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Long COVID in Australia – a review of the literature

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Summary

Long COVID is a complex, multi-system illness with the potential for a substantial impact on society, from increased health care costs to economic and productivity losses. Symptoms may persist for weeks or months following acute SARS-CoV-2 infection, come and go over time, or manifest as new onset chronic conditions, such as heart disease, diabetes, kidney disease and neurological conditions.

Long COVID is an umbrella term used to describe both ongoing symptoms in the medium-term (4–12 weeks) and longer-term sequelae beyond 12 weeks known as *post-COVID syndrome* (National Institute for Health and Care Excellence) or *post COVID-19 condition* (World Health Organization).

This review analyses the available Australian and international literature to understand the impact and scale of long COVID, including:

- incidence and prevalence of long COVID in Australia and internationally
- whether SARS-CoV-2 variants and vaccination modify the risk of developing long COVID
- demographic, clinical and social determinants of long COVID
- outcomes and impact of long COVID on patients, such as burden of disease, health service use, quality of life and patient experience
- data deficiencies and research gaps around long COVID

Many studies from the early phases of the pandemic were conducted before clear definitions were developed and produced wide variation in results. In addition, there has been no consensus on a core set of health outcomes to be measured and reported for long COVID which has also translated into inconsistent findings.

Prevalence of long COVID

As most cases of COVID-19 have occurred in Australia during 2022 studies of the occurrence of long COVID have only recently gathered momentum. From the limited data available, current prevalence estimates of long COVID (defined as >12 weeks) in Australia range from 5% to 10% of COVID-19 cases.

Wide variation in estimates has been reported from international data, ranging from 9% to 81% in a global systematic review. Sources of heterogeneity include methodological differences between studies including definitions of long COVID and follow-up time, geographic region, demographic and clinical profile of study participants and acute COVID-19 disease severity.

Studies using stricter case definitions for long COVID have produced more modest estimates. The prevalence of post COVID-19 condition (>12 weeks) ranged from 8% to 17% in studies from the UK. The global prevalence of post COVID-19 condition was estimated to be 6.2% of symptomatic COVID-19 infections when only symptoms of fatigue, cognitive problems or shortness of breath were counted.

Many studies lack non-COVID-19 comparison groups that are needed to establish whether the prevalence can be attributed to COVID-19, which is particularly important for studies that rely on self-report of a diverse range of signs and symptoms that are not unique to long COVID.

Regardless of the precise definition of long COVID used by individual studies, most studies find a relationship with severity of acute COVID-19. Prevalence is highest in patients who were admitted to an intensive care unit (ICU) for COVID-19, followed by hospitalised patients, and lowest in non-hospitalised patients.

There is growing evidence that the risk of long COVID has been lower during the Omicron wave compared with earlier SARS-CoV-2 variants. However, because many people were vaccinated when the Omicron variant emerged, observed differences in risk of long COVID in relation to different SARS-CoV-2 variants could be due to vaccination. A meta-analysis of 18 studies found that the risk of long COVID was 32% lower (relative risk [RR] 0.68, 95% confidence interval [CI] 0.53–0.87) based on studies using a >4-week definition and 25% lower (RR 0.75, 95% CI 0.64–0.88) for other definitions combined for people double vaccinated against SARS-CoV-2 compared to unvaccinated people.

Determinants of long COVID

There is growing evidence that severity of acute disease, age, female sex and comorbidities are the most common risk factors for the development of long COVID:

- severity of illness during the acute COVID-19 infection has been identified by numerous studies as an important predictor of long COVID. This includes the number of symptoms, length of hospital stay and ICU admission
- long COVID has an inverted U-shaped relationship with age and is most common in middle-aged adults
- studies have consistently shown that females experience a higher prevalence of self-reported long COVID than males, a finding that is independent of demographic and clinical characteristics
- poorer underlying health is also related to an increased risk of long COVID. Pre-existing chronic conditions and their associated risk factors, such as obesity and smoking, increase the risk of developing long COVID.

People from lower socioeconomic groups, certain occupations and ethnic backgrounds may also be at a higher risk of developing long COVID. However, there is a lack of robust research focusing on social determinants and long COVID. Understanding the burden of long COVID in specific population groups is important to target prevention and develop treatment and care programs.

Very few protective factors other than SARS-CoV-2 vaccination have been identified. There is emerging but preliminary evidence that management of acute COVID-19 infection with antiviral medication and physical activity may reduce the risk of long COVID.

Long COVID and chronic conditions

Some people develop a range of multi-organ symptoms that may arise as a direct complication during the acute COVID-19 illness or develop over the longer term leading to new-onset chronic conditions.

Studies of large health databases, predominantly from the US, have identified an increased risk of a range of chronic outcomes, including cardiovascular disease, metabolic disorders, and mental and neurological complaints up to 12 months following infection. Imaging and laboratory studies have demonstrated persistent structural damage to the heart which may result in increased hospitalisation for cardiovascular events such as heart attacks.

One of the most common neurological complaints is ‘brain fog’ characterised as difficulties with cognitive function, attention and memory. Some symptoms of long COVID, particularly

persistent fatigue and post exertional malaise, overlap with myalgic encephalomyelitis (ME), also called chronic fatigue syndrome (CFS). ME/CFS has also been associated with previous viral infections and the underlying pathophysiology between these sets of symptoms may be similar for the 2 conditions. Continued research into long COVID may provide further understanding of ME/CFS. Likewise, established research on ME/CFS may point to clues worth investigating in long COVID.

Impact of long COVID

The review examines 4 dimensions of the impact of long COVID: the population health impact through the burden of disease and mortality, impacts on the health system, quality of life and social impacts, and the patient experience with long COVID.

- In Australia, since the start of the pandemic and up to 30 September 2022, there had been 10,279 deaths due to COVID-19 of which 123 (1.2%) were classified as being due to post COVID-19 condition. Long COVID contributed to 10% of the total burden of disease from COVID-19 in Australia in the first few months of 2022.
- Several studies have reported increased post-acute COVID-19 health care utilisation and costs, including rehospitalisation, emergency department visits, outpatient visits and primary care attendances.
- A significant proportion of people with long COVID report limitations on their daily activities and a reduced quality of life. In the COVID-19 Impact Monitoring Survey, 22% of respondents with symptoms lasting for 3 months or more reported their ability to carry out day-to-day activities had reduced substantially compared to before COVID-19. The impact of persisting symptoms can impact on workforce participation, including delays in return to work, and ongoing residual difficulties that impact the ability to perform the same duties or limit working hours.
- The term ‘long COVID’ emerged as social terminology to describe patient’s experiences of the long-term health effects of SARS-CoV-2 infection. The use of online support groups and social media has been a key tool for patient advocacy, demonstrating the evolution of social attitudes and experiences of long COVID. In the early phase of the pandemic, long COVID sufferers expressed a lack of belief and recognition of their illness by health care professionals and struggled to access medical care. Over time, the sentiments have become more positive, reflecting increased knowledge, acceptance and awareness of long COVID and health system responses to the condition.

Data deficiencies and future research

One of the main limitations of long COVID research is the inconsistency in the definition of long COVID used. Specially, there is difficulty in effectively defining the condition’s symptoms and time course for research and clinical purposes. Two definitions have been developed by the National Institute for Health and Care Excellence (NICE) and the World Health Organization (WHO) that define parameters around the timing and duration of symptoms, but both remain broad in relation to symptoms. An international consensus study has produced a core outcome set for adults with post COVID-19 condition consisting of 12 outcomes in the domains of clinical, life impact and survival to improve harmonisation and comparability across studies.

In September 2020 WHO activated an International Classification of Disease, 10th Revision (ICD-10) code for post COVID-19 condition. Analysis of the use of the code in US health care records has shown that the uptake varies widely and currently underestimates the frequency of long COVID. As use of the code becomes more consistent, health care records will

provide large and rich sources of data to understand the impact of long COVID, such as patterns of health service use among long COVID patients. However, health records may be impacted by behavioural differences in seeking care, the need for care depending on the severity of long COVID symptoms, disparities in the availability of care, obtaining a diagnosis of long COVID and having that diagnosis recorded in the patient record. These issues may lead to lack of representation in health records of some population groups.

Most of the evidence presented in this review has been from research conducted overseas. Some opportunities for research to monitor the impact of long COVID in Australia include:

- The national COVID-19 linked data set is a project being conducted by the AIHW to link COVID-19 infection notifications from states and territories to national administrative health data sets including deaths, hospitals, aged care, immunisation, Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data. This data asset will allow investigation of health outcomes post-COVID-19 infection, including the occurrence, risk factors and impact of long COVID. This information will be valuable for understanding health service demands arising from long COVID and could be useful in designing targeted long COVID models of care.
- Long COVID clinics have been established across Australia to provide specialised care to people having long-term symptoms after COVID-19 infection. These clinics provide an opportunity to collect data on long COVID progression in affected individuals.
- Large-scale national surveys, like those established in the UK and USA, provide rapid and relevant long COVID information including the tracking of the prevalence over time. This information is important for planning prevention and health care demand.
- Several Australian longitudinal studies have included questions on COVID that will allow for analysis of post-COVID-19 outcomes. This includes the 45 and Up Study conducted by the Sax Institute.

Long COVID is a new condition and therefore the evidence so far is limited by a relatively short follow-up time since infection, particularly in Australia where most of the acute burden of COVID-19 has occurred in 2022 to date. Research and monitoring of long COVID is required to understand its impact in the Australian population and to corroborate findings with the evidence from other countries.

1 Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by infection with the SARS-CoV-2 virus. The disease emerged in late 2019 and rapidly spread around the world, with the first case in Australia identified on 24 January 2020 (Caly et al. 2020). COVID-19 was declared a pandemic by the World Health Organization (WHO) in March 2020. The initial reporting focus of COVID-19 was on the acute presentation of COVID-19 and in particular the number of deaths from the virus – by 1 September 2022, more than 600 million cases had been confirmed globally and 6.5 million COVID-19 related deaths (Mathieu et al. 2022).

In Australia, there had been 10 million COVID-19 cases by 1 September 2022 (Department of Health and Aged Care 2022), with over 10,000 registered deaths due to COVID-19 by 30 September 2022 (ABS 2022a). The severity and range of symptoms from a COVID-19 infection varies from person to person. The most common symptoms include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea (CDC 2022b).

While most people who get COVID-19 fully recover within 1–2 weeks (AIHW 2022c), it is now well documented that some people develop persistent symptoms or 'clinical sequelae' for weeks to several months after initial infection. These symptoms have been generally referred to as 'long COVID' and the long-term implications of these ongoing clinical manifestations pose a major challenge for health care systems (Maglietta et al. 2022).

Box 1.1: Where did the term 'long COVID' come from? The Patient Experience

The term 'long COVID' was collectively created by the patient community and in the early stages of long COVID, the symptoms were thought to be pyschological (Callard and Perego 2021). Many patient groups, online communities and support groups have been set up as a support mechanism to those experiencing long COVID symptoms.

Although this literature review will focus on quantitative results, the patient experience is central to better understanding long COVID. A number of patient stories are emerging in the multiple platforms across the media. Generally the experiences reinforce the heterogeneity of long COVID sypmtoms and the impact that it is having on people's lives.

1.1 Purpose of the report

The purpose of this report is to draw on Australian and international literature to understand the impact and scale of long COVID on patients and the health system in Australia, to understand who may be most at risk of developing long COVID so that strategies and preventive measures can be tailored accordingly and to inform and assist health policy and planning and future preparedness.

Long COVID is a significant research priority globally and the evidence base is rapidly developing. There is limited evidence of the impact of long COVID in Australia. Although the prognosis of long COVID is uncertain, it is being recognised as a public health concern, particularly due to its substantial impact on society, from increased health care costs to economic and productivity losses (DHHS 2022).

The broad objectives of the report are to provide information on:

- the incidence and prevalence of long COVID in Australia and internationally

- how SARS-CoV-2 variants and vaccination modify the risk of developing long COVID
- demographic, clinical and social determinants of long COVID (including modifiable risk and protective factors)
- outcomes and impact of long COVID on patients, such as burden of disease, mortality, health service use, quality of life and patient experience
- data deficiencies and research gaps around long COVID.

1.2 Information sources and data collection

Selection of articles

Peer-reviewed literature was identified from PubMed using the search term 'long COVID' under a COVID-19 filter category. The search was conducted on 16 September and automatically covered studies published from the start of the pandemic. The search strategy also incorporated a desktop search of the grey literature from reputable public health sources such as the United States (US) Centers for Disease Control and Prevention (CDC), National Institute for Health and Care Excellence (NICE), WHO, Office for National Statistics (ONS) and the Australian Bureau of Statistics (ABS). MedRxiv was also searched to identify pre-print articles published since 1 January 2022 with the phrase 'long COVID' in the title. Any additional articles identified in reference lists from included studies were also included.

Inclusion criteria consisted of all reports since the beginning of the pandemic examining long COVID (>4 weeks) in humans. Although studies reporting data from different age groups were included, studies specifically examining long COVID in adolescents and children, including the post COVID-19 condition multi-inflammatory syndrome in children (MIS-C), were excluded. Clinical studies investigating treatment and management of long COVID were also excluded.

Reviews, editorials and commentaries, qualitative and quantitative study designs were eligible for inclusion. Case reports, case series studies and study protocols were excluded. Titles and abstracts were screened by 2 independent authors and irrelevant articles were excluded. Articles were categorised according to the following themes:

- defining long COVID
- symptoms and pathophysiology
- prevalence and incidence of long COVID – including hospitalised and non-hospitalised COVID-19 patients and general population samples, but excluding studies of specific clinical patient groups
- demographic, social and clinical determinants
- risks of different underlying chronic conditions
- impact of vaccination and SARS-CoV-2 strains and variants
- long COVID and other post-acute infection syndromes
- patient outcomes – mortality and burden of disease due to long COVID, quality of life, patient experience and societal impacts.

Evidence synthesis

The findings are presented as a narrative synthesis. Due to the rapidly evolving information over the 2 years, not all studies identified through the search and screening process are reported on in this review. Some earlier literature was omitted so that current trends were highlighted rather than an in-depth analysis. In addition, the review prioritised research based on high quality study designs, such as large longitudinal studies with comparison groups (Amin-Chowdhury and Ladhani 2021), and pre-existing systematic reviews.

This report also prioritises literature which meets the definition for post COVID-19 condition of more than 12 weeks (3 months) following infection. However, given the shifting nature of the pandemic and the associated literature, there are some papers included that will reference ongoing COVID-19 symptoms prior to 3 months.

2 What is long COVID?

2.1 Symptoms of long COVID

Long COVID is a multisystem illness that can affect nearly every organ in the body (DHHS 2022). It is characterised by persistent symptoms that can affect an individual's ability to perform daily activities such as work or household chores. Early research compiled more than 200 possible symptoms of long COVID (Davis et al. 2021), however, the symptoms reported can overlap with other conditions that are not related to COVID-19, such as pre-existing health conditions (Castanares-Zapatero et al. 2022). Subsequently, 62 symptoms have been found to be associated with a history of COVID-19 at 12 weeks after the index date independent of sociodemographic factors, baseline symptoms and comorbidity (Subramanian et al. 2022).

Some of the most common symptoms include fatigue, breathlessness, persistent cough and loss of smell but may vary from person to person (Box 2.1). In addition, long COVID can manifest as new-onset chronic conditions, such as heart disease, diabetes, kidney disease and mental and neurological conditions (DHHS 2022). While people who have had a more severe form of COVID-19 are more likely to experience long COVID symptoms, a severe infection is not a prerequisite for long COVID (Cutler 2022). It is important to note that these symptoms may come and go and are not explained by another health problem in order to be considered as long COVID (Johns Hopkins Medicine 2022).

Box 2.1: What are the symptoms of long COVID?

According to the WHO (WHO 2021), the most common symptoms of post COVID-19 condition include:

fatigue

shortness of breath or difficulty breathing

memory, concentration or sleep problems

persistent cough

chest pain

trouble speaking

muscle aches

loss of smell or taste

depression or anxiety

fever.

A recent matched cohort study (Subramanian et al. 2022) found additional symptoms to those listed by the WHO, including:

hair loss

sneezing

ejaculation difficulty

reduced libido.

The vast range of individual symptoms identified tend to fall into major groupings related to organ systems such as respiratory, cardiovascular and neuropsychological abnormalities (Reese et al. 2022; Umesh et al. 2022). It should be noted that some patients may experience multi-organ symptoms across these sub-types (Sahanic et al. 2022). Neuropsychological complaints are the most common group of symptoms, regardless of the severity of initial infection, with fatigue being the most common (Umesh et al. 2022).

Long COVID symptoms can range from mild to severely debilitating with organ damage, however, a clear distinction between long COVID and post-intensive care unit syndrome is often not made in studies (Brodin et al. 2022). Even in studies based on clinical observations, it is difficult to know if an abnormality was present before acute COVID-19 and was consequently diagnosed during additional tests performed following COVID-19 (Deer et al. 2021).

