbruck, Austria	The investigators intend to investigate COVID-19 survivors through clinical examinations, functional lung examinations, HR-CT scans, and by determining the "immunofibrotic" pattern in peripheral mononuclear cells (PBMCs) 1, 3, and 6 months after discharge.

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
	• Signed and dated declaration of consent by the patient according to ICH-GCP Guidelines. **Exclusion Criteria:** • Female and male patients < 18 years • Pregnancy • Dementia • Declaration of consent by the patient according to ICH-GCP Guidelines not signed • Incapacitated patients		
ISARIC (International Severe Acute Respiratory and emerging Infection Consortium) observational study of short and longer term physical and psychosocial consequences of COVID-19 https://osf.io/c5rw3/ Sigfrid: What is the recovery rate and risk of long-term consequences following a diagnosis of COVID-19? - A harmonised, global longitudinal observational study https://www.medrxiv.org/content/10.1101/2020.08.26.20180950v1	The protocol will be used for a sub-set of patients, already included in the existing cohort of more than 85,973 individuals hospitalized with confirmed COVID-19 infection across 42 countries (as of 20 July 2020), using the ISARIC/WHO standardized Core- or RAPID Case Report Forms (CRFs) People aged 16 years and older Laboratory or physician confirmed COVID -19 28 days (-0/+3 months) after discharge from hospital or health centre	International	International open-access prospective, observational multi-site study
Covidiab http://covidiab.e-dendrite.com/	This registry is specifically designed to establish the extent and characteristics of new-onset, COVID-19-related diabetes, and to investigate its pathogenesis, management and outcomes. The Registry also collects data about presentations with severe metabolic disturbance in pre-existing diabetes (DKA, hyperosmolarity; severe insulin resistance).	International	

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
National COVID Cohort Collaborative (N3C) https://academic.oup.com/jamia/advance-article/doi/10.1093/jamia/ocaa196/5893482	An open science community focused on analysing patient-level data from many centers.	International	
Study to Investigate Long-term Pulmonary and Extrapulmonary Effects of COVID-19 NCT04581135	500 participants. 18 years and older.	Switzerland	Prospective Observational Swiss Cohort Study to Investigate Long-term Pulmonary and Extrapulmonary Effects of COVID-19. 36 month follow up.
The COVID Symptom Study	Users of the COVID-19 Symptom Study app	UK	App developed by health science company ZOE and endorsed by the Welsh Government, NHS Wales, the Scottish Government and NHS Scotland. 4,160,711 participants have downloaded the app and are using it to regularly report on their health. App data is being analysed in collaboration with King's College London researchers. Recent publications: • Wise, J. Covid-19: Study reveals six clusters of symptoms that could be used as a clinical prediction tool (BMJ webinar) • Sleat, D. Long Covid: Reviewing the Science and Assessing the Risk
Long-term follow up of adults hospitalised with COVID-19 http://www.isrctn.com/ISRCTN10980107	10,000 adults Patients aged over 18 who were admitted to a UK hospital and discharged following suspected COVID-19	UK The study is led by the University of Leicester and participants will be recruited at multiple hospital sites from across the UK (including Scotland, Wales	The aims of this study are to: 1. Determine the short to long-term chronic health (and health economic) sequelae of COVID-19 infection in post-hospitalisation survivors; to define demographic, clinical and molecular biomarkers of the susceptibility, development, progression and resolution of these health sequelae. 2. Understand the impact of interventions during the acute illness on these long-term sequelae 3. Build the foundation for multiple in-depth

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
		and Northern Ireland)	studies e.g. lung fibrosis, pulmonary and systemic vasculature, cardiometabolic, renal, sarcopenia, rehabilitation, mental health and neurological disease. The findings will inform precision medicine in at-risk groups by directing new clinical trials and care for current and future post-COVID-19 patients. Prospective observational longitudinal study.
Defence and National Rehabilitation Centre (DNRC) M-COVID study	A young/middle aged physically active population (in this case a military population) who have had a range of mild to severe initial infection	United Kingdom	The study includes assessment of heart and lung function. Functional, mental health, cognitive and neurological outcomes will also be investigated. Participants will be followed up for 12 months after baseline assessment. The primary outcomes are cardiopulmonary function as assessed by Cardiopulmonary Exercise Testing (CPET) and the 6-minute walk test at 6 months.
Post-hospitalisation COVID-19 study (PHOSP-COVID) https://www.phosp.org/	10,000 patients who have been hospitalised with COVID-19	United Kingdom	Will study the short (0-6 months), medium (6-12 months) and long term (12 months +) effects of the disease. • As a basis, will collect and analyse routine clinical data (e.g. blood test results, lung volume measurements) for all participants (tier 1) • At some sites will collect enhanced clinical data, such as taking samples to look for the presence or absence of specific molecules, also known as biomarkers; we may also link to other medical records, such as those held in primary care (tier 2) • Will re-call some participants with particular disease characteristics to take part in sub-studies (tier 3)

