Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee*

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Advice 29: Update on Long COVID

Focus

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was asked to provide up-to-date advice on the specific endpoints of Long COVID to the Chief Medical Officer (CMO). This advice aims to assist clinicians with the diagnosis, treatment and management of individuals with Long COVID and to assist healthcare providers to plan future health service requirements.

This advice builds on NCHRAC's Advice 12: *Evidence for long-term consequences/sequelae of COVID-19,* which was provided to the CMO in November 2020. Since that time, more evidence has become available on Long COVID, also known as Post-Acute COVID Syndrome (PACS), Post-Acute Sequelae of COVID-19 (PASC) and Post COVID condition.

Note

This report is point in time and may need further updating as more evidence is available.

This report was developed by an NCHRAC working group, chaired by Professor Alison Venn, with the assistance of Professor Fran Baum and external experts, Professor Martin Hensher, Professor Nigel Curtis and Dr Samantha Chakraborty.

Key Points

Clinical Care

- Long COVID is a complex condition that can impact multiple organs; people with the condition can display a variety of signs and symptoms.
- In addition to physical symptoms, there is evidence that the experience of continued poor health has a clinically observable psychological impact in those with Long COVID.
- Consensus on a case definition for Long COVID is required to ensure consistent and appropriate diagnosis and treatment for individuals.
- Development of a case definition should occur in collaboration with people with lived experience of Long COVID to ensure the criteria are meaningful and relevant to the Australian context.

* 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.

- The development of Medicare Benefit Schedule codes specific to Long COVID would facilitate access to screening, onwards referral and rehabilitation, as well as enable surveillance of health service demand.
- There is emerging international evidence that COVID-19 vaccination reduces the likelihood of developing Long COVID following previous infection, however modelling suggests many Australians will experience Long COVID despite high vaccination rates.
- Some populations are at increased risk of developing Long COVID (e.g. those with pre-existing conditions) see Appendix 1.
- Follow-up for patients recovering from acute COVID-19 infection should include assessment of lung function, exercise capacity, cognitive function and general day-to-day functioning to guide appropriate treatment.

Epidemiology

- There is limited data on the prevalence and incidence of Long COVID in Australia; further research is required.
- It is estimated that 20% of people diagnosed with COVID-19 were still experiencing symptoms after one month and 5% after three months.
- Long COVID is a relatively new public health issue in Australia as most infections occurred recently, i.e. over the summer of 2021/22.
- Individuals and communities in vulnerable socioeconomic circumstances are likely to be disproportionally impacted by Long COVID and experience a higher burden of disease.
- Long COVID can affect people of all ages; however, more research is needed to understand the impacts on children.

Pathophysiology

- Long COVID is a heterogeneous disease with several pathogenesis pathways and manifestations which impacts on prognosis and treatment making it vital to develop disease definitions and diagnostics to ensure appropriate management.

Case definition of Long COVID

Due to variability and vagueness of symptoms reported and duration of symptoms emerging, there is a lack of consensus on the case definition of Long COVID. Definitions provided by the National Institute for Health and Care Excellence (NICE) and the World Health Organization (WHO) are the primary definitions adopted in the literature. The NICE definition has been adopted in several published studies on Long COVID in the United Kingdom (UK). As there are several case definitions used in the literature, the working group considered all literature that considered Long COVID symptoms four weeks post-acute infection of SARS-CoV-2.

NICE identifies and diagnoses the long-term effects of COVID-19 (Long COVID) in various stages:[1]

Acute COVID-19: *Signs and symptoms of COVID-19 for up to 4 weeks.*

Ongoing symptomatic COVID-19: *Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.*

Post-COVID-19 syndrome: *Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.*

The WHO published a clinical case definition of post COVID-19 condition by a Delphi consensus on 6 October 2021. The WHO definition is as follows:[2]

Post COVID-19 condition *occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.*

For the purposes of this paper, the term 'Long COVID' will encompass ongoing symptomatic COVID-19 four week's post-acute infection. Given the time elapsed there is insufficient evidence to determine how long the ongoing effects of a SARS-CoV-2 infection may last.[3,63]

Approach to the review

This advice was informed by systematic reviews, meta-analyses and large longitudinal cohort studies, clinical guidelines, government and non-government organisation reports published from March 2021 – 25 March 2022 (including pre-prints). The term 'Long COVID' in the literature considered, described the signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post COVID-19 syndrome (12 weeks or more). When reviewing the literature, all age cohorts were considered.

A list of readily identified Long COVID research studies currently underway in Australia is available at Appendix 2. This list may not be complete.