Symptoms may also occur in the absence of COVID-19 and, without the use of appropriate control groups in epidemiological studies, the specificity of symptoms to long COVID are not well defined. The importance of a control group is highlighted by a recent pre-print study from the United Kingdom (UK) that compared patterns of symptoms after 12 weeks of COVID-19 onset with individuals who had not had COVID-19 (Bowyer et al. 2022). They found individuals without COVID-19 also reported moderate levels of many symptoms commonly associated with long COVID, including headaches, fatigue and musculoskeletal pain. However, this study was able to demonstrate a higher symptom burden among those who had COVID-19 more than 12 weeks previously compared to those without COVID-19, characterised by fatigue, shortness of breath, muscle pain or aches, difficulty concentrating and chest tightness. A recent systematic review of studies using cardiopulmonary exercise testing (CPET) found exercise capacity was reduced by 4.9mL/kg/min among individuals with long COVID symptoms compared with individuals without symptoms more than 3 months after infection (Durstenfeld et al. 2022).

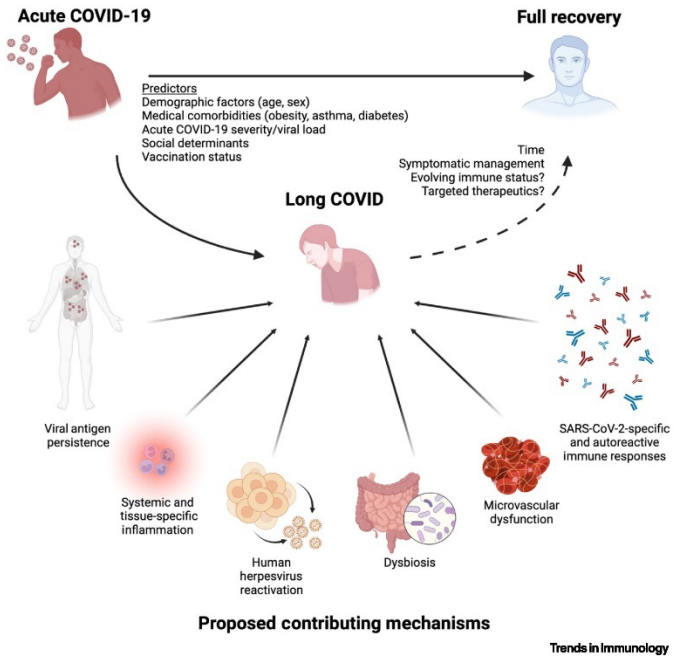
It is still unclear how long symptoms will persist in people with long COVID. Improvement in symptoms and quality of life generally occurs between 3 and 6 months, but some people can experience ongoing symptoms beyond 6 months with only gradual improvement over 2 years (Fernández-de-Las-Peñas, Martín-Guerrero, Cancela-Cilleruelo, Moro-López-Menchero, Rodríguez-Jiménez and Pellicer-Valero 2022; Global Burden of Disease Long COVID Collaborators 2022; Hastie et al. 2022; Torjesen 2021; Vaes et al. 2021).

Ongoing symptoms following recovery from acute infection is not unique to long COVID. Several infectious diseases, such as Epstein Barr virus, Ross River virus and other coronaviruses, also have an increased risk of post-infectious sequelae comprising symptoms of fatigue, musculoskeletal pain, neurocognitive difficulties and mood disturbance (Hickie et al. 2006; Moldofsky and Patcai 2011). Chronic fatigue syndrome (CFS) is often preceded by a viral illness; however, the precise pathophysiology remains unclear (Bansal et al. 2012).

2.2 What causes long COVID?

The underlying pathophysiology of long COVID is still poorly understood. Like the initial acute COVID-19 episode, it is likely that the biological processes involved in the development of long COVID are multiple and overlapping involving a combination of virus and host factors (Figure 2.1) (Peluso and Deeks 2022; Umesh et al. 2022).

Figure 2.1: Predictors and proposed pathophysiologic mechanisms of long COVID



Source: Reprinted from Trends in Immunology, 43, Peluso and Deeks, Early clues regarding the pathogenesis of long COVID, copyright (2022) with permission from Elsevier.

Two overarching mechanisms put forward to explain the underlying pathophysiology of long COVID are organ damage from the initial acute infection phase, and long-term inflammatory mechanisms (Castanares-Zapatero et al. 2022). Some specific hypotheses that have been proposed include (Mehandru and Merad 2022; Merad et al. 2022; Peluso and Deeks 2022):

- unrepaired tissue damage
- residual inflammation
- persistence of viral antigens in tissues
- triggering of autoimmunity after acute viral infection as seen with other viral infections
- alterations in gut microbiome
- microvascular dysregulation.

The specific mechanisms are likely to vary according to the organ system affected (Castanares-Zapatero et al. 2022). For example, injury to lung tissue can result in a persistent cough, ongoing inflammation of blood vessels can lead to fatigue, breathlessness and chest pain, while injury to neural pathways involved in smell can result in loss of smell.

Most studies examining the pathophysiology of long COVID have been conducted overseas. The Australians' Drug Use: Adapting to Pandemic Threats (ADAPT) study in Australia compared the immune response in people with long COVID (defined as fatigue, dyspnea or chest pain >12 weeks after COVID-19) to COVID-19 patients who did not develop long COVID (Phetsouphanh et al. 2022). The study found prolonged activation of the immune system with significant and sustained inflammation even after mild to moderate infection.

Evidence to date, though in its infancy, validates the experience of long COVID patients by demonstrating measurable biological differences. Understanding the underlying mechanisms of long COVID is important to identifying potential interventions and treatment targets.

2.3 How is long COVID defined?

The accumulation of evidence from studies of patients experiencing persistent symptoms following acute infection with SARS-CoV-2 has informed the development of clinical definitions for long COVID (Box 2.2). Despite efforts to harmonise the definition and collection of data on long COVID, there has been no consensus on a core set of health outcomes to be measured and reported for long COVID (Munblit, Nicholson, Akrami et al. 2022). The heterogeneity in measurement of long COVID in current research translates to inconsistent findings.

Box 2.2: Clinical definitions of long COVID

Two long COVID clinical definitions that have been developed are outlined below:

1. The World Health Organization (WHO) used a group consensus technique including input from patients, researchers and others to adopt a clinical case definition, of what has been termed 'post COVID-19 condition' (WHO 2021), that is:

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.

There now exists an International Classification of Disease, 10th Revision (ICD-10), code corresponding to post-COVID-19 condition (Chen et al 2022; WHO 2022a).

2. The National Institute for Health and Care Excellence (NICE) in the UK categorises long COVID into the following definitions (NICE 2021):

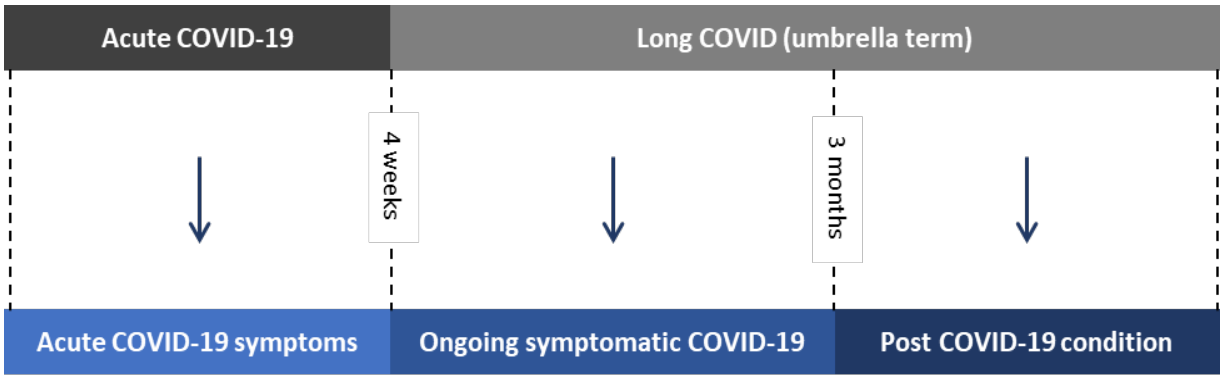
• ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4–12 weeks

• 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.

Both the WHO and NICE definitions describe a *post COVID-19 condition* or *syndrome* as symptoms that continue for more than 12 weeks following an acute episode of COVID-19. Both provide for the onset of new symptoms following recovery from the initial infection. The NICE definition also defines ongoing symptomatic COVID-19 as signs and symptoms of COVID-19 for more than 4 weeks, but less than 12 weeks. Taken together, these 2 definitions are included under the umbrella term of long COVID (Figure 2.2). However, the definitions remain vague and a variety of conditions including those that are psychosomatic in nature become intertwined with true post-COVID-19 illness (Brodin et al. 2022).

This report uses 'long COVID' as a general term to refer to ongoing symptomatic COVID-19 and post COVID-19 syndrome. Other terms that have been used in the literature to describe similar symptoms include 'post-acute COVID', 'post COVID', 'late sequela COVID', 'chronic COVID', 'persistent COVID', 'COVID long haulers', and 'post-acute sequelae of SARS-CoV-2' (PASC).

Figure 2.2: Natural history of the development of long COVID



3 How common is long COVID in Australia?

Estimates of the frequency of long COVID vary. There are 2 main measures used to estimate the frequency of long COVID, which have different purposes and interpretations (Box 3.1). A lack of universal agreement on the clinical definition of long COVID, variation in data sources and methodology produce discordant results (Ledford 2022b). In addition, the experience with COVID-19 in Australia has been quite different to other high-income English-speaking countries such as the United States of America (USA) and UK against which comparisons are usually made. The public health restrictions implemented in 2020 and 2021 kept the COVID-19 infection rate low in the first 2 years of the pandemic compared to the USA and UK, with most cases occurring in Australia in 2022 after many had been vaccinated, when the Omicron variant was dominant, and when antiviral treatment for COVID-19 had improved (AIHW 2022c). These factors may have changed the characteristics of long COVID compared with earlier in the pandemic and we do not know yet if Omicron has a different propensity for long COVID compared with earlier variants.

Box 3.1: Measures used to estimate the frequency of long COVID

Incidence

The number of new cases of long COVID as a proportion of people who tested positive for SARS-CoV-2 in a specified period of time. It is interpreted as the 'risk' of developing long COVID and estimated from longitudinal studies that follow-up COVID cases and collect information on long COVID symptoms. The best evidence comes from studies that include a comparison group of non-COVID cases. These studies can also compare the difference in long COVID risk between population groups and study risk factors for long COVID.

Prevalence

The number of long COVID cases (new and pre-existing) as a proportion of the population of interest (which may be COVID-19 cases or the broader population) either at a point in time or over a specified period of time. It can be estimated from cohort or cross-sectional surveys. Repeated surveys such as those conducted monthly by the UK Office of National Statistics track the prevalence over time and identify population groups with the greatest long COVID burden, which informs health policy and planning.

Adjusted (excess) prevalence

The prevalence of long COVID symptoms in COVID-19 cases minus the prevalence of long COVID-like symptoms in non-COVID-19 controls. It is an estimate of the prevalence of the experience of long COVID symptoms attributable to COVID-19.

3.1 Australian data

Due to the nature of the COVID-19 pandemic in Australia to date, there have been limited studies conducted in Australia to assess the prevalence of long COVID. An early study from New South Wales of 2,000 COVID-19 cases diagnosed in early 2020 found that 80% recovered within 1 month and the incidence of symptoms continuing for 3 months post-diagnosis was 5% (Liu, Jayasundara, et al. 2021).

More recent data collected in March 2022 from the 45 and Up Study estimated 7% of respondents who tested positive for COVID-19 reported persistent symptoms lasting longer than 3 months (Sax Institute 2022). The most common symptoms were fatigue (82%), cough (43%) and poor memory and concentration (40%). Although this study was conducted early in the Omicron wave, there still may have not been enough people who had contracted COVID-19 to provide a generalisable estimate.

The most recent information comes from the COVID-19 Impact Monitoring Survey Series, a probability-based panel study that has monitored wellbeing, attitudes, and behaviours of adult Australians since the start of the COVID-19 period (Biddle and Korda 2022). Based on a survey of 3,510 adults conducted in August 2022 following the large increase in COVID-19 cases in Australia during 2022, 29% with confirmed or suspected COVID-19 reported they had experienced symptoms for more than 4 weeks, and 9.7% had experienced symptoms for 3 months or more. The most common symptoms were tiredness (82%) and weakness (58%). This equates to 14% of adults with symptoms for 4 weeks or more (11% with a reduced ability to carry out day-to-day actions because of long-COVID symptoms) and 4.7% with post-COVID-19 syndrome (3 months or more), or around 1 million Australian adults. However, these figures over-estimate current long COVID cases as it includes people whose symptoms have resolved.

As there is limited information available on long COVID estimates from observational data, model-based estimates under differing scenarios and assumptions have been explored (Angeles et al. 2022). The most recent of these is based on COVID-19 cases to September 2022, which demonstrated a rapid increase in long COVID following the rise in the Omicron wave from December 2021, peaking in October 2022 (Angeles and Hensher 2022). The modelling also estimates several hundred thousand Australians will still have long COVID symptoms by early December 2022, with tens of thousands having symptoms that impact on their daily activities, such as their ability to work.

From the limited Australian data on long COVID available, the prevalence of post-COVID-19 syndrome (symptoms >12 weeks) ranges from 5% to 9.7% of people with COVID-19. However, these figures may be an overestimate as all these studies are based on self-reported long COVID and do not include a control group to adjust for the occurrence of symptoms in people who have not had COVID-19. In addition, the extent to which ongoing symptoms impact on quality of life through limiting daily activities or lead to seeking medical care is unclear, but likely to be significant. Regular time series surveillance data for long COVID in Australia are lacking, which limits the ability to provide rapid estimates of prevalence. This is important information needed by policymakers to understand and prepare for the social and health service impacts of long COVID.

3.2 International data

As the reporting of the occurrence of long COVID in Australia is in its infancy, the literature search looked to larger and more recent international studies and sources of data on which to ascertain estimates.

Several systematic reviews have been conducted that aim to document the frequency of long COVID globally (Alkodaymi et al. 2022; Cabrera Martimbianco et al. 2021; Chen et al. 2022; d'Ettorre et al. 2022; Han, Zheng, et al. 2022; Nittas et al. 2022). All include studies published only in 2020 and 2021 and none include any Australian data (Table 3.1).