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
The COVIDENCE UK Research Study https://www.qmul.ac.uk/covidence/about-the-covidence-uk-study/	People aged 16 years or older. Using an online questionnaire with details about their lifestyle and health. Participants will then be contacted every month to check if they have developed any symptoms of coronavirus disease, and to ask some follow-up questions about participants' more general health and social circumstances.	United Kingdom	The data they collect will be analysed in order to: 1. advance understanding of risk factors for coronavirus disease among UK adults 2. find out how quickly people recover from coronavirus disease and whether there are any long-term complications of this illness 3. evaluate the impact of coronavirus disease on the physical, mental and economic wellbeing of the UK population 4. establish a platform for future research on coronavirus disease in the UK.
Long-term Impact of Infection With Novel Coronavirus (COVID-19) (LIINC) NCT04362150	800 participants. 18 years and older.	United States of America	LIINC is an observational, prospective study of individuals previously infected with SARS-CoV-2 who have recovered from acute illness. The overall objective of the study is to investigate the clinical consequences of SARS-CoV-2 infection. These include the pre-existence and development of medical conditions, measures of immune activation and inflammation, changes in immunologic function, and variability in host responses. There will be a specific focus on demographic differences including age, gender, and race. Enrolled volunteers are seen at San Francisco General Hospital at baseline, monthly for 3 months and then every 3 months for up to 2 years. Visits include a detailed interview, saliva collection, and a blood draw. Baseline visits take approximately 90 minutes, and follow up visits take approximately 20-40 minutes.

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
Long term outcomes of patients with COVID-19 (COVID19 LTFU) https://clinicaltrials.gov/ct2/show/NCT04360538	500 participants Adults who have been admitted to ICU	USA (Chicago)	The investigators hypothesize that those with respiratory failure due to COVID-19 will have different burdens of mental and physical disability than those with respiratory failure who do not have COVID-19. Detecting these potential differences will lay an important foundation for treating long term sequelae of respiratory failure in these two cohorts. The aim of this proposal to is to understand the extent and degree of physical disability, psychological sequelae, and cognitive dysfunction survivors of COVID-19 related critical illness will have upon hospital discharge, 6 months, and up to one year post discharge. These outcomes of interest will be evaluated prospectively. The investigators will perform these measures in Covid-19 patients with respiratory failure and compare them to non-Covid-19 patients with respiratory failure.
Australian New Zealand Clinical Trials Registry (ANZCTR): Registered cohort studies (https://www.anzctr.org.au/)			
Long-term Impact in Intensive Care Survivors of Coronavirus disease-19 (COVID-19) (AFTERCOR)	Sample size target: 200 • Laboratory-confirmed COVID-19 infection by real-time PCR • Written informed consent from the patient at the time of discharge from the ICU • Previous enrolment into the ECMOCARD observational study • Aged older or equal than 18 years • Discharge from an intensive care unit	Australia-based. Recruitment in Australia and internationally.	Patients previously enrolled in ECMOCARD will be approached for informed consent for follow-up assessments up to 2 years. Following discharge from the hospital, recovery up to two years of the following aspects/functions will be assessed: • Health-related quality of life by answering questionnaires (taking approximately 1h at every follow-up visit) • Dynamics of organs dysfunction and recovery (blood draw, taking 5 minutes at every follow-up visit;)