Summary of evidence

Common symptoms

From the available literature, fatigue is the most common persistent symptom reported for Long COVID. As SARS-CoV-2 can affect multiple organs and systems, such as cardiovascular, neurological, renal, gastrointestinal, musculoskeletal and haematological, a broad range of symptoms are reported. Over 200 symptoms have been reported for Long COVID. Following fatigue, the next most common symptoms are dyspnoea, a change in smell or taste, chest pain, sleeping disorders, anxiety or depression, headache and attention disorder or

cognitive dysfunction.[4,5,6,11] Commonly reported symptoms across different physiological systems are in Table 1.[7,63]

Table 1: Commonly reported symptoms of Long COVID

Symptom group	Most common reported symptoms
Respiratory symptoms	• Breathlessness • Cough
Cardiovascular symptoms	• Chest tightness • Chest pain • Palpitations
Generalised symptoms	• Fatigue • Fever • Pain • Reduced activity and functional level • Reduced nutritional status and weight loss
Neurological symptoms	• Cognitive impairment ('brain fog', loss of concentration or memory issues) • Headache • Sleep disturbance • Peripheral neuropathy symptoms (pins and needles and numbness) • Dizziness • Delirium (in older populations) • Mobility impairment • Visual disturbance
Gastrointestinal symptoms	• Abdominal pain • Nausea and vomiting • Diarrhoea • Weight loss and reduced appetite
Musculoskeletal symptoms	• Joint pain • Muscle pain
Ear, nose and throat symptoms	• Tinnitus • Earache • Sore throat • Dizziness • Loss of taste and/or smell • Nasal congestion
Dermatological symptoms	• Skin rashes • Hair loss
Psychological/psychiatric symptoms	• Symptoms of depression • Symptoms of anxiety • Symptoms of post-traumatic stress disorder
Post-intensive care syndrome (PICS)	PICS refers to one or more of the following symptoms that people experience following care in ICU: • anxiety, depression, • cognitive impairment, memory loss, • muscle weakness, dysphagia and reduced quality of life [8,9]

Many individuals who report symptoms of Long COVID present similarly to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), i.e. the presence of severe incapacitating fatigue, pain, neurocognitive disability, compromised sleep, symptoms suggestive of autonomic dysfunction, and worsening of global symptoms following minor increases in physical and/or cognitive activity.[6] It is important to note that although there are some similarities in the presentation of ME/CFS and Long COVID, further research is required on the pathogenesis and symptomatology of Long COVID. Both conditions are complex and not well understood, with the treatment guided by the predominant symptoms displayed. As the symptoms of Long COVID are so varied, treatment plans require a personalised multidisciplinary approach.[10]

The incidence of long-term symptoms post SARS illness has been well documented in historical SARS outbreaks such as SARS-CoV in 2002 and MERS-CoV in 2012, with presentation of long-term symptoms such as shortness of breath, fatigue and psychological symptoms reported.[6] A recent meta-analysis of 28 studies showed respiratory insufficiency in 11% to 45% of SARS-CoV-1 and MERS-CoV survivors 12 months after acute infection. Aerobic capacity, measured using the 6 Minute Walk Test, was reduced in 41% of SARS survivors 3 months after the acute infection, which slowly improved by 12 months.[11] One-third of SARS-CoV-1 survivors had psychological problems, ranging from depression to anxiety, which persisted beyond 6 months.[11]

Another emerging issue post-acute SARS-CoV-2 infection is the increased risk of cardiovascular outcomes such as cerebrovascular disorders, dysrhythmia, inflammatory heart disease, ischemic heart disease, thrombotic disorders, cardiac arrest and heart failure. The risks and burden of disease increased in a graded fashion according to the care setting during the acute phase, i.e. non-hospitalised, hospitalised and admitted to intensive care.[12]

Ongoing myocardial inflammation has been reported after recovery from COVID-19 infection, even in mildly symptomatic or asymptomatic patients.[13] This is illustrated by the cardiac magnetic resonance imaging of Ohio State University athletes which revealed that 15% had myocarditis after experiencing mild COVID-19 symptoms.[14] In a separate cohort study of 100 recently recovered COVID-19 patients, magnetic resonance imaging showed cardiac involvement in 78% of participants, and ongoing myocardial inflammation in 60% of participants.[15] The findings were independent of the severity and overall course of illness during acute infection, pre-existing conditions, and time from initial diagnosis. A recent review into the cardiovascular complications of Long COVID found a connection between COVID-19 and myocardial damage in the months following recovery from the acute infection. Patients who had a rise in cardiac troponin during the acute phase of infection were found to be particularly at risk.[16] There are a number of potential mechanisms for a raised troponin elevation in this population, however many of these represent indirect effects of COVID-19 on the heart (e.g. right ventricular strain due to lung involvement and/or pulmonary emboli, a type 2 myocardial infarction due to hypoxemia or secondary to a systemic inflammatory response), rather than direct myocardial injury or inflammation causing myocarditis.[13] The occurrence of pericarditis is thought to originate from a

secondary inflammatory reaction as pericardial effusions examined have been sterile, i.e. free of virus.

Symptoms of Long COVID experienced in children have not been widely reported in the literature and evidence is only emerging.[17] The UK Government's short report on Long COVID noted that cardiac and respiratory symptoms were less common in children than adults.[18] In a review of 14 studies on Long COVID in children, it was reported that the most common Long COVID symptoms reported in children and adolescents were:[17]

- headache
- fatigue
- sleep disturbance
- concentration difficulties
- abdominal pain
- myalgia or arthralgia.