Table 3.1: Long COVID prevalence estimates from systematic reviews (ordered by most recent search date)

Study	Search date	Inclusion criteria	Number of studies (participants)	Primary outcomes	Method of synthesis	Prevalence of long COVID and symptoms
Chen et al. 2022	13 March 2022	Papers relating to post COVID-19 condition that examine prevalence, risk factors, and/or duration published during the years 2020-22	50 (1.68 million)	At least 28 days after index date. Stratified by follow-up time: 30, 60, 90 120 days	Meta-analysis of 31 studies reporting overall prevalence	Overall: 43% (95% CI 39–46) Ranged from 9% to 81% Sources of heterogeneity: study population, sex, region, follow-up time, long COVID definition. Hospitalised patients: 54% (95% CI 44–63); varied from 22% to 81% Non-hospitalised patients: 34% (95% CI 25–46); varied from 23% to 53% 30 days: 37% (95% CI 26–49) 60 days: 25% (95% CI 15–38) 90 days: 32% (95% CI 14–57) 120 days: 49% (95% CI 40–59)
Han, Zheng et al. 2022	6 November 2021	Cohort, cross-sectional or case series studies reporting at least 1-year follow-up	18 (8,591)	Post-COVID-19 symptoms lasting 12 months after acute infection	Meta-analysis	Most common symptoms: Fatigue: 28% (95% CI 18–39) Arthromyalgia: 26% (95% CI 8–44) Depression: 23% (95% CI 12–34) Anxiety: 22% (95% CI 15–29) Breathlessness: 18% (95% CI 13–24) Memory problems: 19% (95% CI 7–31) Concentration difficulties: 18% (95% CI 2–35) Insomnia/sleep difficulties: 12% (95% CI 7–17) High level of heterogeneity across studies

(continued)

Table 3.1 (continued): Long COVID prevalence estimates from systematic reviews (ordered by most recent search date)

Study	Search date	Inclusion criteria	Number of studies (participants)	Primary outcomes	Method of synthesis	Prevalence of long COVID and symptoms
Alkodaymi et al. 2022	September 2021	Peer-reviewed cohort, case-control and cross-sectional studies that reported prevalence of persistent symptoms among individuals with severe COVID-19	63 (257,348)	Prevalence of symptoms at 3 to <6 months, 6 to <9 months, 9 to <12 months, ≥12 months	Meta-analysis of individual symptoms at different follow-up periods.	Fatigue was most common symptom 3 to <6 months: 32% (95% CI 22–44) 6 to < 9 months: 36% (95% CI 27–46) 9 to < 12 months: 37% (95% CI 16–62) ≥ 12 months: 41% (95% CI 30–53) Sources of heterogeneity: world region, sex, diabetes, COVID-19 severity, study quality
Nittas et al. 2022	9 July 2021	Reviews thematically focused on long COVID Surveys or cohort studies included in a review or related article search with at least 6 weeks follow-up	23 reviews and 102 primary studies, 40 reported prevalence	Prevalence of long COVID at 12 weeks Adjusted prevalence (% cases minus % controls)	Narrative	Prevalence estimates ranged from 7.5% to 41% in non-hospitalised adults, 2.3% to 53% in mixed adult samples, 38% in hospitalised adults, and 2% to 3.5% in primarily non-hospitalised children. 6 studies with data available to calculated adjusted prevalence: ranged from 7.5% to 16% in non-hospitalised adults, 38% in hospitalised, and 7.8% to 28% in mixed samples
Cabrera Martimbianco et al. 2021	1 February 2021	Clinical trials, cohort, cross-sectional, before-and-after and case series.	25 (5,440)	Frequency of long COVID or post-acute COVID-19 or persistence of clinical manifestations after the acute phase (follow-up varied from 3 weeks after acute phase to 24 weeks after hospital discharge)	Narrative	Long COVID ranged from 4.7 to 80%
d'Ettore et al. 2022	31 January 2021	Original articles reporting post-COVID-19 symptoms in working age adults (15–67 years)	13	Post-COVID-19 symptoms and/or signs (follow-up varied from 9 days after hospital discharge to 10 months after symptom onset) Respiratory sequelae most common outcome studied, investigated by 10 studies	Narrative	Prevalence of post-COVID-19 symptoms ranged from 16% to 87% Breathlessness ranged from 15% to 71% of COVID-19 patients

CI = confidence interval

The most recently published systematic review at the time of writing undertook a meta-analysis of 31 studies published by 13 March 2022 to examine the global and regional prevalence of long COVID at least 28 days after the index date (Chen et al. 2022). Most studies included in the meta-analysis were based on COVID-19 cases from 2020, prior to COVID-19 vaccination. The global overall prevalence was estimated to be 43% (95% confidence interval [CI] 39–46) which equates to 200 million people based on a WHO estimate of 470 million worldwide COVID-19 cases at the time of the study. To reflect the NICE and WHO definitions of post COVID-19 condition more closely (>12 weeks), the prevalence of symptoms at 90 days was 32% (95% CI 14–57) and 49% (95% CI 40–59) at 120 days. The higher prevalence at 120 days was attributed to the predominance of studies of hospitalised patients underlying this estimate.

However, there was wide variation in the estimates – from 9% to 81% (28 days definition). Sources of variation include methodological differences between studies, geographic region, the demographic and health profile of study participants, and acute COVID-19 disease severity (Chen et al. 2022). Studies also generally rely on subjective self-reporting of symptoms, without clinical evaluation, and report a vast array of individual symptoms that are not specific to long COVID. Control groups are needed to estimate the 'adjusted prevalence' that is, the prevalence that can be attributed to COVID-19 (the difference between the estimate for cases and for controls). The review by Nittas et al. (2022) reported the adjusted prevalence from 6 population-based studies (Table 3.1), with estimates ranging from 7.5% to 37.6% depending on the mix of hospitalised and non-hospitalised patients.

A recently published longitudinal study from the Netherlands found the adjusted prevalence of persistent symptoms at 90–150 days to be 13% (21% cases and 8.7% controls) during 2020 and 2021 (Ballering et al. 2022). This study also controlled for pre-existing symptoms, seasonal fluctuations, and non-infectious health aspects of the pandemic.

Many of the studies summarised so far were conducted prior to the development of the NICE and WHO definitions, which have been applied in more recent studies. An analysis of COVID-19 cases from early 2020 identified in 10 population-based longitudinal studies in the UK found 7.8% to 17% of cases reported symptoms for 12 or more weeks, with the proportion higher amongst older age cohorts (Thompson et al. 2022). Between 1.2% and 4.8% reported symptoms that limited day-to-day activity. This is consistent with data from the UK's Office of National Statistics (ONS) *Coronavirus (COVID-19) Infection Survey* (CIS) which found that nearly 14% of people who tested positive for COVID-19 between April 2020 and March 2021 continued to experience symptoms for at least 12 weeks after infection (ONS 2021). Similarly, in Canada 14.8% of cases to August 2022 reported they had symptoms at least 3 months after a positive COVID-19 test or suspected infection (Statistics Canada 2022).

A recent study used a more restrictive application of the WHO definition post COVID-19 condition and found a substantially lower global prevalence than in previous studies (Global Burden of Disease Long COVID Collaborators 2022). This study focused on the 3 clusters of symptoms explicitly included in the WHO definition: fatigue, cognitive problems, and shortness of breath. The study estimated that globally, 6.2% (95% CI 2.4–13.3) of symptomatic COVID-19 infections experienced one or more of the 3 symptom clusters 3 months after infection. The prevalence was higher in cases admitted to intensive care units (43%) and general hospital wards (27%) than less severe community cases (5.7%).

Some studies have explored the documentation of a long COVID diagnostic code in medical records. From primary care records in the UK, only 0.4% of people with a COVID-19 diagnostic code also recorded a long COVID code (Thompson et al. 2022). Another study of the same data set found fragmented, variable and under-ascertainment of long COVID

based on primary care records (Walker et al. 2021). A study of the US Department of Veterans Affairs health care system also found great variability in the documentation of long COVID care across geographic regions and medical centres (Ioannou et al. 2022). Nevertheless, the positive predictive value of diagnosis codes for long COVID was found to be high supporting the utility of registry-based studies of long COVID (Duerlund et al. 2022).

There are several potential explanations for the disparity between results from population data and health care records. Self-reported symptoms of long COVID in population-based surveys may be subject to over-reporting and symptoms may have an alternative explanation. Health care records are limited to those who seek care, receive a long COVID diagnosis and have the diagnosis correctly recorded in the health record.

An important limitation from an Australian perspective, is that most data relate to cases from the early phase of the pandemic and there are a lack of data on long COVID from the Omicron surge in 2022. In the USA, a recent cross-sectional study from a nationally representative sample conducted in July 2022 during the Omicron BA.5 surge indicated 7.3% of the population (18.5 million people) were experiencing persisting symptoms for 4 weeks or more (Robertson et al. 2022).

There are 2 sources of international data that now provide ongoing contemporaneous data on the prevalence of long COVID using clear definitions (Box 3.2).

Box 3.2: Key sources of information on international estimates of the prevalence of long COVID

Coronavirus (COVID-19) Infection Survey (UK)

Random sample of private households in England, Scotland, Wales and Northern Ireland (excludes people living in care homes, communal establishments and hospitals) with continuous recruitment and longitudinal follow-up (monthly). The survey includes people aged 2 years and over. Nose and throat swabs are collected to test for SARS-CoV-2 and blood to test for antibodies. Survey questionnaire obtains demographic information and symptoms, vaccination, and pandemic experiences including long COVID (ONS 2022a). Long COVID is defined using the NICE categories of symptoms lasting >4 weeks and >12 weeks. It provides monthly information on the proportion of the UK population with long COVID symptoms and estimates of the overall frequency of long COVID in confirmed cases of COVID-19.

Household Pulse Survey (USA)

Random sample of households for which an email or cell phone number could be identified. The study commenced in April 2020 to measure the impact of the COVID-19 pandemic on households across the USA from a social and economic perspective. The survey was administered as a 20 minute online questionnaire every 2 weeks in the early phases moving to a 2-weeks on 2-weeks off schedule from 1 December 2021. Long COVID is defined as symptoms lasting longer than 3 months that were not present prior to having COVID-19 (United States Census Bureau 2022a).

Data from the CIS show that the prevalence of long COVID (>4 weeks) has increased over time, from around 1 million people for each month in 2021 (1.5% of the population) to nearly 2 million (3.1%) in April 2022 (ONS 2022c). As at 1 October 2022, an estimated 2.1 million people (3.3%) reported ongoing symptoms for more than 4 weeks and 1.8 million (2.8%) for at least 12 weeks (ONS 2022b). Approximately 300,000 people reported having their day-to-day activity greatly limited (0.5%).

A question on long COVID has been recently added to the Household Pulse Survey that will be used to track the prevalence of long COVID in the USA over time (September 2022)

(CDC 2022a). In the first survey conducted using this question, 30% of adults (18 or over) who had previously had COVID-19 indicated that they had long COVID symptoms that had lasted longer than 3 months (United States Census Bureau 2022b). Of these, 51% indicated that they currently had symptoms, equating to 15% of COVID-19 cases and 6.8% of the adult population.

In conclusion, estimates of the incidence and prevalence of long COVID are variable, being hampered by inconsistent approaches to the measurement and definition of long COVID and lack of non-COVID comparison groups. Studies that have addressed either of these issues are reporting lower estimates than earlier studies, with a higher prevalence in hospitalised compared to non-hospitalised patients.

Data from Australian surveys suggest up to 10% of adults with COVID-19 experienced or are experiencing ongoing symptoms for longer than 12 weeks which is consistent with, and possibly lower than international data. It is unclear however, what proportion of the Australian population may currently have long COVID as the prevalence is highest in the medium-term following infection (4–12 weeks) and some people will have recovered. Point prevalence estimates of long COVID also depend on the recent burden of acute COVID-19 cases and were estimated to affect around 2% and 7% of the UK and US populations, respectively, in September 2022. Robust Australian data are required.

3.3 Long COVID and COVID-19 variants

The course of the pandemic has been shaped by the emergence of different variants of the SARS-CoV-2 virus. Due to the time needed to follow-up and identify patients with long COVID, many studies included in this review are based on COVID-19 cases from the early phase of the pandemic. A small study on hospitalised, non-vaccinated individuals in Madrid, Spain, found the mean number of post-COVID-19 symptoms was higher in patients infected with the Wuhan variant than those with the Alpha or Delta variants (Fernandez-de-Las-Penas, Cancela-Cilleruelo et al. 2022). This study should be interpreted cautiously however, as each variant cohort only consisted of approximately 200 people.

Research on the impact of different variants on risk of developing long COVID is still emerging. Some inferences can be suggested based on what we know about the likelihood of each variant to cause severe disease. A WHO report utilising data from South Africa suggested that there is reduced severity of disease with Omicron in comparison to Delta (WHO 2022b). This is supported by Australian evidence showing the proportion of cases experiencing a severe outcome was lower in the Omicron wave than the Delta wave in New South Wales (AIHW 2022c). As discussed later in this report, more severe disease is associated with higher risk of experiencing long COVID.

In addition, because many people were vaccinated when the Omicron variant emerged, observed differences in risk of long COVID in relation to different SARS-CoV-2 variants could be due to vaccination.

Analysis from the UK COVID Symptom Study App found that 4.5% of Omicron cases experienced long COVID symptoms 4 weeks or more after infection, compared to 11% among Delta cases (Antonelli et al. 2022). Omicron cases were less likely to experience long COVID symptoms than Delta cases whether vaccination was <3 months, 3–6 months or >6 months prior to infection.

Data from the ONS CIS to 27 May 2022 suggest that, of triple-vaccinated adults, 4.5%, 4.2% and 5.0% self-reported long COVID compatible with Omicron BA.1, Omicron BA.2 or Delta variants, respectively (ONS 2022d). The data showed no statistical difference in odds of

reporting long COVID by these variants after adjusting for socio-demographic characteristics and time since last vaccine dose.

While there is some evidence that the risk of developing long COVID in those infected with Omicron compared to previous variants may be lower regardless of the underlying mechanism, the sheer volume of Omicron cases compared to earlier variants means that the burden will be substantial. For example, the ONS CIS data showed an increase in monthly prevalence of long COVID from 2021 and 2022 in the adult population consistent with the increasing burden of Omicron infections (ONS 2022c).

3.4 How does vaccination affect long COVID?

The rollout of vaccinations has had a significant impact on the COVID-19 pandemic in Australia and world-wide. It is of interest to researchers, physicians and sufferers to determine the impact of vaccination on long COVID. For example, a long COVID clinic in England reported a 79% drop in referrals that followed the rollout of the second dose of COVID-19 vaccinations and despite 4 times as many cases of COVID-19 over the same period (Krishna et al. 2022).

Two peer-reviewed systematic reviews (Gao, Liu et al. 2022; Notarte et al. 2022) and one pre-print scoping review (Mumtaz et al. 2022) of the effect of SARS-CoV-2 vaccines on long COVID have been published to date. The most recent study pooled the results from 18 observational studies published up to 19 September 2022 in a meta-analysis covering 185,689 vaccinated and 759,987 unvaccinated participants (Gao, Liu et al. 2022). Overall, they found that vaccination was associated with a 29% lower risk of long COVID on average, although uncertainty in the estimate suggests this may be as low as 13% or as high as 42% (relative risk [RR] 0.71, 95% CI 0.58–0.87). The study found that the protective effect was similar for people vaccinated with 2 doses (RR 0.83, 95% CI 0.74–0.94) or a single dose (RR 0.83, 95% CI 0.65–1.07), although the association for a single dose was not statistically significant.

Some studies have investigated the impact of vaccination on long COVID when vaccines were administered prior to SARS-CoV-2 infection, and others have examined long COVID when vaccinated after infection. Further analysis by Gao, Lui et al. (2022) found a similar effect for vaccination before (RR 0.82, 95% CI 0.74–0.91) and after (RR 0.83, 95% CI 0.74–0.92) infection.

The studies included in the meta-analysis varied in their definition of long COVID, with 7 measuring symptom development >4 weeks and the remainder using a variety of definitions. The risk of long COVID was 32% (RR 0.68, 95% CI 0.53–0.87) lower based on studies using a >4-week definition and 25% lower for other definitions combined (RR 0.75, 95% CI 0.64–0.88).

All reviews of the topic to date highlight that the estimates of the effect size of vaccination on long COVID varies across studies. In the meta-analysis, RRs from individual studies ranged from 0.30 to 1.08 (Gao, Liu et al. 2022). Some of the variation may be explained by differences in populations studied, data collection and analytical methods, and follow-up time. Further variation may be caused by the different vaccination doses and types, timing of study and differences between vaccinated and unvaccinated people that are unaccounted for.

There is a risk of bias across all the studies as they were observational designs. Some differences between studies include:

- the populations studied – studies of hospitalised patients will have had more severe disease during the acute COVID-19 infection than non-hospitalised cases
- selection of participants – the choice to participate in a study, particularly online surveys, may be influenced by personal experience with acute COVID-19 infection, long COVID and vaccination
- measurement of outcomes – including both the symptoms considered to be long COVID and the time frame in which symptoms need to be present
- vaccinated and unvaccinated populations differ on other factors which could account for the findings, although some studies used advanced techniques to account for this
- timing of a study in relation to COVID-19 variants.

The overall picture suggests that 2 vaccination doses could reduce the risk of long COVID between 6% and 26%. Severity of acute COVID-19 infection is a major risk factor for long COVID (see Section 4 What are the determinants of long COVID?) and it is plausible that the observed association between vaccination prior to COVID-19 and development of long COVID could be due to the reduction of severe disease during the acute infection (Stokel-Walker 2022). The evidence to date also suggests that vaccination may be effective in preventing long COVID in people who have already had COVID-19. One explanation for both observations is that vaccination increases antibody levels, which eliminate viral reservoirs (Sivan et al. 2022).

As with much COVID-19 research, the ever-changing landscape of the pandemic introduces new factors that will need to be considered for further research in this area. This includes the effects of booster vaccinations, re-infection and new variants. Further research is required beyond observational studies to measuring longer term outcomes in randomised controlled trials. Such research could inform how chronic outcomes of COVID-19 infection are considered in future vaccination policies.

4 What are the determinants of long COVID?

As discussed previously, the aetiology of long COVID is a combination of viral and host factors (see Section 2.2 What causes long COVID?). Like other chronic conditions, the determinants of long COVID are multifactorial in nature, comprising:

- biomedical determinants, such as such as severity of acute COVID-19 infection and pre-existing comorbidities
- lifestyle behaviours such as smoking
- demographic and social factors.

Health determinants comprise *risk factors* that increase the probability and *protective factors* that reduce the probability of developing long COVID. It is important to note that the identification of a risk factor does not mean that it *causes* the health outcome of interest and may instead be correlated with other causal and non-causal factors. However, identification of population groups at increased risk of long COVID helps develop and target prevention and management strategies.