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
			• Pulmonary function tests (taking approximately 2h at every follow-up visit) Follow-up assessments with the complete work-up will be at 3, 6, 12, 18 and 24 months.
Persistent lung and arterial inflammation following COVID-19 pneumonia	Sample size target: 30 • Both males and females aged 50 years or greater. • At minimum of 30 days and no more than 45 days post COVID-19 pneumonia diagnosis. Recovered as defined by nasal or oropharyngeal swab confirmed as negative for SARSCoV-2 in the recovery phase of their illness. • Evidence of pulmonary infiltrates on chest x-ray or Chest CT (multilobar, interstitial or ground glass opacities) suggestive of pneumonia during index admission.	Australia-based. Recruitment in Australia.	The study is a multi-centred prospective observational study involving a cohort of 30 adults who are at least 30 days and no more than 45 days post COVID-19 pneumonia diagnosis. Recruited patients will have an 18F-FDG PET/CT scan, which will be assessed for persistent areas of increased inflammation in their lung tissue and for inflammation of blood vessels, indicated by measuring the amount of FDG seen in the aorta. The scan will be performed no less than 30 and no more than 45 days from the date of the COVID-19 diagnosis.
Post-Intensive Care Nutrition Status in Patients with COVID-19	Sample size target: 200 Only patients included in Short Period Incidence Study of Severe Acute Respiratory Infection (SPRINT-SARI) (https://www.anzics.com.au/current-active-endorsed-research/sprint-sari/) will be included in this nutrition study. Patients admitted to the participating sites and enrolled in SPRINT-SARI will be screened at ICU discharge for eligibility for inclusion in the study. All investigators involved in screening and recruitment are employed by the corresponding sites and will have access to identifiable patient information purely for the purpose of study eligibility and study data collection. The SPRINT-SARI patient identification number (PIN) will be recorded as a case report form data point to allow for data linkage at a later date.	Australia-based. Recruitment in Australia.	As an observational study, data will be collected with the aim of quantifying the effect of the COVID-19 respiratory pandemic on nutrition intake, processes and dietetic resourcing in patients admitted to intensive care in Australia that survive to the ward. Nutrition data will be collected for patients once they are discharged to an acute hospital ward for every 7 days up to hospital discharge or day 28. Data will be collected retrospectively for patients' ICU admission, including patient demographics and nutrition data. Therefore, data may be collected retrospectively for patients who were admitted and enrolled into the SPRINT-SARI study,

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
	SPRINT-SARI will enrol all patients admitted to hospital with suspected or proven acute novel Coronavirus (nCoV) infection as main cause for admission. The study population for SPRINT-SARI, as follows: All patients newly admitted to participating hospitals, of any age, presenting with SARI during the study period. Patients will be eligible for the study if the patient meets the case definition for SARI. A suspected or proven acute respiratory infection requiring new inpatient admission with onset within the past 14 days. With one or more of the inclusion criteria. **Inclusion Criteria:** • A history of feverishness or measured fever of greater than, or equal to, 38 degrees C • Cough • Dyspnoea (shortness of breath) OR Tachypnoea. **Additional inclusion for this study:** • COVID-19 positive diagnosis • Admitted to an Intensive Care Unit (ICU)		the date of which may be prior to this trial registration and study commencement.
ADAPT - COVID-19 Study - A prospective, observational cohort study at St Vincent's Hospital Sydney (See also: https://kirby.unsw.edu.au/project/adapt-study)	Sample size target: 300 1. Age greater than or equal to 18 years 2. Confirmed SARS-CoV-2 by nucleic acid testing 3. Able to provide informed consent The ADAPT study is following patients diagnosed with SARS-CoV-2 infection through St Vincent's Hospital clinical service at regular intervals over a	Australia-based. Recruitment in Australia.	This is a prospective, observational cohort study of all patients at St Vincent's Hospital, Sydney, who test positive for COVID-19 infection. The cohort will consist of two components. • Cohort A - Mild disease patients recruited through the community cohorts

Cohort name and acronym (with link when applicable)	Eligible	Country	Notes
	minimum of one-year post diagnosis. All patients including those managed in the community and hospitalised are eligible to participate. Patients diagnosed from other clinical services may also enrol.		• Cohort B - Moderate-severe patients recruited through the inpatient service at St Vincent's Hospital Sydney. Each patient shall be followed for a period of 12 months from the time of COVID-19 diagnosis. The study will run for 2 years in total. The study will examine the short, medium and long term effects of COVID-19 on the immune system. The study will also examine how the immune system responds to COVID-19 to form antibodies and the long-term effects of COVID-19 on heart, lung and brain function and also a person's mental health and effect on a person's activities of daily living.
Neonatal CoVID-19 Study to evaluate the population health impacts of COVID-19 in mothers and their newborn infants cared for in tertiary and non-tertiary hospitals in Australia. (NCoS)	Sample size target: 1000 COVID-19 confirmed infants or infants born to COVID-19 confirmed mothers	Australia-based. Recruitment in Australia.	This project uses a quantitative research methodology that will collect data using a prospective population based registry via a RedCap™ online database. Data collected on the study database is already routinely collected clinical data such as resuscitation details at birth, APGAR scores, need for ICU or HDU admission, feeding details and follow-up at 2 years of age. All data collection will occur from relevant hospital records and no specific input from patients is required. This methodology is appropriate to answer the research question because it allows for de-identified input from multiple study sites, and ongoing quantitative analysis and reporting including longer term outcomes for neonates at 2 years of age.