The review noted that there was significant variation in the results due to a lack of a clear case definition, a wide age group range, lack of control groups and selection bias. There is currently a lack of quality data on the impacts and risks of Long COVID in children. Most studies to date on children and adolescents are limited in that they use self-reporting methods to capture and monitor symptoms rather than objective measures such as imaging or biomarker testing. The subjective nature of self-reporting symptoms combined with the lack of control groups, means that the indirect effects of the pandemic such as interrupted schooling may cause symptoms that resemble those of Long COVID, and it can be difficult to distinguish between the two.[17]

Finally, several studies have reported that psychological symptoms such as depression, anxiety, post-traumatic stress disorder (PTSD) and obsessive-compulsive symptomology have been occurring in patients' months after diagnosis with prevalence ranging from 18 to 40%.[11] Psychological symptoms were also observed in a study which followed up hospitalised and non-hospitalised COVID-19 patients who were experiencing persisting complaints. At three months follow up, 37% of overall patients had symptoms of PTSD, 35% had symptoms of anxiety and 46% had symptoms of depression.[19] These rates remained high at six months follow up, suggesting psychological symptoms can linger. The indirect effects of the pandemic have impacted society as a whole and psychological impacts have also been observed in those who have so far avoided infection.[11] A recent systematic review examining the long-term impacts of COVID-19 on mental health, found mild or no associations between a COVID-19 infection and adverse mental health impacts indicating that the indirect psychosocial factors (rather than direct impact of the infection) may be the overriding mechanism for any increased depression and anxiety.[20]

Multi-inflammatory Syndrome in Children

There is concern about children developing Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) also known as Multisystem Inflammatory Syndrome (MIS-C) after an acute SARS-CoV-2 infection. MIS-C is a post-infectious manifestation of COVID-19, occurring after acute infection with SARS-CoV-2, which may have been asymptomatic. MIS-C is a rare but very

serious complication of acute SARS-CoV-2 infection. One retrospective study found that 810 of 1,075 COVID-19-associated MIS-C cases were asymptomatic during their COVID-19 illness.[21] This suggests that biological factors beyond organ injury alone may contribute to chronic symptoms in such patients.[11] A detailed discussion of the management of MIS-C is out of scope of this paper. For further information please refer to *NCHRAC Advice 20: Severity of COVID-19 Illness in Children*.

Diagnosis, assessment and management

The diagnosis, treatment and management of Long COVID still has many unknowns with many health professionals unsure of what clinical and laboratory tests they should use to make a definitive diagnosis. This is further hindered by a lack of consensus on the case definition of Long COVID. There are no specific Medicare Benefits Schedule (MBS) fee codes for the condition which affects general practitioners' provision of care and coordination of care amongst the person's health care team and hinders analysis of data on health service use for Long COVID. Current Royal Australian College of General Practitioners (RACGP) advice for health professionals is to use MBS code 721, which is for a GP Management Plan.[22] Additionally, Long COVID has similarities with other conditions that may be considered life threatening, therefore on patient safety grounds these need to be excluded before a diagnosis of Long COVID is made.[1,63]

The National Clinical Evidence Taskforce has living guidelines for the treatment and management of Long COVID. The guidelines advise that the primary health care team be the central point that coordinates person-centred care along with the carer and/or significant other. Best practice care would be provided by a multidisciplinary team that could be accessed through community health, rehabilitation programs or post-COVID-19 clinics.[7] The RACGP guideline to assist general practitioners in treating and managing individuals with Long COVID specifies that health professionals should adopt a personalised approach when assessing physical, cognitive, psychological and psychiatric symptoms, as well as functional abilities.[22] The NICE guidelines recommend a holistic approach in the treatment and management of Long COVID, which usually begins with a thorough assessment and screening using validated tools such as the COVID-19 Yorkshire rehabilitation questionnaire (recommended by the UK National Health Service (NHS))and the modified International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) global paediatric COVID-19 follow-up questionnaire.[1]

Evidence on the best practice approaches to the management of Long COVID is emerging. Currently, patient management is pragmatic and guided by the presenting signs and symptoms. Support for common symptoms such as fatigue may include a focus on diet, nutrition, sleep and other lifestyle factors such as recommending a cautious approach with return to exercise (reduce if there is any increase in symptoms). A monitored return to physical activity can be supported through a referral for rehabilitation by an exercise physiologist or physiotherapist. For patients suffering chest pain or breathlessness, referral for tests for cardiovascular conditions and medical imaging should form part of the treatment management plan.[22]

Further research on the underlying causes of Long COVID is needed to inform appropriate treatment for individuals, especially for those with vague or complex symptoms. Some literature has suggested specialised Long COVID clinics for the management of symptoms,

however no research could be identified to support this approach as being more effective in achieving better outcomes than management via primary care. The emergence of such clinics is relatively new in Australia, with two opening in the ACT and Sydney respectively in recent weeks.[23,24]

Epidemiology

Risk factors

Several risk factors for developing Long COVID have been identified in the literature and highlight the disease's heterogeneous nature and its varying pathophysiologic mechanisms and presentations. A summary of the evidence of both inherent and manageable risk factors are discussed below and summarised in Table 2.