This section summarises the current available evidence on determinants of long COVID highlighting both the factors that increase the risk of developing long COVID and protective factors. Evidence comes from cohort (longitudinal) and case-control studies that report the strength of a relationship between a determinant and the probability of developing long COVID. The strength of the relationship is usually expressed using relative measures of association. The specific measure depends on the study design (Box 4.1).

Box 4.1: Relative measures of association

Many of the estimates presented across the literature use ratio estimates to compare the occurrence of a health outcome in a group of interest to a reference group. There are 4 main measures.

Risk ratio (relative risk): compares the risk of a health event (e.g., diagnosis of long COVID) among one group with the risk among another group. It is calculated by dividing the incidence (as a proportion) of the health event in a group of people with a particular characteristic by the incidence in another group without that characteristic. It can be calculated from data collected using cohort and cross-sectional study designs.

Rate ratio: compares the incidence rates (using person-time data) between 2 population groups as for the risk ratio. It assumes that the rate is constant over time and is obtained from cohort studies.

Hazard ratio: similar to the rate ratio but allows for a change in the rate over time. Obtained from multivariable analysis of cohort data using Cox proportional hazard models.

Odds ratio: indicates the odds of a characteristic in cases compared to the odds of that characteristic in controls. It is the measure of choice in a case-control study because risk and rate ratios can not be calculated (the size of the population that cases came from is unknown).

(continued)

Box 4.1 (continued): Relative measures of association

All measures of association indicate the strength of the relationship a factor has to long COVID, relative to the reference group. A ratio greater than 1.0 indicates a positive association (greater risk), a ratio less than 1.0 indicates an inverse association (reduced risk) and a ratio equal to 1.0 indicates no association.

Ninety-five percent (95%) confidence intervals are also presented to indicate statistical precision and significance. The result is interpreted as having statistically significant impact (that is, not due to chance) if the interval does not cross the value of 1.

Sources: CDC 2012; Knol et al. 2012

There is growing evidence that severity of acute disease, age, female sex and comorbidities, including obesity, are the most common risk factors for the development of long COVID (Chen et al. 2022; Nittas et al. 2022). The RECoVERED Study, which tracks COVID-19 cases in Amsterdam, Netherlands, diagnosed via the local public health service and from hospitals, found that female sex and obesity were the most important determinants of speed of recovery from COVID-19 over 12 months (Wynberg et al. 2022).

Severity of acute COVID-19 infection is an important predictor for long COVID

The severity of illness during the acute COVID-19 infection has been identified by numerous studies as an important predictor of long COVID.

An umbrella review (review of reviews) of 23 reviews encompassing 102 primary studies published to 9 July 2021 suggested that people experiencing more than 5 symptoms during the acute COVID-19 illness had a higher risk of developing long COVID (Nittas et al. 2022).

A systematic review and meta-analysis of 20 studies published to 30 September 2021 aimed to identify factors present during COVID hospitalisation that were associated with the increased risk of long COVID (>12 weeks) (Maglietta et al. 2022). Acute disease severity, based on symptom characteristics, intensive care unit (ICU) use and length of hospital stay, was associated with respiratory symptoms (odds ratio [OR] 1.66, 95% CI 1.03–2.68).

Both reviews concluded that studies were of low to moderate quality and had multiple methodological issues such as wide variation in definitions, follow-up duration, selection bias related to loss to follow-up and/or lack of comparison between participants and non-participants. In addition, the evidence was inconclusive as to whether severity of illness was related to long COVID independently of other factors.

Several recent large longitudinal studies of health care systems predominately in the USA using advanced statistical methodology have provided stronger evidence that severity of COVID-19 infection is an independent predictor of long COVID.

- The National COVID Cohort Collaborative (31 health systems) found long COVID cases (ICD-10 code U09.9 or a long COVID clinic visit) had higher odds of severe acute illness compared to COVID-19 cases without long COVID (Hill et al. 2022). Specific associations were: hospitalisation associated with COVID-19 (adjusted odds ratio [aOR] 3.8, 95% CI 3.05–4.73), long (8–30 days, aOR 1.69, 95% CI 1.31–2.17) or extended (30+ days, aOR 3.38, 95% CI 2.45–4.67) hospital stay, and receipt of mechanical ventilation (aOR 1.44, 95% CI 1.18–1.74).
- The US Department of Veterans Affairs health system examined documentation of COVID-19 related ICD-10 codes (U07.1, Z86.16, U09.9, J12.82) 3 or more months following acute infection in patients diagnosed between February 2020 and April 2021 (Ioannou et al. 2022). As seen with other studies, the risk of long COVID was higher

for individuals requiring hospitalisation (aOR 2.60, 95% CI 2.51–2.69) or mechanical ventilation (aOR 2.46, 95% CI 2.26–2.69) and in patients with documented symptoms at the time of infection (aOR 1.71, 95% CI 1.65–1.78).

- Another analysis of the US Department of Veterans Affairs database compared the excess burden of PASC (>12 weeks) in cases diagnosed between March 2020 and March 2021 with non-infected controls, followed-up for 6 months (Xie et al. 2021). Excess burden of PASC was defined as the presence of at least one incidence clinical manifestation (ICD-10 codes of 33 predefined post-acute COVID-19 outcomes) in excess of non-infected controls. Burden of PASC per 1000 persons at 6 months was higher for those admitted to ICU (227, 95% CI 216–239), or hospitalised (158, 95% CI 153–164) than for those who were non-hospitalised (41, 95% CI 39–42).
- The TriNetX database measured the development of long COVID features up to 6 months following COVID-19 diagnosis in patients with confirmed COVID-19 compared to patients diagnosed with influenza and matched on baseline characteristics (Taquet, Dercon, et al. 2021). This study found that the risk of experiencing any of 10 pre-defined long COVID features was significantly higher in patients who had more severe COVID-19 illness indicated by hospitalisation and ICU admission.

Outside of the USA, the LONG-COVID-EXP study of COVID-19 patients hospitalised during the first wave of the pandemic (20 February to 31 May 2020) in Madrid, Spain, found that a higher number of symptoms at hospital admission was the most relevant risk factor for developing symptoms after COVID-19 (OR 1.31, 95% CI 1.15–1.49) (Fernández-de-Las-Peñas, Pellicer-Valero et al. 2022).

Evidence is emerging that management of acute COVID-19 infection with antivirals may reduce the risk of long COVID. There are numerous studies underway which will investigate the effect of antivirals such as molnupiravir and nirmatrelvir+ritonavir underway (Ledford 2022a), however, due to the limited time since the introduction of these treatments few studies have been published. A single-centre study from Italy found treatment with the antiviral drug remdesivir during acute COVID-19 infection had a protective effect on the diagnosis of long COVID 30 and 180 days after discharge (aOR 0.64, 95% CI 0.41–0.78) (Boglione et al. 2022). Remdesivir only became available to patients in Italy in September 2020 and this study included hospitalised patients from March 2020. Consequently, the influence of temporal bias on the study result needs to be considered.

Poorer underlying health is a risk factor for long COVID

Poorer underlying health is also related to an increased risk of long COVID. In particular, pre-existing chronic conditions and their associated risk factors, such as obesity and smoking, increase the risk of developing long COVID.

A UK study of non-hospitalised adults using primary care data found there was a small increased risk for smokers (adjusted hazard ratio [aHR] 1.12, 95% CI 1.08–1.15) and former smokers (aHR 1.08, 95% CI 1.05–1.11) at least 12 weeks after infection compared to those who had never smoked (Subramanian et al. 2022); however, this association was not apparent in population-based data (Thompson et al. 2022).

In both primary care and population data, overweight or obesity was associated with an increased risk of long COVID (Subramanian et al. 2022; Thompson et al. 2022). After adjusting for sociodemographic and clinical factors there was a 10% increase in relative risk of those with a body mass index >30 kg/m^2 compared with those who had a lower body mass

index (18.5–25 kg/m^2) (Subramanian et al. 2022). Existing chronic conditions such as poor mental health, asthma and COPD were also associated with long COVID in these 2 studies.

A study of primary care data from Germany also identified that a diagnosis of lipid metabolism disorders (OR 1.46, 95% CI 1.28–1.65) or obesity (OR 1.25, 95% CI 1.08–1.44) were risk factors for the development of long COVID (Loosen et al. 2022). In the USA, the National COVID Cohort Collaborative found increased risk of long COVID in those with obesity (OR 1.23, 95% CI 1.16–1.3), depression (OR 1.50, 95% CI 1.40–1.60) and chronic lung disease (OR 1.63, 95% CI 1.53–1.74) (Hill et al. 2022).

Psychological health may also impact long COVID risk. A study conducted in participants from the longitudinal Nurses' Health studies in the USA and Canada found that pre-infection psychological distress including worry about COVID-19, perceived stress, loneliness, depression and anxiety are risk factors for long COVID (Wang et al. 2022). Participants who reported 2 or more types of distress had an almost 50% increased risk of long COVID (RR 1.49, 95% CI 1.23–1.80).

The level of comorbidity was identified as a risk factor in two studies that analysed the US Department of Veterans Affairs database. Ioannou et al. (2022) found that a high Charlson Comorbidity Index Score was significantly associated with long COVID. Xie et al. (2021) found that the burden of individual sequela was consistently higher in those with a higher number of comorbidities.

Only one review identified in an umbrella review (Nittas et al. 2022) discussed protective factors, indicating that physical activity might reduce the risk of long COVID (de Sire et al. 2021).

Long Covid is most common in middle-aged adults

Findings from the ONS CIS in the UK for the 4-week period ending 1 October 2022, report the lowest prevalence of long COVID (symptoms>12 weeks) was among children aged 2–11 (0.35%, 95% CI 0.25–0.45) and highest among people aged 35–49 (4.0%, 95% CI 3.8–4.2) and 50–69 (4.0%, 95% CI 3.9–4.1). For people aged 70 or more, the prevalence was 2.3% (95% CI 2.4–2.4) (ONS 2022b).

The inverted U-shaped relationship with age reported by the ONS CIS was also found in the study of UK primary care data (Thompson et al. 2022), where the proportion of COVID cases with long COVID increased for each decade of adult life to around 60 years of age and then declined.

Subramanian et al. (2022) found long COVID decreased with increasing age in their analysis of primary care data that persisted after accounting for the influence of demographic and clinical factors – adults aged 70 or over had a 25% lower risk (aHR 0.75, 0.70–0.81) of long COVID compared to those in the 18–29-year-old age group.

Women are more likely to report long-COVID

Several studies have found that women are more likely to report symptoms of long COVID compared with men. Data from the ONS CIS have consistently shown that females experience a higher prevalence of self-reported long COVID than males. For the 4-week period ending 1 October 2022, the prevalence of long COVID (symptoms >12 weeks) was 3.2% (95% CI 3.1–3.3) for females and 2.3% (95% CI 2.2–2.4) for males (ONS 2022b).

Analysis of UK primary care data adjusting for demographic and clinical factors is consistent with this finding, reporting that women were 1.5 times as likely to have long COVID (>12 weeks) than men (aHR 1.52, 95% CI 1.48–1.56) (Subramanian et al. 2022). A similar relationship was also observed in the primary care data and population-based data analysed by Thompson et al. (2022).

Systematic reviews with coverage of data from outside of the UK have also found a higher prevalence of long COVID in women than men. The global meta-analysis by Chen et al. (2022) found a higher proportion of women (47%) had long COVID than men (37%). Female sex was associated with any symptoms (OR 1.52, 95% CI 1.27–1.82), with mental health symptoms (OR 1.67, 95% CI 1.21–2.29) and with fatigue (OR 1.54, 95% CI 1.32–1.79) in a meta-analysis of studies of hospitalised patients (Maglietta et al. 2022).

A study of hospitalised patients in Spain found the number of long COVID symptoms was higher in females (2.25) than for males (1.5) (Fernández-de-Las-Peñas, Martín-Guerrero, Pellicer-Valero, et al. 2022). The study also found female sex was associated with ≥3 long COVID symptoms (aOR 2.54, 1.67–3.86) and with specific, individual long COVID symptoms including fatigue, pain and mood disorders.

A systematic review of sex differences in long COVID covered 9 articles published before June 2021 and found the likelihood of long COVID (>4 weeks) was 20% higher for females compared with males (OR 1.22, 95% CI 1.13–1.32) (Sylvester et al. 2022). The study also found differences in the types of symptoms reported, with females more likely to report gastrointestinal, ear nose throat, psychiatric and mood and neurological, and dermatological symptoms and other symptoms (including fatigue), and males were more likely to have endocrinology complications and renal disorders. These findings should be interpreted with caution as the findings were based on small data sets from published studies during the first 18 months of the pandemic. The authors hypothesise that the difference may be due to differences in immune system function where females have more rapid and robust innate and adaptive immune responses, which may be protective from initial severity of infection but can in doing so can increase the risk of prolonged auto-immune-related diseases (Sylvester et al. 2022).

Female sex has also been found to be higher in attendances to long COVID clinics – 75% of the first 108 patients to attend the Mayo Clinic post-COVID-19 care clinic were female (Ganesh et al. 2022). Investigation of these early patients found that females presented more commonly with a fatigue-predominant phenotype than men and that this was associated with elevated interleukin-6 levels.

In Australia, there also appears to be a gender imbalance with females making up two-thirds of the patient load at a Nepean Hospital long COVID clinic as of July 2022 according to Dr Sharon Wong, a physician working in the clinic (Om 2022).

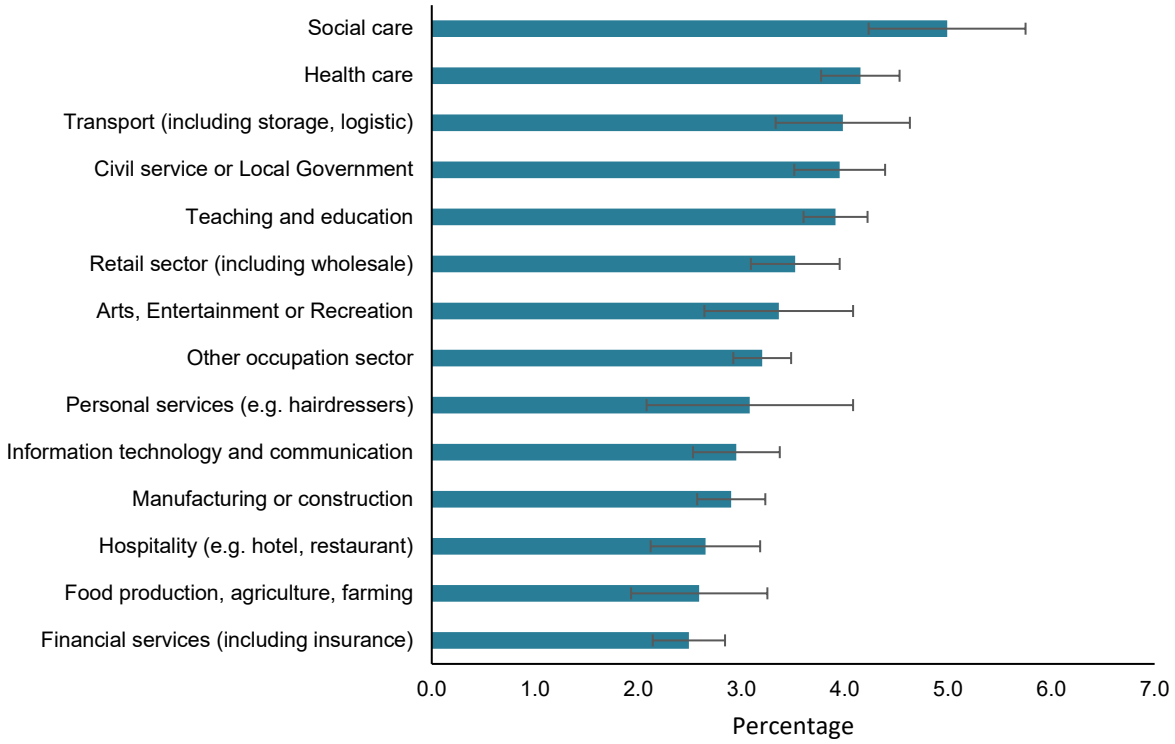
The reasons for the higher risk of long COVID in females are likely complex and multifactorial involving biological, behavioural and wider determinants of health (Stewart et al. 2021). A commentary published in *The Lancet Regional Health – Europe* suggests that because female sex and age under 50 are common risk factors for long COVID, sex hormones and perimenopause and menopause may be contributing factors (Stewart et al. 2021). The overlap of many long COVID symptoms with those of perimenopause and menopause, such as fatigue, brain fog, muscle aches and sleep disturbance, creates a diagnostic challenge. On one hand, clinicians may fail to adequately provide menopause care and on the other, women with symptoms of menopause or perimenopause may be misdiagnosed with long COVID. The authors conclude that there is a need for further research to understand the epidemiology and underlying biological mechanisms for sex differences in long COVID.

Those in ‘caring-type’ service occupation may be at higher risk of long COVID

There is some evidence to suggest that as a higher number of females work in occupations such as social care, nursing, education or carers, that have higher exposure risks, they are more likely to be predisposed to COVID-19 and therefore at greater risk of long COVID. In the UK for example, those working in social-care occupations such as teaching, education

and health care are more affected as a proportion of the UK population (Figure 4.1). These results are purely descriptive and do not control for other factors which may increase long COVID risk in these professions such as age and sex.

Figure 4.1: Estimated percentage of people living in private households in the UK with self-reported long COVID (>12 weeks) for the 4-week period ending 01 October 2022



Source: ONS 2022b.

The high levels of long COVID reported in specific occupations are important to understanding the societal impacts of long COVID. A paper by the US Department of Health and Human Services on long COVID postulates that as those experiencing long COVID disproportionately work in the service sector, this has knock-on effects resulting in a labour shortage in this industry, which may contribute to inflation (Office of the Assistant Secretary for Health 2022).

Ethnicity and socioeconomic position

The study of primary care data in the UK (Subramanian et al. 2022) found associations between long COVID (>12 weeks) and ethnicity, controlling for other demographic and clinical factors including COVID vaccination, with an increased risk seen for Black Afro-Caribbean ethnic groups (aHR 1.21, 95% CI 1.10–1.34), mixed ethnicity (aHR 1.14, 95% CI 1.07–1.22) and other minority groups including patients from native American, Middle Eastern or Polynesian backgrounds (aHR 1.06, 95% CI 1.03–1.10) compared with white ethnic groups.

A commentary focused on the effects of long COVID on migrants and ethnic minorities concluded that the limited studies that include data on these populations suggest they are disproportionately impacted by long COVID (Norredam et al. 2022). The authors highlight that inequalities in health and sociodemographic factors in migrant populations may

contribute to a greater long COVID burden and therefore data from these communities are required.

The risk of long COVID symptoms increased with increasing levels of socioeconomic disadvantage; there was an 11% (aHR 1.11, 95% CI 1.07–1.16) increase in risk for those who were most deprived compared to those who were least deprived (Subramanian et al. 2022).

In an analysis of cross-sectional online survey data from Norway, the UK, the USA and Australia, there was no association between the sociodemographic variables of age, sex, education, relationship status or employment and long COVID (Bonsaksen et al. 2022). This should be interpreted with caution as the number of people who reported long COVID in this study was small (87 persons).

In conclusion, many of the studies identified to date investigating determinants of long COVID use populations that come into contact with health services, and therefore capture more severe cases. It is also unclear whether different risk factors are associated with different sets of symptoms. For example, data from the US Department of Veterans Affairs database found sleep disorders, headache, mood disorders and smell problems were more common in young adults; chest pain arrhythmia, headache, smell problems, hair loss, skin rash were more common in females (Xie et al. 2021).

5 Long COVID and chronic conditions

Chronic conditions are the leading cause of illness, disability and death in Australia (Australian Health Ministers' Advisory Council 2017), and long COVID will likely increase the burden of non-communicable disease (Narayan and Staimez 2022). This section of the report summarises the evidence around the association between COVID-19 and post-acute new-onset chronic conditions.

The relationship between chronic conditions and COVID-19 is complex and bi-directional.

- People with comorbidities such as cardiovascular disease, chronic lung disease, obesity, and diabetes have an increased risk of severe disease from COVID-19, with higher rates of intensive care unit (ICU) admissions and deaths (Feldman et al. 2020; Liu, Spokes et al. 2021; Zheng et al. 2020).
- Some people develop a range of multi-organ symptoms that may arise as a direct complication during the acute COVID-19 illness or develop over the longer term (Tobler et al. 2022). As a consequence, a number of studies have reported an increased incidence in new-onset chronic conditions following an episode of COVID-19.

There is accumulating evidence that COVID-19 can result in organ damage and give rise to new diagnoses of chronic conditions in the post-acute phase. As seen in previous sections of this report, the strongest evidence to date comes from large, population-based longitudinal studies that compare the development of post-COVID-19 sequalae in a case group of people who have COVID-19 against a control group of people who have not had COVID-19.

Analysis from the US Department of Veterans Affairs database measured the excess burden of 379 post-acute diagnoses at 6 months (beyond 30 days following acute illness) (Al-Aly et al. 2021). Excess burden was expressed as the additional number of new cases of a specific diagnosis for every 1,000 people in the COVID-19 group compared to the non-COVID group. The most common excess burden was for respiratory conditions, ranging from 3.37 (95% CI 2.71–3.92) for respiratory failure to 28.5 (95% CI 26.4–30.5) for respiratory signs and symptoms. Other pertinent findings were:

- diseases of the nervous system: 3.17 (95% CI 2.24–3.98) for neurocognitive disorders, 4.10 (95% CI 2.49–5.58) for headache and 14.3 (95% CI 12.2–16.4) for nervous system signs and symptoms
- mental health: 14.5 (95% CI 11.5–17.4) for sleep-wake disorders and 5.4 (95% CI 3.4–7.3) for anxiety and fear-related disorders. The study also found an excess burden of incident drug use including anti-depressants (7.8, 95% CI 5.2–10.3).
- metabolic disorders: lipid metabolism (12.3, 95% CI 8.2–16.2), diabetes mellitus (8.2, 95% CI 6.4–9.9) and obesity (9.5, 95% CI 7.5–11.4)
- cardiovascular system: hypertension (15, 95% CI 11–19), cardiac dysrhythmias (8.4, 95% CI 7.2–9.5), circulatory signs and symptoms (6.6, 95% CI 5.2–8.0), chest pain (10, 95% CI 8.6–11.4), coronary atherosclerosis (4.4, 95% CI 3.0–5.7) and heart failure (3.9, 95% CI 3.0–4.8)
- gastrointestinal system: oesophageal disorders (6.9, 95% CI 4.6–9.1), gastrointestinal disorders (3.6, 95% CI 2.1–4.9), dysphagia (2.8, 95%CI 1.8–3.8) and abdominal pain (5.7, 95% CI 3.7–7.6)

- general wellbeing: malaise and fatigue (13, 95% CI 11–14), muscle disorders (5.7, 95% CI 4.6–6.7), musculoskeletal pain (14, 95% CI 10–18) and anaemia (4.8, 95% CI 3.5–5.9).

5.1 Chronic respiratory conditions

Almost one-third (31%) of Australians are estimated to have at least one chronic respiratory condition based on self-reported information in the 2017-18 National Health Survey.

The most common chronic respiratory conditions are allergic rhinitis (19%), asthma (11%) and chronic sinusitis (8.4%).

4.8% of Australians aged 45 and over were estimated to have chronic obstructive pulmonary disease.

Source: AIHW 2022b.

Respiratory symptoms such as breathlessness, cough and chest pain are frequent symptoms of long COVID thought to arise from damage to lung tissue during the acute infection and ongoing, persistent inflammation. Analysis of the US Department of Veterans Affairs database identified new diagnoses of respiratory conditions up to 6 months following infection, such as respiratory failure, and increased use of bronchodilators, antitussive and expectorant agents, anti-asthmatic agents and glucocorticoids (Al-Aly et al. 2021). Respiratory impairment and lung damage in individuals with long COVID has been demonstrated in clinical and radiological studies.

A systematic review of 7 studies that used pulmonary function tests (spirometry, lung volumes and diffusion capacity) in post-infection COVID-19 patients found 39% of patients had altered diffusion capacity (Torres-Castro et al. 2021). However, most studies included in the review assessed patients within a fairly short time frame since infection, ranging from 2 weeks to 3 months.

Another systematic review found that exercise capacity was reduced more than 3 months after COVID-19 (Durstenfeld et al. 2022). Specifically, a meta-analysis of 9 studies reported that mean peak oxygen consumption (Vo2) was lower among those with long COVID symptoms than those without (-4.9 mL/kg/min, 95% CI -6.4 to -3.4). The overall quality of the evidence was rated as poor due to small sample sizes, selection bias, variability in symptom measurement and inadequate methods to address confounding.

Radiological findings such as ground-glass opacification (GPO) and interstitial fibrotic changes are common in patients at presentation with COVID-19, particularly for patients with more severe disease, and may persist for 6 months or longer (Gao, Liang et al. 2022).

Much of the published research to date on post-acute COVID-19 respiratory complications evaluates outcomes in COVID-19 cases that occurred early in the pandemic and are likely to be biased towards more severe clinical courses. Further longitudinal research on cases that occurred in the Omicron wave with high vaccination coverage are likely to have greater relevance for the Australian population.

5.2 Cardiovascular disease

Based on self-reported data from the ABS 2017–18 National Health Survey:

- 6.2% of adults had one or more conditions relating to heart, stroke or vascular disease
- 3.1% of adults had coronary heart disease, the most common type of cardiovascular disease.

Cardiovascular disease was the underlying cause of 25% of all deaths in 2019 in Australia

Source: AIHW 2021.

There are a range of cardiovascular complications that can arise during the acute phase of COVID-19 infection, such as myocarditis, pericarditis, acute coronary syndrome, heart failure, pulmonary hypertension, right ventricular dysfunction and arrhythmia (Tobler et al. 2022). However, cardiovascular complications over the longer term including cerebrovascular disorders, ischaemic heart disease, heart failure, thrombotic disorders and arrhythmia are being increasingly recognised (Satterfield et al. 2022; Tobler et al. 2022).

Emerging long-term outcomes data from the US Department of Veterans Affairs national health care database found an excess 12-month burden of a set of 20 pre-specified incident cardiovascular outcomes such as dysrhythmias, ischaemic heart disease, inflammatory heart disease, heart failure and thrombotic disorders in patients 30 days post-COVID-19 when compared with 2 control groups (Xie, Xu, Bowe et al. 2022). The study found a 60% increased risk (aHR 1.63, 95% CI 1.59–1.68) of any one of these complications over the 12-month time frame. For every 1,000 people studied, there were 45 more people in the COVID-19 group than in the control group who had a new cardiovascular diagnosis. The highest burden of excess risk in cases compared to controls was seen for heart failure (12 per 1,000 people) and atrial fibrillation (11 per 1,000), while 4 more people per 1,000 in the case group experienced a stroke.

These results were apparent regardless of health risk factors and demographic characteristics. They also found that the risk increased as the severity of the acute phase of COVID-19 increased, that is, from non-hospitalised, to hospitalised and those in ICU. The study also adjusted for vaccination and found that COVID-19 remained associated with an increased risk of myocarditis and pericarditis.

Although the veteran population included in this study consists predominantly of white men and the results may not be generalisable to the broader population (Sidik 2022), findings from studies in other settings corroborate these results (Ayoubkhani et al. 2021; Daugherty et al. 2021; Tobler et al. 2022). In addition, several imaging and laboratory studies have demonstrated persistent structural damage to the heart which may result in increased hospitalisation for cardiovascular events such as heart attacks (Satterfield et al. 2022; Tobler et al. 2022).

Population-wide analysis of English and Welsh linked electronic health records of 48 million people demonstrated an increased risk of arterial thromboses and venous thromboembolic events up to 12-months following acute infection, particularly for people who had been hospitalised with COVID-19 (Knight et al. 2022). This study also demonstrated that the risk was highest in the first 1–2 weeks following infection and rapidly declined over time. It should be noted that this study was conducted on data from 2020 prior to COVID-19 vaccination.

The precise mechanisms that lead to cardiac injury are unclear and the following theories have been proposed:

- direct toxicity by the SARS-CoV-2 virus because it gains entry to myocardial cells via a receptor that is expressed heavily on myocardial and alveolar (lung) surfaces
- cardiotoxic and pro-thrombotic effects of inflammation during the acute infection
- patients with severe COVID-19 are older and more likely to have underlying cardiovascular disease, and therefore at greater risk of increased cardiovascular morbidity and mortality (Tobler et al. 2022).

In addition, disruption to cardiac care related to the pandemic, such as obtaining preventive care or delays in presenting to hospital, plus reduced access to care for some population groups, may also contribute to poorer cardiovascular outcomes over the longer term in COVID-19 survivors (Satterfield et al. 2022). Currently there is little evidence to suggest this had an impact on deaths from cardiovascular disease in Australia. For example, counts of deaths from ischemic heart disease in 2020 and 2021 were 11% and 9% lower than the 2015–19 average, and 7.8% and 6.9% lower for cerebrovascular disease in 2020 and 2021, respectively (ABS 2022b).

Longer term data, especially data collected during 2022 when Australia experienced its highest burden of COVID-19 cases during the pandemic, will shed light on the impact of COVID-19 on cardiovascular sequelae. Disentangling new-onset cardiovascular disease from underlying pre-existing but undiagnosed conditions is a particular challenge. However, there is plausible epidemiological and biological evidence that infection with SARS-CoV-2 can lead to cardiac injury, which if true, will add to the already high burden of cardiovascular disease seen in Australia and globally.

5.3 Diabetes

Around 5% of Australians were living with diabetes in 2020, based on linked data from the National Diabetes Services Scheme and Australasian Paediatric Endocrine Group state-based registers. This includes people with type 1 diabetes, type 2 diabetes and other diabetes, but excludes gestational diabetes.

Diabetes contributed to 10.8% of all deaths in 2020 in Australia (17,500 deaths). Diabetes was the underlying cause in 29% of diabetes deaths (5,100) and an associated cause in 71% of diabetes deaths (12,300).

Source: AIHW 2022c.

COVID-19 has been linked to the development of new-onset diabetes and exacerbation of metabolic dysfunction in patients with pre-existing diabetes in the post-acute period (Department of Health and Aged Care 2021).

A recent systematic review of studies published to 8 June 2022 identified 10 articles involving 11 retrospective cohorts (47.1 million patients) mostly from the USA, with 3 from Europe (Lai et al. 2022). The overall risk of new-onset diabetes was increased by 64% (RR 1.6, 95% CI 1.5–1.8) in patients with COVID-19 compared with non-COVID controls. This translates to an additional 701 cases of diabetes per 10,000 persons (95% CI 558–865). The risk was higher for type 2 (RR 1.8, 95% CI 1.6–2.0) than for type 1 diabetes (RR 1.42, 95% CI 1.38–1.46). Diabetes risk was slightly higher for males (RR 1.45, 95% CI 1.37–1.53) than females (RR 1.35, 95% CI 1.30–1.41), however, results may be unreliable and were inconclusive for other sub-groups, such as age, as there were only limited number of cohorts available for each sub-group analysis. A strength of the review is that it found consistent findings for different control groups, including historical controls and respiratory infection controls.

Despite the strong evidence emerging from well-designed cohort studies, certain limitations remain. The nature of observational study designs mean that biases may still be present and residual confounding may exist even in fully adjusted models (Lai et al. 2022). Some diabetes cases may be missed, and it is unclear to what extent findings may be due to exacerbation of pre-existing but undiagnosed diabetes.

The mechanisms that can lead to metabolic dysfunction and new-onset or exacerbation of pre-existing diabetes are not well known. Some hypotheses are:

- decreased insulin release due to viral damage to pancreatic β cells or local inflammation
- increased insulin resistance associated with persistent inflammation
- effects of the pandemic such as lockdown that could progress development of type 2 diabetes in at-risk populations (Lai et al. 2022).

5.4 Kidney disease

An estimated 11% of people (1.7 million Australians) aged 18 and over had biomedical signs of chronic kidney disease (CKD) in 2011–12, according to AIHW analysis of the Australian Bureau of Statistics latest National Health Measures Survey (NHMS) (ABS 2013) – the most recently available data on the total number of people affected by CKD in Australia (the 'prevalence').

There were around 5,100 new cases of kidney failure (also known as end stage kidney disease) in Australia in 2013, which equates to around 14 new cases per day. Of these, around 50% were receiving treatment in the form of dialysis or a kidney transplant.

CKD contributed to around 17,700 deaths in 2020 (11% of all deaths in Australia). CKD was recorded as the underlying cause of death in 24% of these deaths.

Source: AIHW 2022a.

Kidney involvement during the acute phase of COVID-19 is common in patients hospitalised with COVID-19 (Copur et al. 2022; Yende and Parikh 2021). Ongoing inflammation and injury can lead to a progressive decline in kidney function over many months, leading to CKD, however, the precise mechanism remains unclear.

Data from the US Department of Veterans Affairs database found an increased risk of post-acute kidney outcomes at 6 months and beyond the first 30 days of illness including acute kidney injury (AKI) (aHR 1.94, 95% CI 1.86–2.04) and end-stage kidney disease (ESKD) (aHR 3.0, 95% CI 2.5–3.5) in models adjusted for a wide range of demographic, health and clinical characteristics (Bowe et al. 2021). For every 1,000 people, these results corresponded to an additional 11.5 (95% CI 10.9–12.1) cases of AKI and 1.5 (95% CI 1.3–1.6) cases of ESKD. The study also reported a decline in kidney function as measured by the estimated glomerular filtration rate, which was related to acute COVID-19 severity, being highest in patients admitted to ICU compared to non-hospitalised patients.