There is a good understanding of how pre-existing conditions affect the risk of developing severe COVID-19. However, how pre-existing conditions affect the likelihood of developing Long COVID following the acute phase of infection is less clear. A clinical review of Long COVID found that hypertension, obesity, a psychiatric condition, or an immunosuppressive condition decreased the likelihood of returning to usual health following COVID-19.[25] An expanded table of how pre-existing diseases and conditions affect the likelihood of a person developing Long COVID is included in Appendix 2.

Long COVID is not associated with high ongoing SARS-CoV-2 viral load but there is evidence that higher viral load when suffering from acute COVID-19 infection is associated with vulnerability to developing Long COVID.[26,27] A recent study looking at quantifiable Long COVID risk factors found that levels of SARS-CoV-2 RNA at the time of acute infection was predictive in the development of the condition. This study also found strong associations with type 2 diabetes, Epstein-Barr virus viremia, and specific auto-antibodies.[28] In addition to the impact of viral load during acute infection, there could also be a link between the site of viral infection and long-term symptoms. A study of the mechanisms of the neurological symptoms associated with Long COVID found that retrograde neuronal transport can facilitate SARS-CoV-2 access to areas of the central nervous system such as the brainstem.[29]

Female gender is believed to be associated with a higher risk of developing Long COVID. Recent data released by the UK's Office for National Statistics (ONS) observed a higher female prevalence of Long COVID (24% females compared to 21% males).[30] Similarly, a cohort study undertaken in Wuhan, China, reported a higher percentage of female patients hospitalised with COVID-19, experienced at least one symptom at a 6-month follow-up (females 81% compared to males 73%).[31]

Nutrition following acute SARS-CoV-2 infection is a key component of recovery. A 2020 study of 549 COVID-19 hospitalised patients found that 36.0% had persistent malnutrition six months following discharge. The authors implicated malnutrition as both a contributing factor and symptom of Long COVID and suggest that nutritional screening and support of those recovering from COVID-19 would prevent some post-acute complications.[32] The impact of poor nutrition is compounded by several Long COVID symptoms, i.e. loss of taste and smell, isolation impacts, reduced appetite, fatigue and gastrointestinal symptoms,

which are potential obstacles to adequate food intake. In recognition of the impact of poor nutrition on Long COVID, the NHS have published nutrition guidelines to assist in recovery.[33] As poor nutritional intake has been associated with lower socioeconomic position in Australia, this places an increased burden of disease on those in vulnerable economic circumstances.[34]

Due to the required bed rest for severe disease (and ventilatory support/immobilisation), post-acute COVID-19 rehabilitation requires management of impaired lung function, physical deconditioning and cognitive impairments.[35] A lack of opportunity to engage with appropriate physical and respiratory rehabilitation is thought to be predictive of poor outcomes and a risk factor for developing Long COVID.[36]

There is growing evidence that COVID-19 vaccination offers some protection against Long COVID. A recent rapid review of the evidence by the UK Health Security Agency analysed 15 observational studies on the effectiveness of vaccination (double dose) against Long COVID. One of the key findings was that recipients of full schedules of Pfizer, AstraZeneca, Moderna or Janssen were approximately half as likely to develop Long COVID following SARS-CoV-2 infection. The most pronounced impact was observed in people over 60 years of age. It was also reported that vaccination after SARS-CoV-2 infection reduced the duration of Long COVID symptoms.[37]

In a sample of UK adults, aged 18 to 69 years, receiving two doses of a COVID-19 vaccine at least two weeks before a confirmed COVID-19 infection was associated with a 41.1% decrease in the odds of self-reported Long COVID at 12 weeks. This was relative to a socio-demographically similar study of participants who were not vaccinated when infected.[38]

Table 2: Long COVID risk factors

Inherent risk factors	Risk factors with opportunity for public health intervention
• Female gender • Some pre-existing health conditions (see Appendix 1) • Obesity • High viral load during acute SARS-CoV-2 infection	• Poor post-acute rehabilitation and exercise • Poor nutrition during recovery (links to lower socioeconomic position) • No/incomplete COVID-19 vaccination

Prevalence

Although the evidence suggests that patients who were hospitalised with a SARS-CoV-2 infection report greater levels of debilitating symptoms post-acute infection, many home isolated patients in the UK who had a mild to moderate acute infection are also reporting symptoms six months after infection.[39] Self-reported Long COVID was most prevalent in the following groups:[40]

- people aged 35 to 69 years of age
- female gender
- those living in the most deprived areas
- those working in health or social care
- those with a pre-existing activity-limiting health condition.

While there is uncertainty around the prevalence of Long COVID, there are a growing number of people that report lingering symptoms post SARS-CoV-2 infection. Data from the UK estimates the prevalence of Long COVID to be 21.0% at five weeks and 13.7% at three months post infection.[41,42] Outcomes of a NSW population-based cohort study found that 20% and 5% of people diagnosed with COVID-19 were still experiencing post-acute, or Long COVID, symptoms after one and three months, respectively.[43]

Deakin University Institute for Health Transformation has published estimates of the likely numbers of Long COVID in a briefing paper, based on the Doherty modelling of re-opening options and recent outbreaks. The following predictions were made:[44]

- August – October 2021 outbreak in Victoria (67,803 cases) would generate between 16,962 and 22,019 cases of Long COVID.
- June – October 2021 outbreak in NSW (69,681 cases) would generate between 17,377 and 22,559 cases of Long COVID.

In a subsequent briefing (January 2022), the Institute for Health Transformation published updated modelling that considered the impact of vaccination and the Omicron wave over the 2021/2022 summer period which is presented in Table 3.[45] It worked from an estimate of 3.16 million confirmed COVID-19 infections between 26/11/21 and 09/03/22 (actual subsequent confirmed cases were 3.29 million for this period) and assumed that the protective effect of vaccination is 46%. The four models utilised different data sources to predict the likelihood of developing Long COVID:

- Liu *et al*: Long COVID estimate using the extrapolated NSW data.[42]
- ONS 1: Long COVID prevalence estimates released by the ONS for the UK incorporating the prevalence of any of the 12 symptoms such as fever, headache, muscle ache, weakness/tiredness, nausea/vomiting, abdominal pain, diarrhoea, sore throat, cough, shortness of breath, loss of taste, and loss of smell at a point in time after infection.[46]
- ONS 2: Long COVID prevalence estimates released by the ONS for the UK incorporating the prevalence of continuous symptoms after infection.[46]

- ONS 3: Long COVID prevalence estimates released by the ONS for the UK incorporating the prevalence of self-reported Long COVID.[46]

Table 3: Modelled Long COVID-19 cases emerging due to the Omicron wave

	Week	NSW	VIC	AUSTRALIA
Lui et al. (NSW extrapolated data)	**5**	166,190	102,940	454,266
	12	49,246	30,503	134,609
	52	56	35	154
ONS 1 (UK extrapolated data – any of 12 symptoms)	**5**	55,963	34,664	152,971
	12	40,960	25,371	111,959
	52	6,983	4,325	19,086
ONS 2 (UK extrapolated data – continuous symptoms)	**5**	60,104	37,229	164,289
	12	21,103	13,072	57,684
	52	56	35	154
ONS 3 (UK extrapolated data – self reported)	**5**	94,235	58,370	257,583
	12	84,008	52,035	229,629
	52	43,807	27,134	119,741

NOTE: Calculations based on double the actual reported figures. NSW 1,156,344, VIC 716,252 and Australia 3,160,769

This modelling shows that Australia could see over 200,000 people experiencing Long COVID symptoms at 12 weeks post infection. The authors noted that there was significant variation between models for the case numbers predicted at 52 weeks post infection and considered the low numbers of 52 week estimates for the Liu *et al.* and ONS 2 models not consistent with other evidence. The ONS 3 model predicted that the 2021/2022 summer Omicron wave could result in just under 120,000 people experiencing symptoms a year after infection in Australia.

The Medical Research Future Fund – *Coronavirus Research Response – 2021 COVID-19 Treatment Access and Public Health Activities Grant Opportunity* is in the process of funding a national linked data platform that integrates relevant existing health data sets for the purposes of strengthening evidence-based public health and health system planning and management for future pandemics. There are several longitudinal studies currently underway in Australia however, there are limited results available. Follow up on the outcomes of these studies will be important to understand the impact of Long COVID in Australia. A list of the studies that could be readily identified can be found at Appendix 3.

The disproportionate burden of COVID-19 on Australians who are economically disadvantaged is well understood.[47] It is reasonable to expect that these groups will be overrepresented in Long COVID cases and impact those who rely on casual or insecure employment. Thus, further research into the economic and health system impacts in Australia is required. The likely impact of Long COVID on health and social care workers is also of considerable concern.

There is little evidence available for the long-term health and productivity impacts of Long COVID on the lives of Australians. One pre-print study modelling this impact using disability-adjusted life years (DALYs), found that Long COVID and post-intensive care syndrome

accounted for at least 19% and 3% of the total base case DALYs respectively. The authors suggest that the Australian health system needs to prepare for an influx of patients with Long COVID with specialised clinics and coordinated primary care support. Whilst vaccination will also offer some protection against developing Long COVID, the overall impact of high vaccination coverage will result in lower mortality. This preparation is therefore of high importance as Australia will continue to see the burden of COVID-19 transition from mortality to longer term morbidity.[37,48]

The following factors need to be considered when investigating the prevalence and burden of Long COVID:

- The symptoms of Long COVID are of common occurrence in the general population and symptoms may be misinterpreted by both patients and clinicians.[49,50]
- Most studies on Long COVID in children and adolescents have significant limitations such as, the possible bias with self-reported data and inaccurate testing that creates uncertainties of infection status of participants in the control group.[17,51,52]
- In the literature it has been observed that some of the commonly reported cognitive Long COVID symptoms have been experienced by children who are seronegative in equal rates to children who have experienced mild COVID-19.[49] Similar observations have been made in adults suggesting that the symptoms associated with Long COVID may be caused by factors other than SARS-CoV-2 infection.[53,54]
- Experiences of long-term symptom persistence following respiratory illness are common. For example, fatigue is reported at high frequencies for patients three months post infection with pneumonia.[55]

It is important to note that even if 'Long COVID like' symptoms do not stem from a novel condition following SARS-CoV-2 infection, a focus on treatment and rehabilitation should remain a public health priority.