5.5 Mental health and neurological problems

In Australia mental and behavioural conditions was the most prevalent chronic condition experienced in 2020–21 according to the 2021 census, with 1 in 5 people experiencing a mental or behavioural condition.

The 2021 National Study of Mental Health and Wellbeing estimated that 44% of Australians aged 18–65 had experienced a mental disorder during their lifetime.

Source: AIHW 2022e.

Persistent symptoms of poor mental health are commonly reported following COVID-19 infection. A survey of 3,510 Australian adults in August 2022 found life satisfaction was lowest in patients with long COVID who reported this had led to restrictions to carry out their daily activities compared to people without long COVID, controlling for life satisfaction pre-COVID-19, age and sex (Biddle and Korda 2022).

A meta-analysis of 51 studies that were published by 20 February 2021 found a high prevalence of anxiety disorders in the first 6 months following infection (Badenoch et al. 2022). Furthermore, a recent narrative review of the neuropsychiatric manifestations of long COVID concluded there is consistent evidence of an increase in mental health symptoms

post infection (Efstathiou et al. 2022). This review also concluded, however, that there is conflicting evidence on whether these symptoms worsened, improved or ceased over time. This highlights the need for further longitudinal studies over longer time periods. Some more recently published studies are outlined below.

A retrospective study using the TriNetX database analysed electronic health records of 236,379 patients with a COVID-19 diagnosis during 2020 and a matched control cohort with influenza over the same period (Taquet, Geddes et al. 2021). TriNetX is a worldwide data source with records primarily from the USA, but also from Australia, the UK, Spain, Bulgaria, India, Malaysia and Taiwan. The study found there was a high prevalence of psychological outcomes diagnosed in patients 6 months after infection (34%, 95%CI 33–34). This study also found a 17.4% incidence of anxiety disorder diagnosed in the cohort (95% CI 17.0–17.7). Interestingly, these outcomes were significantly more prevalent in patients after COVID-19 infection than after influenza infection (HR 1.44, 95%CI 1.40–1.47 for any outcome and HR 1.45 95% 1.40–1.49 for anxiety disorder).

A study using data from the US Department of Veterans Affairs health database found similar results at one year post COVID-19 infection (diagnosed between 1 March 2020 and 15 January 2021) in comparison to a contemporary control cohort without previous COVID-19 infection (Xie, Xu and Al-Aly 2022). The study found an increased risk of incident anxiety disorders, depressive disorders and stress and adjustment disorders. In addition, this study identified an increased risk of incident use of antidepressants and benzodiazepines and increased opioid prescriptions.

A subsequent study investigated a larger cohort of over 1.25 million records in the TriNetX health records network diagnosed between 20 January 2020 and 13 April 2022 (Taquet et al. 2022). This second study analysed the risk of mental health outcomes over a 2–year period. Increased incidence of mood and anxiety disorders in the COVID-19 infected group was observed, however the risk returned to baseline after 1–2 months and was equivalent to that in the matched comparison group after just over a year.

The associations between long COVID and worsening mental health may not be straight forward. As previously indicated, psychological distress prior to COVID-19 infection is a risk factor for many long COVID symptoms (Wang et al. 2022). Additionally, some initial research suggests that a higher level of depression and anxiety is associated with a greater number of long-COVID symptoms, findings that were moderated by levels of life satisfaction and social support (Ocsovszky et al. 2022). This research also found that pre-existing mental health problems were associated with a higher number of long COVID symptoms and current levels of depression and anxiety. These findings suggest that the relationship between mental health symptoms and long COVID symptoms may be bidirectional, with poorer mental health being both a contributing factor to the perception of long COVID symptoms and an outcome of the syndrome.

Deteriorating mental health may also be influenced by the impact of the patient experience of long COVID. In a qualitative study involving interviews of people experiencing long COVID, it was reported that their mental health and wellbeing is impacted by their symptoms causing severe disruption to daily life, lack of service and treatment options, uncertainty of illness trajectories, experiences of care and understanding from others and changes to identity (Burton et al. 2022).

Cognitive complaints (see Box 5.1 ‘Brain fog’) have also been associated with increased anxiety and depression in patients after COVID-19 infection (Almeria et al. 2020). It is important to note, many of the measurement tools that are used to assess cognitive impairment or sleep quality and symptoms of anxiety and depression have overlapping

diagnostic criteria. This may contribute to these findings and more generally confound the research in this area.

Box 5.1: 'Brain fog'

One of the common ongoing complaints of people post COVID-19 infection is 'Brain fog'. Brain fog is a general term describing the experience of neurological symptoms such as difficulties with cognitive function, attention and memory.

A group in Ireland attempted to characterise 'brain fog' by conducting several questionnaires and clinical assessments in participants with long COVID who self-reported brain fog (Jennings et al. 2022). This study found that brain fog can be described as a recognisable symptom cluster characterised by fatigue, dizziness, myalgia, word-finding difficulties and memory impairment. This study also demonstrated that brain fog is associated with adverse psychological and psychomotor performance.

Similarly, another study attempting to objectify the symptoms of brain fog post COVID-19 infection found mild decline in attention, executive functions and memory, though within the normative range (Bungenberg et al. 2022). Interestingly, the study found that fatigue severity was associated with reduced attention and psychomotor speed tasks. This could indicate that the fatigue experienced by long COVID patients may be a contributing factor to some of the neurological symptoms.

A mixed cross-sectional/longitudinal study called the COVID and Cognition Study (COVCOG) is being conducted at the University of Cambridge, UK, to specifically investigate the cognitive effects post COVID-19 infection. The study involves analysis of cognitive performance across a range of domains in persons post COVID-19 infection and concurrently tested controls. To date, 2 studies have been published using the data from COVCOG. The first study found that predictors of cognitive symptoms were neurological/psychiatric symptoms and fatigue during initial illness and neurological, gastrointestinal, and cardiopulmonary/fatigue symptoms during the ongoing illness (Guo et al. 2022a).The second study found memory deficits in previously infected individuals (Guo et al. 2022b). The deficits were increased with increased severity of ongoing post-infection symptoms. Fatigue during initial illness and ongoing neurological symptoms, such as headache, confusion and numbness, were predictors of cognitive performance. These findings support the findings of Bungenberg (2022), further indicating the role of fatigue in the cognitive effects experienced post COVID-19 infection.

Australian-led research has investigated potential pathological pathways behind the neurological effects of long COVID (Charnley et al. 2022). The authors identified that there are similarities between the early stages of neurological diseases such as Alzheimer's disease and Parkinson's disease and post-COVID-19 neurological symptoms. These similarities prompted the study to investigate the presence of clumps of proteins called amyloid assemblies, finding that there are some SARS-CoV-2 proteins that can aggregate to form amyloid assemblies and these assemblies are highly toxic to neuronal cells. The study suggests that this may trigger the type of neurological symptoms experienced in long COVID. The authors caution overinterpreting these results and stress that this result does not infer that long COVID is chronically degenerative like Alzheimer's.

Zhao et al. (2022) found that objective testing of neurological consequences demonstrated significantly worse episodic memory up to 6 months post infection and greater decline in vigilance with time on task 9 months post infection. Importantly, the study found these changes were not significantly different to normal after 6–9 months. This may demonstrate evidence of recovery over time for neurocognitive symptoms of long COVID.

(continued)

Box 5.1 (continued): ‘Brain fog’

This objective quantitiative research into brain fog in long COVID can be complemented by qualitative research of the patient experience of brain fog. In research using interviews and focus groups conducted in the UK, participants highlighted the impact of neurocognitive symptoms on relationships, personal and professional identity and self-perceptions of guilt, shame and stigma (Callan et al. 2022). This research is important to understanding the social consequences of long COVID and to inform the importance of validation of patient’s experience by health care workers.

The current research available in the area of mental health and long COVID highlights the need for mental health clinicians to be involved in the assessment and management of long COVID. Furthermore, given the high rates of mental and behavioural conditions already present in the Australian population, policymakers will need to consider the potential for long COVID to exacerbate the demand/strain on mental health services.

6 Long COVID and other post-viral illness

Myalgic encephalomyelitis (ME), also called chronic fatigue syndrome (CFS), is a disorder that has been linked to long COVID due to their similar aetiologies. Some symptoms of ME/CFS overlap with those experienced in long COVID, specifically persistent fatigue and post-exertional malaise (Wong and Weitzer 2021). ME/CFS has been associated with previous viral infections, including Epstein-Barr virus (EBV), human herpesviruses and cytomegalovirus. As long COVID and ME/CFS are both post-viral illnesses, similarities in symptoms may suggest related causes. However, further research is needed to investigate the relationships between the 2 conditions and care should be taken not to conflate the 2 conditions until more is understood.

A literature review of the similarities between long COVID and ME/CFS acknowledges the highly heterogenous nature of the long COVID condition and focuses on the aspects of long COVID with most relevance to ME/CFS (Sukocheva et al. 2021). The review identifies similarities in symptoms and immunological patterns. It suggests that large groups of long COVID patients may meet the criteria for ME/CFS. It is feasible that they are similar conditions, however, it may also be true that a subset of long COVID patients is actually suffering from ME/CFS.

Conversely, some research demonstrates differences between ME/CFS and long COVID. A study of patterns of symptoms in a small group of long COVID patients compared to a group of ME/CFS patients found that the long COVID patients reported more severe symptoms in the immune (e.g., sore throat, fever) and orthostatic (e.g., shortness of breath, nausea, dizziness) domains initially and over time exhibited significantly less severe symptoms in all except in the orthostatic domain (Jason et al. 2021).

Despite being first defined by the US Centers for Disease Control and Prevention in 1988 (Holmes et al. 1988), ME/CFS is still not well understood. Continued research into long COVID may provide further understanding of ME/CFS. Likewise, established research on ME/CFS may point to clues worth investigating in long COVID.

Ongoing symptoms post infection is not limited to long COVID and ME/CFS. Various other infections have been known to cause ongoing chronic symptoms collectively referred to as post-acute infection syndromes (PAIS) (Choutka et al. 2022). Many PAIS conditions demonstrate parallels in their presentation of symptoms and there is limited understanding of the mechanisms that lead to these symptoms. Knowledge and experience of other PAIS can also be leveraged to understand and respond to long COVID (Choutka et al. 2022).

7 Impact of long COVID

7.1 Burden of disease and mortality

Estimating the burden of disease due to long COVID is challenging, mainly due to the variation in estimates of incidence and severity of long COVID (Smith 2022).

A US study estimated disability-adjusted life years (DALYs) for 2021 for 3 models of severity using CFS disability weights (Smith 2022). The study found that most morbidity was due to disability associated with long COVID and delayed death from organ damage rather than immediate death during acute COVID-19 illness. Other studies have also attempted to model the burden of disability associated with long COVID.

A study from the UK modelled quality-adjusted life years (QALYs) due to COVID-19 illness (acute COVID-19 and long COVID) but not deaths (Martin et al. 2021). The study found 299,730 QALYs were lost within one year of infection (90% due to symptomatic COVID-19 and 10% due to permanent injury) and 557,764 QALYs were lost within 10 years of infection (49% due to symptomatic COVID-19 and 51% due to permanent injury).

A recent study from Australia published as a pre-print estimated the burden of disease for symptomatic COVID-19 infections from 10 December 2021 to 9 April 2022 during the Omicron BA.1/BA.2 wave (Howe et al. 2022). The total DALY attributable to COVID-19 was estimated as 50,900 (95% uncertainty interval [UI] 21,000–80,800). Long COVID contributed 10.2% to the DALY total, compared to 3.6% from acute COVID-19. Furthermore, long COVID contributed to 74% of overall years lived with disability (YLD) from COVID-19 (5,200, 95% UI 2,100–8,300) compared to 1,800 (95% UI 1,100–2,600) from acute infection. Unlike the US modelling (Smith 2022), the largest burden was from death during the acute COVID-19 illness accounting for 86% of the DALY. The results should be interpreted with caution due to the high level of uncertainty in the results related to severity estimates, and potential biases that may over-estimate the prevalence of long COVID. The analysis was also limited to persistent symptoms and did not include morbidity from long-term organ damage and incident chronic conditions.

There are currently little data on mortality from long COVID and studies have tended to focus on all-cause mortality in COVID-19 cases. For example, analysis of the US Department of Veterans Affairs database found the rate of excess death was estimated at 8.39 (95% CI 7.09–9.58) per 1,000 patients with COVID-19 at 6 months compared to non-COVID-19 controls (Al-Aly et al. 2021).

In Australia, since the start of the pandemic and up to 30 September 2022, there had been 10,279 deaths due to COVID-19 of which 123 (1.2%) were classified as being due to post COVID-19 condition (ICD-10 code U09) (ABS 2022a).

7.2 Impact on the health system

A few studies have demonstrated an association between a positive COVID-19 diagnosis and increased post-acute activity within health care settings.

A case-control study of linked data in England analysed changes in primary care (general practice [GP] doctor and nurse attendances and GP prescriptions), secondary care (emergency department [ED] attendances, outpatient consultations, elective and non-elective admissions), community care (contacts), and mental health care (contacts) from 3 months before to 3 months after positive COVID-19 diagnoses occurring in 2020 (March 2022).

In those aged <65, the study found a statistically significant increase in non-elective admissions for COVID-19 cases who were hospitalised during acute infection. For those not hospitalised, there were statistically significant increases in GP doctor and nurse attendances and GP prescriptions for all ages, ED attendances for females <65, mental health contacts for males and females ≥65, and outpatient consultations for males ≥65.

A study from Italy, also based on cases from the first wave of the pandemic in 2020, observed a greater risk of rehospitalisation, ED attendance and outpatient visits in the 6 months following infection for patients who were admitted to ICU and medical wards compared to patients managed at home (Mannucci 2022).

A study from the USA also found that a COVID-19 diagnosis between March and September 2020 was associated with increased health care utilisation and costs over a 6-month period following diagnosis (Koumpias et al. 2022). COVID-19 diagnosis was associated with 0.73 (95% CI 0.71–0.74) more health care visits per month and an additional US$224 (95% CI 218–229) total monthly medical expenses. The largest increases were seen for inpatient visits, emergency care and telemedicine.

Another US study of electronic health records across 40 health care systems analysed common procedures and medications among patients with a long COVID ICD-10 code (U09.9) assigned between 1 October 2021 and 26 May 2022 (Pfaff, Madlock-Brown et al. 2022). Common procedures around the time of the U09.9 index date included radiographic imaging (19.3%), electrocardiography (23.6%) and echocardiography (16.9%) in younger patients aged <21 years. The study also indicated that patients were receiving physical and occupational therapy in the 60 days following diagnosis and the proportion increased with age. Common medications included respiratory system drugs, antibacterials and corticosteroids. The authors concluded that such findings highlight the type of care being provided for long COVID patients and can inform the development of treatment guidelines. As there was no control group used in the analysis it is unclear whether the procedures and treatment described were specific to the management of long COVID. However, uptake of the U09.9 code is variable across health organisations and the absence of a U9.09 code does not exclude long COVID.

7.3 Quality of life and social impacts

Most research has focused on symptom burden and clinical sequalae in patients with long COVID. However, patients with persistent COVID-19 symptoms may experience a decreased quality of life and limitations on daily activities.

In Australia, the COVID-19 Impact Monitoring Survey found 22.5% of participants with symptoms lasting more than 4 weeks and 21.6% with symptoms lasting for 3 months or more reported their ability to carry out day-to-day activities had reduced substantially compared to before COVID-19 (Biddle and Korda 2022).

Two reviews have documented the impact of long COVID on measures of health-related quality of life (HRQoL) from studies published to early 2021 (Malik et al. 2022; Poudel et al. 2021). The pooled prevalence of poor quality of life (using the EQ-VAS instrument) was estimated to be 59% (95% CI 42–75) among post-recovery COVID-19 patients and was highest among patients with ICU admission and fatigue (Malik et al. 2022). However, follow-up periods ranged from 36 to 156 days. Based on 4 studies of patients with long COVID (>4 weeks from onset of symptoms), mean EQ-5D-5L scores ranged from 0.612 (0.612–0.613) to 0.71 (0.67–0.75) (Poudel et al. 2021). A study from Spain suggests that self-perceived limitations in a range of domains including daily living and leisure/social activities decrease

during the year following infection (Fernández-de-Las-Peñas, Martín-Guerrero, Cancela-Cilleruelo, Moro-López-Menchero, Rodríguez-Jiménez, Navarro-Pardo et al. 2022).