Mechanisms and pathophysiology

Mechanisms

The biological mechanisms that cause Long COVID are still being investigated through continued research on the virus to understand how and why symptoms persist. Long COVID is a heterogeneous condition with several pathogenic pathways, with these pathways still under investigation. A summary of these mechanisms is outlined in Figure 1. These pathways can also overlap resulting in many manifestations of the disease.

There are several theories emerging and possible links to previous SARS illnesses and ME/CFS.[6] ME/CFS is a complex and controversial clinical condition without established causative factors. The infectious agents related to ME/CFS have been Epstein-Barr virus, cytomegalovirus, enterovirus and herpesvirus and as such there is speculation that SARS-CoV-2 can be added to the viral agents' list causing ME/CFS.[56]

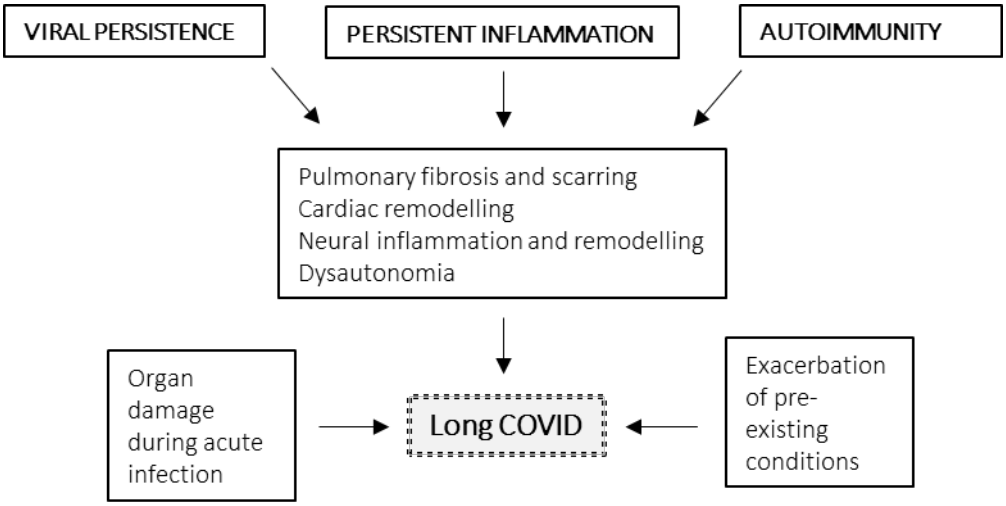

Figure 1: Probable mechanisms that contribute to the pathogenesis of Long COVID.
Reproduced and simplified from the Nature Immunology paper "Pathological sequelae of long-haul COVID".[57]

Exacerbation of pre-existing comorbidities may influence the development of Long COVID. Also, in people with immune systems that are weakened, challenged or dysregulated the SARS-CoV-2 virus may change its gene expression or protein production. This may drive a range of persistent symptoms.[14] For example, more than 90% of humans harbor at least one strain of herpesvirus,[58] but most infections are kept in latency by host interferons.[59,60] By disabling the host interferon response, SARS-CoV-2 may allow persistent herpesviruses to take advantage of acute COVID-19.[61] Early studies and case histories demonstrate that herpesviruses are indeed reactivating in COVID-19 patients.[62,63]

Multiorgan damage and complications in infected subjects are not unexpected, given that the SARS-CoV-2 entry receptor, ACE2, is expressed in multiple tissues. However, the biological mechanisms that drive the long-term health consequences have not yet been defined, nor have effective treatments or rehabilitation measures in clinical trials to date.[11]

SARS-CoV-2 can persist in several tissues such as the gastrointestinal tract, central nervous system and other ACE-2 expressing organ systems months after the virus has been cleared from the nasopharynx. This does not occur exclusively in patients with Long COVID and has been observed in patients with have fully recovered from acute COVID-19.[57,64] This is consistent with reports that people experiencing Long COVID have had symptom improvement upon receiving a SARS-CoV-2 vaccine; however, further studies need to be conducted to determine if such viral reservoirs are eradicated from the body following vaccination.[65]

An autoimmune response that persists after the SARS-CoV-2 virus has been eliminated is also thought to be a mechanism for the development of Long COVID. Viral mimicry, a breakdown of tolerance against self-antigens, epitope spreading and presentation of cryptic antigens are proposed to be involved in this dysregulatory immune response.[57] This is yet to be fully understood; however, there is evidence that patients with Long COVID have abnormal immune profiles.[66,67,68,69] One study with long-term follow up of patients (12

months post initial symptom onset) with Long COVID, found neurocognitive symptoms to be associated with elevated antinuclear antibody (ANA) titres (reflecting autoimmunity).[70]

Another proposed mechanism for the development of Long COVID is defects and/or delay in the resolution of the inflammatory response to SARS-CoV-2 infection. Ongoing inflammation could explain persistence of symptoms at infection sites such as the respiratory tract and lungs and may be more relevant to patients who had symptomatic COVID-19.[57] Studies on the specific immune response and biomarkers are emerging with one recent study correlating results with this theory with a set of analytes identified (IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6) that are highly associated with Long COVID.[71] These analytes are also associated with severe disease at the acute stage of SARS-CoV-2 infection.[72,71]

Biomarkers

Due to the heterologous nature of Long COVID, diagnostic techniques are guided by the presenting symptoms. Emerging studies examining the testing of biomarkers and medical imaging may explain the cause of some of the symptoms. However, there is a need to standardise biological measures such as peripheral blood markers of genetic, inflammatory, immune, and metabolic function to compare studies. There are still inconsistencies with some of the results and further research is required to provide reliable clinical outcome measures. Further details from recent literature can be found in Appendix 3.

Elevated biomarkers for highly activated innate immune cells have been found in studies, which implies that high inflammatory levels during acute SARS-CoV-2 put patients at higher risk of developing Long COVID.[71]

Imaging biomarkers, particularly chest and brain CT's and X-rays, has been used across several studies to monitor post-acute COVID health effects. In one systematic review, 34% of patients analysed had abnormalities detected in chest imaging.[5] Cardiac magnetic resonance imaging can be used to demonstrate myocarditis after mild COVID-19 and track ongoing myocardial inflammation of recovered COVID-19 patients.[72,73] Further research on the correlation between the abnormal imaging and biomarkers with Long COVID will inform the underlying causes of the condition and how it can be prevented and treated effectively.

Neuropathy is emerging as a persistent and debilitating symptom of Long COVID, with patients in one longitudinal study (N=7) reporting various neuropathic ailments from skin biopsies, electrodiagnostic tests and autonomic function tests.[74] Over half of patients reported long term improvement, however no patients reported complete resolution of symptoms. A limitation of this study includes a low number of participants (seven) creating potential sample bias with the results.[74]

Areas for further research

When reviewing the literature, NCHRAC noted several limitations:

- There is significant variation in the definition of Long COVID which impedes the application of consistent and adequate clinical diagnosis and subsequent treatment and management of the condition.

- High-quality evidence about the longer-term sequelae of COVID-19 is missing due to the relatively short time since the emergence of the disease.
- Existing studies have often lacked adequate control groups which makes it difficult to draw reliable conclusions.
- There is limited data on Long COVID that are disaggregated by socio-economic status, geography, and ethnicity and cultural alignment which limits understanding Long COVID in populations in vulnerable circumstances and devising appropriate responses.[75]
- Inequalities in access to care for Long COVID in rural/remote areas in Australia and other populations is an important area for further consideration but out of scope of this paper.

Attachments

- Appendix 1: Long COVID Risk Factors
- Appendix 2: Current Long COVID studies in Australia
- Appendix 3: Literature review of Long COVID biomarkers

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APPENDIX 1: Long COVID Risk Factors

Factor	Risk
Age	Being aged 35 or above is associated with risk of Long COVID symptoms.[1]
Gender	Female – increased risk for: • decreased physical function[2] • psychiatric morbidity[3] • fatigue[4] • Olfactory dysfunction [5] • PTSD symptom severity and hence protracted symptoms (see below)[6] • Any persistent symptom[7]
Body mass index (BMI)	Moderate and severe obesity (BMI ≥ 25-35 kg/m^2) is associated with a greater risk of Long COVID.[8,9]
High viral load during initial SARS-CoV-2 infection	Increased risk of developing Long COVID.[10]
Large number of initial symptoms	Increased risk for: • Any long-term symptom[11] • Depression, anxiety, PTSD[12]
Pre-existing diabetes	Individuals with pre-existing diabetes mellitus have an increased risk of developing Long COVID.[10]
Pre-existing respiratory condition such as asthma or Chronic Obstructive Pulmonary Disease (COPD)_	Not associated with Long COVID overall, but asthma was associated with neurological and mood and behavioural changes and chronic pulmonary disease was associated with chronic fatigue REF.[13]
Pre-existing infection with Epstein Barr virus	Individuals who have had a previous infection with Epstein-Barr virus may have the dormant infection re-activated during acute SARS-CoV-2 infection leading to an increased risk of developing Long COVID.[10]
Dyspnoea:	Increased risk for: 1. Any long-term symptom[11] 2. Physical decline/fatigue[14]
Delirium	Increased risk for developing neurocognitive impairment[3]
Autoimmune/ rheumatologic disorders	Nominal association with increased risk for long-term symptoms[11]
Neurocognitive impairment	Increased risk for psychiatric morbidity[3]

Factor	Risk
Smoking status	Associated with increased complications/increased severity but current evidence does not suggest a link to delayed return to health[1]
Stress-related symptoms	Increased risk for developing neurocognitive impairment[3]
Anxiety disorder	Nominal association with increased risk for long-term symptoms[11]
Pre-existing diagnosis of depression/anxiety	Increased risk for fatigue[4]
Moderate to severe PTSD (IES-R score)	Increased risk for any long-term symptom (sole predictor)[6] 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.
Vaccination status (unvaccinated against COVID-19)	Increased risk for development of any Long COVID symptom.[15]

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APPENDIX 2: Current Australian Long COVID studies

There are many studies on Long COVID currently and emerging in Australia. This list is not an exhaustive but highlights some of the larger longitudinal studies to capture evidence in the future if required.