Most studies to date have been conducted in hospitalised patients. A prospective cohort study of adult outpatients with acute COVID-19 in 2020 found 40% of participants had a clinically important improvement in quality of life (EQ-VAS) from one month prior and 6–11 months after COVID-19 diagnosis (Han, Womack et al. 2022). The study also found that a higher attributable persistent COVID-19 symptom score (the difference in severity of a prespecified set of symptoms between follow-up and baseline) was associated with a lower quality of life measured using the EQ-5D-5L at follow-up (aOR 0.65, 95% CI 0.59–0.72) adjusting for age, race, ethnicity, education and income.

The impact of persisting symptoms may also impact on workforce participation. A systematic review found that although the ability for people to return to work following COVID-19 increased over time, residual difficulties persisted for a few months after suffering COVID-19 for some people, which influenced their ability to perform the same duties or limited their working hours (Gualano et al. 2022). A national study in Sweden found that 13% of people on sickness benefit for COVID-19 in 2020 were on sick leave for at least 12 weeks and were presumed to have long COVID (Westerlind et al. 2021). In Australia, 11% of survivors had not returned to work by 6 months following critical illness (ICU patients) from COVID-19 (Hodgson et al. 2021).

A qualitative study of workers predominantly from the health, social care and education sectors examined barriers and enablers of ‘workability’ following COVID-19 and concluded that longer term, flexible, co-developed and regularly reviewed return to work plans are necessary for accommodating the unpredictable nature of post COVID-19 recovery, the benefits of which also extend to other conditions with unpredictable symptoms such as CFS (Lunt et al. 2022).

7.4 Patient experience

Long COVID emerged as social terminology to describe patient’s experiences of the long-term health effects of SARS-CoV-2 infection. Through collective gathering and sharing of subjective evidence on digital platforms, long COVID advocates converted a patient-made term to a recognised disease concept (Roth and Gadebusch-Bondio 2022). In a commentary published in the *European Respiratory Journal* (Di Mattei et al. 2022), the authors discuss the importance of belief and recognition of patient’s illness. Without this recognition, long COVID patients experienced significant fear, isolation, anxiety and self-doubt which exacerbated their distress.

Qualitative evidence from patients with long COVID has highlighted that the experience of dismissive attitudes from health care professionals is a consistent theme. A survey of 334 long COVID patients in late 2021 investigated the experience of obtaining medical care in the USA (Au et al. 2022). The study found common themes of dismissive health professionals with use of the language ‘medical gaslighting’ to frame their experience.

A similar experience was found in a study of patients seeking medical care for long COVID in the UK (Baz et al. 2022). The pre-print study conducted interviews with 40 patients from November 2021 to February 2022 and found a large proportion of participants perceived inadequate support when accessing primary care. For ethnic minorities, mistrust and fear of services were further barriers to accessing care. The research also conducted 12 interviews with health care professionals and found that they reported systematic barriers to delivering services.

An analysis of 5 studies published in 2020 found the patient experience seeking long COVID care was characterised by barriers to access such as unclear messaging and complex processes, and a perceived lack of knowledge of the condition and its treatment amongst health care professionals (Macpherson et al. 2022). The analysis also demonstrated the significant emotional impact of long COVID particularly on self-identity due to changes in ability to perform jobs and interact with family. This evidence is from earlier in the pandemic, however, the patient experience of long COVID has evolved as the understanding and recognition of the condition in the medical field developed.

The narrative of long COVID and patient's experiences of it has been significantly influenced by patient advocacy. Online support groups have emerged as a resource for long COVID patients. A thematic analysis of 11 interviews investigated the impact interactions with these support groups has had for patients (Day 2022). The analysis highlighted benefits across several themes; filling professional care gaps, societal awareness, engagement behaviour, diversity and social connectedness. The potentially harmful impacts of participation in these groups were also discussed including sharing of unproven therapies and negative emotions such as fear and jealousy which can arise from comparison to other's experience.

Analysis of social media data has demonstrated the evolution of social attitudes and experiences regarding long COVID. An analysis of social media from March 2020 to January 2021 found a disparity in the narratives and terminology from social media users and official health communication (Miyake and Martin 2021). There was an overwhelming negative sentiment with the key areas of concern identified as time/duration, symptoms/testing, emotional impact and lack of support and resources.

Interestingly, an analysis of 62,232 tweets from March to April 2022 demonstrated comparable levels of positivity and negativity towards long COVID in this period (Awoyemi et al. 2022). In this study positive sentiments were associated with the words research, support, health, hope and recovery. Negative sentiments were associated with the words symptoms, infection, risk, haulers and disease. In a similar analysis also conducted in 2022 the words support, protect, cure, safe and healthy were predominant in tweets with positive sentiments and symptoms, infection, risk, suffering and sick were predominant in tweets with negative sentiments (Bhattacharyya et al. 2022). This demonstrates a shift in attitudes in comparison to the earlier study conducted in the first wave which found an overwhelmingly negative sentiment (Miyake and Martin 2021). This may reflect the increasing knowledge and acceptance of long COVID and awareness of ongoing research and health system responses to the condition.

Although there appears to have been progress in the understanding and treatment of long COVID patients, stigma is still experienced. A UK study investigated different types of stigma experience by long COVID patients (Pantelic et al. 2022). Stigma was characterised as anticipated stigma (expectation of bias/poor treatment by others), internalised stigma (internalising negative associations with long COVID and accepting them as self-applicable) or enacted stigma (overt experiences of discrimination). Internalised and anticipated stigma were more frequently experienced than enacted stigma by long COVID patients.

8 Data issues in long COVID research

8.1 Defining long COVID

One of the main limitations of long COVID research is the inconsistency in the definitions of long COVID used. There is difficulty in effectively defining the condition's symptoms and time course for research and clinical purposes. As discussed in Box 2.2, the WHO developed a clinical case definition for post COVID-19 condition via a group consensus technique (WHO 2021). This definition is broad in relation to symptoms, stating they may fluctuate or relapse over time. WHO's consensus definition has not been consistently adopted in research studies or guidelines.

One of the main differences between the WHO definition and other definitions used in research is the time after COVID-19 infection that symptoms occur. The WHO definition defines post COVID-19 condition as occurring 3 months from the onset of COVID-19 (WHO 2021). The NICE guideline distinguishes between ongoing symptomatic COVID-19, that is symptoms that occur 4–12 weeks after infection, and post-COVID-19 syndrome, that is symptoms that develop during or after initial infection and continue for more than 12 weeks (NICE 2021).

Both definitions also allow for the development of new symptoms, which has resulted in a large number of symptoms and post-acute sequalae of COVID-19 infection to be reported in the literature. Many of the symptoms are non-specific and sometime vague or ill-defined themselves (e.g., brain fog) and are inconsistently reported across studies in the absence of a standard framework for identifying and assessing symptoms or clinical features. Mapping of 287 terms used by research studies to describe long COVID clinical manifestations to a standardised phenotypic ontology identified 18 categories – for example, 30 different features were mapped to the category 'neuropsychiatric findings' (Deer et al. 2021).

Additionally, long COVID is notably heterogenous, meaning not everyone will experience the same symptoms. Consistent amongst many definitions is that symptoms cannot be explained by an alternative diagnosis. This is clinically important but difficult to implement in research where sufficient investigation of other potential causes is unlikely to be adequately performed.

Ultimately, long COVID is an umbrella term that likely encompasses multiple conditions. There is also significant overlap with long COVID and other conditions which may be related or concurrent such as post-intensive-care syndrome, deconditioning and side-effects of treatments (e.g., steroids).

The above discussion highlights the difficulties in defining long COVID in research studies. As demonstrated throughout this report, some research has used very broad definitions with limited restrictions on time frames or symptoms and others have used a more succinct definition. The practical implications of this choice should be considered when evaluating long COVID research. A broad definition could produce inconsistent findings and difficulty identifying clinically meaningful results. Conversely, a more restrictive definition could limit the generalisability and translation of results. A consistent definition would allow better comparison between studies. It should be acknowledged that the definition used will change as our understanding of long COVID progresses.

8.2 Identifying long COVID in health records

Identifying long COVID in hospitals data is dependent on the assignment of ICD codes to an episode of care. In September 2020, the WHO activated an ICD-10 code U09.9 for 'post COVID-19 condition, unspecified' (WHO 2022a). The advice released with the code highlighted that it is to be used to establish a link with COVID-19 and is not to be used where the patient is still presenting with COVID-19 infection. The US CDC approved the code for implementation from 1 October 2021. Analysis of the use of the U09.9 code in US health care records has shown that the diagnoses that have been concurrently coded with U09.9 vary widely and differ with age (McGrath et al. 2022). A similar investigation of the US National COVID Cohort Collaborative population also found a large variation of diagnoses coded with U09.9 (Pfaff, Madlock-Brown et al. 2022). Both studies found that a large proportion (~30%) of those that have a recorded diagnosis of post COVID-19 condition do not have a recorded diagnosis of initial infection.

The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) is used to classify diseases, injury and related health problems in admitted patient care in Australia. Code U07.4 is used to identify conditions that are due to previous COVID-19 infection which is allocated where there is documentation of long COVID. See Box 8.1 for further details of the definition and use of this code. Where a causal relationship is not established between a patient's condition and previous SARS-CoV-2 infection the supplementary code U07.3 can be assigned to identify a personal history of COVID-19 disease.

Box 8.1: Classification of long COVID in ICD-10-AM

ICD-10-AM 12th edition contains the code U07.4 Post coronavirus disease 2019 [COVID-19] condition. According to the Australian Coding Standard 0050, this code can not be asssigned as a principal diagnosis code. Therefore U07.4 is used in addition to a code for the current condition, where there is documentation that the current condition is due to previous COVID-19 infection.

Australian Coding Standard 0113 provides instructions and an example on how this code is assigned.

Instructions

• Code first the condition associated with previous COVID-19.

• Assign U07.4 in addition to a code for a current condition, where the current condition is due to a previous COVID-19 diagnosis or SARS-CoV-2 infection.

Example

A patient was diagnosed with interstitial lung disease due to previous COVID-19.

Codes:

J84.9 Interstitial pulmonary disease, unspecified

U07.4 Post coronavirus disease 2019 [COVID-19] condition.

In this example, U07.4 is assigned in addition to J84.9 to identify that the interstitial lung disease is due to the previous diagnosis of COVID-19.

With the emergence of large-scale, complex data on long COVID, advanced analytical techniques and machine learning are being used to develop novel ways to identify long COVID cases. A study conducted in the USA demonstrated how machine learning can be implemented in research using health records to identify long COVID cases (Pfaff, Girvin et

al. 2022). The investigators examined demographics, health care utilisation, diagnoses and medications for almost 597 adults with long COVID to train models to identify long COVID cases. The models were then used on a database of almost 100,000 adults with previous COVID-19 infection. The models performed well at identifying people who potentially have long COVID in all COVID-19 patients, hospitalised COVID-19 patients and non-hospitalised COVID-19 patients. This demonstrates how advanced analytical techniques can be effectively implemented to address the complexities of long COVID research.

8.3 Methodological issues in long COVID research

Several common limitations have been identified throughout the studies discussed in this review. Confirmation of previous COVID-19 infection is inconsistently conducted across studies. Confirmation of infection ensures that those included in the long COVID group have definitively had COVID-19 infection. Variation in testing availability and policies throughout the pandemic may have caused limitations in testing accessibility. Excluding people who have history consistent with infection, but no confirmation could limit sample sizes and bias samples to not include certain demographics which had limited testing access.

To elucidate 'true' long COVID symptoms and risk factors for the development of long COVID, appropriate comparison groups are needed. Selection of comparison groups in long COVID research is difficult. Some participants may not be aware they had COVID-19, or may not have documented infection as they did not get tested. This means in studies where non-infected comparison groups were used, they may contain some people with a history of COVID-19. Additionally, as infection rates go up the ability to recruit people who have not had COVID-19 is diminished. Alternatively, some studies have used comparison groups of people who have had COVID-19 but are not experiencing ongoing symptoms, which may have more real-world relevance. Well thought out comparison groups will be important for distinguishing the effects of long COVID from the effects of societal changes in response to pandemic.

There is a lack of standard tools for use in long COVID research. For example, a lack of framework for identifying and assessing symptoms makes it difficult to define clear inclusion/exclusion criteria for studies and a lack of uniform outcomes measures make measurements of effect difficult. All of these methodological issues lead to highly varied study designs and study cohorts. This makes it difficult to compare findings amongst studies and to pool data for meta-analysis. Altogether this makes it challenging for policy makers and health care professionals to implement research into practice.

A group of researchers and physicians involved in long COVID treatment and research has called for a core outcome set for post COVID-19 condition to be developed promptly (Munblit, Nicholson, Needham et al. 2022). They argue that a core outcome set will improve data quality, harmonisation and comparability between different geographical locations. To address this an international consensus study was recently conducted that produced a set of 12 outcomes, shown in Box 8.2 (Munblit, Nicholson, Akrami et al. 2022). The authors suggest that these should be used to establish instruments that appropriately measure these outcomes.

Box 8.2: Core outcome set for adults with post COVID-19 condition

Physiological or clinical outcomes

1 Cardiovascular functioning, symptoms and conditions

2 Fatigue or exhaustion

3 Pain

4 Nervous system functioning, symptoms and conditions

5 Cognitive functioning, symptoms and conditions

6 Mental functioning, symptoms and conditions

7 Respiratory functioning, symptoms and conditions

8 Post-exertion symptoms

Life impact outcomes

9 Physical functioning, symptoms and conditions

10 Work or occupational and study changes

Survival

11 Survival

Outcome from previous COS

12 Recovery *

*Outcome was included in a previously published COS for COVID-19 and, owing to its relevance to post COVID-19 condition, was automatically included in this COS.

COS = core outcome set.

Source: Munblit, Nicholson, Akrami et al. (2022).

8.4 Data sources

The research presented in this review has used varying data sources including electronic health records, surveys and mobile phone applications. Each data source has limitations that should be considered when interpreting the results.

Health records are advantageous as they provide researchers with large data sets for analysis. However, health records may be impacted by behavioural differences in seeking care, the need for care depending on the severity of long COVID symptoms, disparities in the availability of care, obtaining a diagnosis of long COVID and having that diagnosis recorded in the patient record. The use of health records is subject to the quality of record keeping of the providers, therefore good quality control processes are paramount. All of these issues may lead to lack of representation in health records of certain population groups such as lower socioeconomic groups, some culturally and linguistically diverse (CALD) populations, and people who live in rural and remote areas.

Surveys and mobile phone applications have the advantage of being specifically designed to collect the information of interest. However, they are subject to selection biases and the results may not be representative of the intended population. For example, people with long COVID symptoms may be more motivated to participate in a survey and people from some population groups may be less willing to participate. Data sources that rely on self-reported

information on long COVID and its symptoms by the respondent are susceptible to recall bias.

Given the limitations of each data source, it is important that the evidence base for long COVID incorporates a variety of sources from a range of settings and population groups.

8.5 Long COVID impact in disadvantaged groups

Certain population groups are at greater risk of contracting SARS-CoV-2. Furthermore, certain population groups are at greater risk of severe disease and death due to COVID-19. This includes the elderly, people with pre-existing conditions, and unvaccinated individuals, lower socioeconomic groups and some CALD groups (ABS 2022a; AIHW 2022d). These population groups may therefore be at an increased risk of developing long COVID, but this has not been confirmed with robust research.

Additionally, in Australia there are known disparities in health for Aboriginal and Torres Strait Islanders, people from low socioeconomic backgrounds and people who live in rural and remote areas. There is a risk these disparities will be exacerbated in those with long COVID, particularly if there are cultural, economic, or geographical factors inhibiting access to long COVID care.

This highlights the necessity to consider the impact of long COVID on vulnerable populations. Research should be designed to specifically investigate the burden of long COVID in these communities. Treatment and care programs will need to be constructed to adapt to the needs of these communities.

9 Monitoring the impact of long COVID in the future

This review has summarised the current evidence on long COVID. Most of the evidence presented has been from research conducted overseas. Though much of this is likely still relevant in the Australian context, particularly evidence from studies conducted in the UK where the vaccinations used are the same, there is a need to corroborate these findings with Australian data.

9.1 The national COVID-19 linked data set

The AIHW has been funded through a grant from the Medical Research Future Fund to develop a national COVID-19 linked data set, which will provide a valuable asset for long COVID research in Australia. The project will link COVID-19 infection notifications from states and territories to national administrative health data sets including deaths, hospitals, aged care, immunisation, MBS and PBS data. The resultant data set will be a large de-identified research asset of COVID-19 infected individuals. It will allow investigation of health outcomes post-infection, impact of vaccination and health service use.