Study	**Details**
ADAPT study	The ADAPT observational study through St Vincent's Hospital and Kirby Institute: The ADAPT study is following patients diagnosed with SARS-CoV-2 infection through St Vincent's Hospital clinical service at regular intervals over a minimum of one-year post diagnosis.
DHHS Long COVID Survey	The team are planning to send the survey to 20000 cases and 5000 controls. Cases will be identified through the Victorian Agency for Health Information database.
Royal Melbourne Hospital and Doherty Institute	Prospective cohort of hospitalised patients recruited from the beginning of the pandemic. They are collecting biological samples and broad data collection on multiple systems that may be affected in Long COVID (respiratory, neurocognitive).
Barwon Health, CSIRO and Geelong Hospital Long COVID study	
Sydney Children's Hospital Network study	Cohort study with questionnaire follow up of COVID+ children (initially from the Delta outbreak)

APPENDIX 3: Long COVID biomarker literature

Diagnostic measure	Type of review	Results
Cardio pulmonary biomarkers and imaging	Systematic review/meta-analysis	Pulmonary dysfunction: 34% of patients analysed had abnormal results from chest Xray and computed tomography scans (95% CI 27-42). Elevated cardiac markers in patients were: D-dimer (20%, 95% CI 6-39); N-terminal (NT)-pro hormone BNP (NT- pro BNP) (11%, 95% CI 6-17); C-reactive protein (CRP)(8%, 95% CI 5-12); serum ferritin (8% 95% CI 4-14); procalcitonin (4% 95% CI 2-9) and interleukin-6 (IL-6) (3% 95% CI% 1-7)[1]
Pulmonary biomarkers	Cohort study of patients who were hospitalised with their acute SARS-CoV-2 infection	More than a third of recovered patients developed lung fibrotic abnormalities such as: elevated lactate dehydrogenase (LDH); D-dimer; decreased alveolar volume and K CO indicating impaired diffusion capacity.[2] Both stable and progressive fibrotic lung disease result in excessive deposition of extracellular matrix molecules such as fibronectin, collagen, and laminin in parenchymal lung tissue. This leads to epithelial/endothelial injury and thickened alveolar walls, which can hinder gas exchange in the lungs and increase symptoms of fatigue, dyspnoea, and exercise intolerance. [3]
Innate immune system biomarkers	ADAPT Cohort longitudinal study	Patients with Long COVID had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Using a log-linear classification model, the researchers defined an optimal set of analytes that had the strongest association with LC among the 28 analytes measured. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with Long COVID with 78.5–81.6% accuracy.[4] In summary, the data indicates an ongoing, sustained inflammatory response following even mild-to-moderate acute COVID-19, which is not found following prevalent coronavirus infection. The drivers of this activation require further investigation, but possibilities include persistence of antigen,

Diagnostic measure	Type of review	Results
		autoimmunity driven by antigenic cross-reactivity or a reflection of damage repair. These observations describe an abnormal immune profile in patients with COVID-19 at extended time points after infection and provide clear support for the existence of a syndrome of Long COVID.
CT imaging biomarkers of grey matter thickness or volume	Cohort/longitudinal study	The study identified significant longitudinal effects when comparing the two groups, including: (i) greater reduction in grey matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus, (ii) (ii) greater changes in markers of tissue damage in regions functionally-connected to the primary olfactory cortex (iii) greater reduction in global brain size. The infected participants also showed on average larger cognitive decline between the two timepoints based on a significant difference in the time taken to complete numeric and alphanumeric cognitive function testing.[5]
Neuropathy Biomarkers	Longitudinal study	Among 17 patients (mean age 43.3 years, 69% female, 94% Caucasian, and 19% Latino), 59% had ≥1 test interpretation confirming neuropathy. These included 63% (10/16) of skin biopsies, 17% (2/12) of electrodiagnostic tests and 50% (4/8) of autonomic function tests. One patient was diagnosed with critical illness axonal neuropathy and another with multifocal demyelinating neuropathy 3 weeks after mild COVID, and ≥10 received small-fiber neuropathy diagnoses. Longitudinal improvement averaged 52%, although none reported complete resolution.[6]

Literature reviewed for this table consisted of a combination of systematic reviews, meta-analyses and cohort studies. Articles were assessed for relevance based on a PubMed search for papers published between January 2021-March 2022. Additional studies were identified by snowballing, incorporating studies identified by relevant experts and members of the working group. This list is not an exhaustive count of all studies conducted on the biomarkers associated with Long COVID. The studies listed were not assessed for quality and there is potential selection bias.

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