Use of linked data in long COVID research has proven valuable. Linked data from primary care, secondary care, mental health and community services in the UK were used to investigate health care utilisation post COVID-19 illness (Murch et al. 2022). The study found increased health care service use post-acute infection. Specifically, there was increased GP and nurse attendances, and increased GP prescriptions for men and women of all ages, increased ED presentations for women ≥ 65 years, increased mental health contacts for males and females ≥65 years and increased outpatient consultations for males ≥ 65 years. This information is valuable in understanding health service demands arising from long COVID and could be useful in designing targeted long COVID models of care.

9.2 Long COVID clinics

Long COVID clinics have been established across Australia to provide specialised care to people having long term symptoms after COVID-19 infection. These clinics provide an opportunity to collect data on long COVID progression in affected individuals. For example, the Kirby Institute's ADAPT Study is collecting details on people's symptoms at regular intervals after infection and blood samples to assess immunological function (The Kirby Institute 2022).

9.3 Surveys

Surveys can provide valuable insights into the impacts of long COVID populations. As has been demonstrated throughout this review, the ONS CIS in the UK has been a key data source for long COVID information. The US National Centre for Health Statistics in partnership with the US Census Bureau on 1 June 2022 added questions regarding long COVID to their Household Pulse Survey (CDC 2022a). These large-scale national surveys provide rapid and relevant long COVID information and are particularly valuable in estimating prevalence of the condition.

9.4 Longitudinal studies

Established longitudinal studies can provide a useful resource for monitoring long term health impacts of COVID-19 infection. Longitudinal surveys follow cohorts over time with repeated monitoring of health and health behaviours. Several Australian longitudinal studies have included questions on COVID-19 that will allow for analysis of post-COVID-19 outcomes. This includes the 45 and Up Study conducted by the Sax Institute (Sax Institute 2022), the Life in Australia Study conducted by the Social Research Centre at the Australian National University (Biddle and Korda 2022) and the Australian Longitudinal Study on Women's Health (ALSWH 2022). A key advantage of these studies is that as the survey cohorts were established prior to the pandemic, they include measures of pre-pandemic characteristics.

10 Conclusion

Long COVID is a new condition and therefore the evidence so far is limited by a relatively short follow-up time since infection, particularly in Australia where most of the acute burden of COVID-19 has occurred in 2022. As time progresses, data should become available to evaluate the longer-term consequences of long COVID.

Timely surveys to estimate and track the frequency of long COVID in Australia are lacking. The ONS CIS in the UK that was originally established for national reporting of COVID-19 infections was able to rapidly pivot to include information on long COVID. The regular, monthly reports and publication of detailed data by key demographic variables enable the tracking of the prevalence over time and identification of population groups with the highest burden of illness. These data allow targeted prevention strategies and health policy to be developed.

Estimates of the prevalence of long COVID in Australia range from 5% to 10% of COVID-19 cases and are based on findings from self-reported symptoms from small surveys. Therefore, the estimates may be subject to biases and not be representative of the Australian population. Research has shown that many of the symptoms reported for long COVID are non-specific and are also reported in a substantial proportion of people who have not had COVID-19. Therefore, inclusion of an uninfected control group is important to provide an estimate on the prevalence based on the difference between cases and controls. It is also important to correct for pre-existing symptoms prior to SARS-CoV-2 infection.

Another key data gap that will only be overcome with time is further understanding of the impact of variants on long COVID. Current evidence is limited as there has not been sufficient time since Omicron infections to truly comprehend the long-term consequences of this variant in comparison to earlier variants such as Delta and Alpha, and whether this is a consequence of vaccination and improved treatment for COVID-19 infections compared to that available during the early phases of the pandemic.

Research conducted using large data sets such as the US health care organisations, UK primary care data and linked data has provided insights into the risk factors and outcomes associated with long COVID. The longitudinal nature of the data sets including look back periods to account for symptoms, comorbidities and health system usage prior to COVID-19 has provided some of the most robust evidence to date. In addition, these studies can corroborate self-reported symptoms through clinical evaluation and objective measurements of physical and psychological function. However, these studies have several limitations. They are based on people who have contact with the health system and the evidence is therefore based on findings for more severe cases of long COVID and people who seek care. A diagnosis of long COVID is dependent on it being recognised and investigated by a health care provider and at least in the early stages of the pandemic patients felt their symptoms were dismissed and they did not receive adequate support. Finally, a diagnosis of long COVID needs to be documented in a patient's health record.

Research and monitoring of long COVID is required to understand its impact on the Australian population and to corroborate findings with the evidence from other countries.

Priority research areas identified through consultation with patients, carers, clinicians and clinician researchers included establishing diagnostic tools, identifying underlying mechanisms of long COVID, understanding the trajectory of recovery, and evaluation of the role of interventions during the acute and persistent phases of the illness (Houchen-Wolloff et al. 2022). Other research gaps include development of care models, impacts of long COVID on social factors such as education, income and employment, and specific impacts on

certain occupational or vulnerable populations (Jin et al. 2022).

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Abbreviations

ABS	Australian Bureau of Statistics
ADAPT	Australians' Drug Use: Adapting to Pandemic Threats
aHR	adjusted hazard ratio
AIHW	Australian Institute of Health and Welfare
AKI	acute kidney injury
aOR	adjusted odds ratio
CALD	culturally and linguistically diverse
CDC	Centers for Disease Control and Prevention (US)
CFS	chronic fatigue syndrome
CI	confidence interval
CIS	Coronavirus (COVID-19) Infection Survey (UK)
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
DALY	disability-adjusted life year
EBV	Epstein-Barr virus
ED	emergency department
EQ-VAS	EuroQol visual analogue scale
ESKD	end-stage kidney disease
GP	general practice
HR	hazard ratio

HRQoL	health-related quality of life
ICD	International Classification of Diseases
ICU	intensive care unit
MBS	Medicare Benefits Schedule
ME	myalgic encephalomyelitis
MIS-C	multi-inflammatory syndrome in children
NICE	National Institute for Health and Care Excellence (UK)
ONS	Office for National Statistics
OR	odds ratio
PAIS	post-acute infection syndromes
PASC	post-acute sequelae of SARS-CoV-2
PBS	Pharmaceutical Benefits Scheme
QALY	quality-adjusted life year
RR	Relative risk or risk ratio
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UI	Uncertainty Interval
UK	United Kingdom
US	United States (of America)
USA	United States of America
WHO	World Health Organization
YLD	years lived with disability

Glossary

adjusted (excess) prevalence: The difference in the **prevalence** of a condition between 2 population groups.

bias: An error in research findings that can arise from the way participants are recruited to a study (selection bias), or through data collection processes (measurement bias) and analysis (confounding). For example, individuals in a study may differ from the population of interest leading to an error in the result. In studies where participants are required to self-report information they are more or less likely to recall information on exposures depending on their outcome. A confounding factor is something, other than the thing being studied, that could be causing the results seen in a study. Confounding can be controlled in the study design or analysis; however, residual confounding may persist if all sources have not been identified, measured and controlled for.

brain fog: A general term describing the experience of neurological symptoms such as difficulties with cognitive function, attention and memory following acute COVID-19 infection.

burden of disease: the quantified impact of a disease or injury on a population, using the **disability-adjusted life years** (**DALYs**) measure.

cardiovascular disease/condition: Any disease of the cardiovascular system, namely the heart (cardio) or blood vessels (vascular). Includes angina, heart attack, stroke and peripheral vascular disease. Also known as circulatory disease.

case-control study: An epidemiological research study design where the distribution of health **determinants** in a group of people with a health condition (cases) are compared with a group of people without that condition (controls).

case-series study: Description of the characteristics of a small number of people experiencing a particular health condition. Does not include a comparison group.

chronic COVID: See **long COVID.**

chronic diseases/conditions: A diverse group of diseases/conditions, such as heart disease, cancer and arthritis, which tend to be long lasting and persistent in their symptoms or development. Although these features also apply to some communicable diseases, the term is usually confined to non-communicable diseases.

chronic kidney disease (CKD): Refers to all conditions of the kidney, lasting at least 3 months, where a person has had evidence of kidney damage and/or reduced kidney function, regardless of the specific cause.

cohort study: An epidemiological research study design where participants are followed over time to measure the development of health outcomes (conditions, behaviours, clinical measurements). The proportion or rate of development is compared across different sub-groups, such as people who were exposed to a risk factor for a condition compared to people who were not. Also referred to as a **longitudinal study**.

confidence interval: A range determined by variability in data, within which there is a specified (usually 95%) chance that the true value of a calculated parameter lies.

comorbidity: Defined in relation to an index disease/condition, comorbidity describes any additional disease that is experienced by a person while they have the index disease. The index and comorbid disease/condition will change depending on the focus of the study.

COVID-19 (Coronavirus disease 2019): An infectious disease caused by the SARS-CoV-2 virus.

COVID long haulers: See **long COVID.**

cross-sectional study: A survey of a defined population of people administered at one point in time. Used to calculate the proportion of the population with specific health conditions (**prevalence**) and **determinants**, and to draw comparisons between them.

data linkage/linked data: Bringing together (linking) information from 2 or more data sources believed to relate to the same entity, such as the same individual or the same institution. The resulting data set is called linked data. In this report, data linkage is used to bring together information from data sets that indicate a population of interest (such as people with dementia) with other data sets that include information on other characteristics or service usage.

determinant: Any factor that can increase the chances of ill health (risk factors) or good health (protective factors) in a population or individual. By convention, services or other programs that aim to improve health are usually not included in this definition.

diabetes (diabetes mellitus): A chronic condition in which the body cannot properly use its main energy source, the sugar glucose. This is due to a relative or absolute deficiency in insulin, a hormone that is produced by the pancreas and helps glucose enter the body's cells from the bloodstream and then be processed by them. Diabetes is marked by an abnormal build-up of glucose in the blood, and it can have serious short- and long-term effects. For the three main types of diabetes see **type 1 diabetes**, **type 2 diabetes** and **gestational diabetes**.

disability-adjusted life year (**DALY**): A year (1 year) of healthy life lost, either through premature death or equivalently through living with disability due to illness or injury. It is the basic unit used in burden of disease and injury estimates.

disease: A physical or mental disturbance involving symptoms (such as pain or feeling unwell), dysfunction or tissue damage, especially if these symptoms and signs form a recognisable clinical pattern.

electronic health records: A longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting.

emergency department presentation: The presentation of a patient at an emergency department is the earliest occasion of being registered clerically and occurs following the arrival of the patient at the emergency department.

EQ-5D-5L: one of a family of instruments (EQ-5D) to describe and value health. On the EQ-5D-5L patient's rate their health on the 5 dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels of severity.

EQ-VAS: The EuroQol visual analogue scale (EQ-VAS) records a patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'the best health you can imagine' and 'the worst health you can imagine'.

fatal burden: Quantified impact on a population of premature death due to disease or injury. Measured as years of life lost (**YLL**).

general practitioner: A medical practitioner who provides primary comprehensive and continuing care to patients and their families in the community.

gestational diabetes: A form of **diabetes** when higher than optimal blood glucose is first diagnosed during pregnancy (gestation). It may disappear after pregnancy but signals a high risk of diabetes occurring later on.

health outcome: A change in the health of an individual or population due wholly or partly to a preventive or clinical intervention.

health-related quality of life (HRQoL): An individual's or group's perceived physical and mental health.

hospitalisation: An episode of hospital care that starts with the formal admission process and ends with the formal separation process (synonymous with admission and separation). An episode of care can be completed by the patient's being discharged, being transferred to another hospital or care facility, or dying, or by a portion of a hospital stay starting or ending in a change of type of care (for example, from acute to rehabilitation).

incidence: The number of new cases (of an illness or event, and so on) occurring during a given period of time. Compare with **prevalence**.

International Statistical Classification of Diseases and Related Health Problems (**ICD):** The World Health Organization's internationally accepted classification of death and disease. The 10th Revision (ICD-10) is currently in use. The ICD-10-AM is the Australian Modification of the ICD-10; it is used for diagnoses and procedures recorded for patients admitted to hospitals.

late sequala COVID: See **long COVID.**

long COVID: An umbrella term used to describe ongoing, persistent or new symptoms following acute infection with SARS-CoV-2. See also **post Covid-19 condition** and **post-COVID-19 syndrome.**

longitudinal study: See **cohort study.**

mental health: A state of wellbeing in which the person realises their own abilities, can cope with normal stresses of life, can work productively and can contribute to the community. Mental health is the capacity of individuals and groups to interact with one another and their environment in ways that promote subjective wellbeing, optimal development and the use of cognitive, affective and relational abilities.

mental illness (or **mental health disorder**): A clinically diagnosable disorder that significantly interferes with an individual's cognitive, emotional or social abilities. The term covers a spectrum of disorders that vary in severity and duration, including anxiety disorders, affective disorders (such as depression), psychotic disorders and substance use disorders.

meta-analysis: Statistical pooling of numerical results from a number of similar research studies.

morbidity: The ill health of an individual and levels of ill health in a population or group.

mortality: Number or rate of deaths in a population during a given time period.

musculoskeletal: A term that relates to the muscles, joints and bones.

neurology: A branch of medicine concerned especially with the structure, function and diseases of the nervous system.

non-fatal burden: The quantified impact on a population of ill health due to disease or injury. Measured as **years lived with disability** (YLD), which is also sometimes referred to as **years of healthy life lost due to disability**.

obesity: Marked degree of overweight, defined for population studies as a body mass index of 30 or over. See also **overweight**.

odds ratio: This measure is derived by comparing 2 groups for their odds of exposure to a health **determinant**.

overweight: Defined for the purpose of population studies as a body mass index of 25 or over. See also obesity.

persistent COVID: See **long COVID.**

post-acute COVID-19: See **long COVID.**

post COVID: See **long COVID.**

post COVID-19 condition (WHO): 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.

post-COVID-19 syndrome (NICE): Signs and symptoms that develop during or after a COVID-19 infection, continue for more than 12 weeks and are not explained by an alternative diagnosis.

post-acute sequalae of SARS-CoV-2 infection (PASC): See **long COVID.**

prevalence: The number or proportion (of cases, instances, and so forth) in a population at a point in time or over a specified period of time. Compare with **incidence**.

primary care: The first point of contact an individual has with the health system and relates to the treatment of non-admitted patients in the community.

protective factors: Factors that enhance the likelihood of positive outcomes and lessen the chance of negative consequences from exposure to risk.

relative risk: This measure is derived by comparing 2 groups for their likelihood of an event. It is also called the risk ratio because it is the ratio of the risk in the 'exposed' population divided by the risk in the 'unexposed' population.

risk factors: Any factor that represents a greater risk of a health disorder or other unwanted condition or event. Some risk factors are regarded as causes of disease; others are not necessarily so. Along with their opposites (protective factors), risk factors are known as **determinants**.

social determinants of health: The circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness. These circumstances are in turn shaped by a wider set of forces: economics, social policies and politics.

total burden: The sum of fatal burden (YLL) and non-fatal burden (YLD). See **burden of disease**.

type 1 diabetes: A form of mostly arising among children or younger adults (but can be diagnosed at any age) and marked by a complete lack of insulin. Insulin replacement is needed for survival. It is a lifelong disease, for which the exact cause is unknown, but believed to be the result of an interaction of genetic and environmental factors.
See **diabetes** (**diabetes mellitus**).

type 2 diabetes: The most common form of diabetes, is a condition in which the body becomes resistant to the normal effects of insulin and gradually loses the capacity to produce enough insulin in the pancreas. The condition has strong genetic and family-related (non-modifiable) risk factors and is also often associated with modifiable risk factors.
See **diabetes** (**diabetes mellitus**).

vaccination: The process of administering a vaccine to a person to produce immunity against infection.

vaccine: A substance used to stimulate the production of antibodies and provide immunity against one or several diseases. It is prepared from the causative agent of a disease, its products, or a synthetic substitute, and treated to act as an antigen without inducing the disease.

years lived with disability (**YLD**): A measure calculated as the prevalence of a condition, multiplied by a disability weight for that condition. YLD represent non-fatal burden. Sometimes referred to as **years of healthy life lost due to disability**.

years of healthy life lost due to disability: See years lived with disability (YLD).

years of life lost (**YLL**)**:** for each new case, years of life lost equals the number of years between premature death and the standard life expectancy for the individual.

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Related publications

Australian Institute of Health and Welfare (2022) *The impact of a new disease: COVID-19 from 2020, 2021 and into 2022*, AIHW, Australian Government. https://www.aihw.gov.au/reports/australias-health/australias-health-2022-data-insights

Australian Institute of Health and Welfare (2022) *Establishing a COVID-19 linked data set,* AIHW, Australian Government. https://www.aihw.gov.au/reports/covid-19/establishing-a-covid-19-linked-data-set/contents/about

Long COVID is a multi-system illness characterised by ongoing persistent symptoms that can last for weeks or months following COVID-19 infection. This review investigates the scale and impact of long COVID in the Australian context. The review found that most information is from research conducted in the USA and UK on long COVID related to COVID-19 infections in the first two years (2020-21) of the pandemic.

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