Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

International review of the epidemiology of long COVID

Submitted to the EAG: 7 March 2023

Published: 31 May 2023

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

1 Table of Contents

1.1 List of abbreviations

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
aPR	adjusted prevalence ratios
aRR	adjusted risk ratio
BMI	body mass index
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
EAG	expert advisory group
ENT	ear, nose and throat
EQ-5D	EuroQol, Five Dimensions, quality of life index
EQ-5D-Y	EuroQol, Five Dimensions, Youth, quality of life index
FiO2	fraction of inspired oxygen
GI	gastrointestinal
HRQoL	health-related quality of life
HIQA	Health Information and Quality Authority
HR	hazard ratio

HSE	Health Service Executive
HTA	Health Technology Assessment
ICU	intensive care unit
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
NCHS	National Center for Health Statistics
NICE	National Institute for Health and Care Excellence
MS	multiple sclerosis
ONS	Office of National Statistics
OR	odds ratio
PedsQL	Paediatric Quality of Life Inventory
PaO2	arterial partial pressure of oxygen
PASC	post-acute sequelae of SARS-CoV-2 infection
PCR	polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	post-traumatic stress disorder
QoL	quality of life
RADT	rapid antigen diagnostic test
RCGP	Royal College of General Practitioners

RD	risk difference
RR	risk ratio
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
VTE	venous thromboembolism
Web-EDSS	web-based Expanded Disability Status Scale
WHO	World Health Organization

1.2 Acknowledgements

HIQA would like to thank all members of the Expert Advisory Group (EAG) listed below who provided their time, advice and information in support of this work.

Membership of the Expert Advisory Group involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to the HSE. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

The membership of the EAG was as follows:

Dr Máirín Ryan (Chair)	Director of Health Technology Assessment & Deputy Chief Executive Officer, HIQA
Dr Emer Ahern	National Clinical Advisor and Group Lead Older Persons, HSE
Dr Ciaran Bannan*	Consultant in infectious diseases and general internal medicine, St James's Hospital, HSE
Dr Máirín Boland	Consultant in Public Health Medicine, National Clinical Lead, Health Threats Preparedness Programme, HSE
Dr Eimear Brannigan	Consultant in Infectious Diseases, Clinical Lead Antimicrobial Resistance and Infection Control, HSE
Ms Tanja Buwalda*	Long COVID Advocacy Ireland
Prof Karina Butler	Consultant Paediatrician and Infectious Diseases Specialist & Chair of the National Immunisation Advisory Committee
Dr Jeff Connell	Assistant Director, UCD National Virus Reference Laboratory, University College Dublin
Dr Eibhlín Connolly	Deputy Chief Medical Officer, Department of Health
Prof Máire Connolly	Professor of Global Health and Development, National University of Ireland, Galway
Ms Sinead Creagh	Laboratory Manager, Cork University Hospital & Academy of Clinical Science and Laboratory Medicine
Dr Ellen Crushell	Consultant Paediatrician, Co-Clinical Lead, National Clinical Programme Paediatric/Neonatology, HSE

Dr John Cuddihy	Specialist in Public Health Medicine & Area Director of Public Health, HSE
Dr Cillian de Gascun	Consultant Virologist & Director of the National Virus Reference Laboratory, University College Dublin
Ms Josephine Galway	National Director of Nursing, Infection Prevention Control and Antimicrobial Resistance, AMRIC Division, HSE
Prof Orla Hardiman	Consultant Neurologist, Clinical Lead, National Clinical Programme Neurology, HSE
Dr David Hanlon	General Practitioner & National Clinical Advisor and Group Lead Primary Care, HSE
Dr Patricia Harrington	Deputy Director, Health Technology Assessment, HIQA
Dr Martina Healy	Consultant Intensivist, Clinical Lead, National Clinical Programme Intensive Care, HSE
Dr Grant Jeffrey	Director, Workplace Health and Well Being Unit, HSE
Dr Paul Kavanagh*	Public Health Medicine Lead, HSE
Prof Mary Keogan	Dean of the Faculty of Pathology & Consultant Immunologist, Beaumont Hospital
Dr Greg Martin	Director, Health Protection Surveillance Centre, HSE
Dr Gerard McCarthy	Consultant in Emergency Medicine, Cork University Hospital & Clinical Lead, National Clinical Programme for Emergency Medicine, HSE
Dr Michele Meagher	Medical Officer, Health Products Regulatory Authority
Prof George Mellotte	Consultant Renal Physician, Clinical Lead, National Clinical Programme Renal Services, HSE
Dr Stanley Miller	Consultant Respiratory Physician, Clinical Lead, National Clinical Programme Respiratory Medicine, HSE
Dr Eavan Muldoon	Consultant in Infectious Diseases, Mater Misericordiae University Hospital, National Clinical Lead for CIT and OPAT programmes & National Clinical Programme Infectious Diseases, HSE

Dr John Murphy	Consultant Paediatrician & Co-Clinical Lead, National Clinical Programme Paediatric/Neonatology, HSE
Dr Amir Niazi	National Clinical Adviser and Group Lead Mental Health, HSE
Ms Sarah O' Connell*	Long COVID Advocacy Ireland
Dr Sarah O'Brien	Acting National Clinical Advisor & Group Lead for Chronic Disease (NCAGL), Office of the NCAGL for Chronic Disease, HSE
Dr Gerard O'Connor	Consultant in Emergency Medicine, Mater Misericordiae University Hospital & National Clinical Programme for Emergency Medicine, HSE
Dr Éamonn O'Moore	Director of National Health Protection, National Health Protection Service of Ireland, HSE
Ms Michelle O'Neill	Deputy Director, Health Technology Assessment, HIQA
Dr Stefano Savinelli*	Consultant in Infectious Diseases, St Vincent's University Hospital, Dublin
Ms Jacqueline Sexton*	Patient Representative
Prof Susan Smith	General Practitioner & Professor of General Practice, Trinity College Dublin
Dr Susan Spillane	Deputy Director, Health Technology Assessment, HIQA
Dr Patrick Stapleton	Consultant Microbiologist, UL Hospitals Group, Limerick & Irish Society of Clinical Microbiologists
Mr Mervyn Taylor	CEO, SAGE Advocacy
Dr Conor Teljeur	Chief Scientist, Health Technology Assessment, HIQA

* Ad hoc member for this meeting only.

Members of the Evaluation Team

Karen Cardwell, Marie Carrigan, Paul Carty, Fearghal Comaskey, Aislinn O'Mahony, Patricia Harrington, Louise Larkin, Cillian McDowell, Carol McLoughlin, Leah McManus, Niamh Merriman, Michelle Norris, Michelle O'Neill, Máirín Ryan, Debra Spillane, Susan Spillane, Conor Teljeur, Barrie Tyner.

Not all members of the Evidence Synthesis Team are involved in the response to each research question.

Conflicts of interest

None declared.

2 Advice to the Health Service Executive

The purpose of this evidence synthesis is to provide advice to the Health Service Executive (HSE) on the following policy areas:

1. The epidemiology and clinical burden of long COVID internationally.
2. The evidence of associations between risk/protective factors and development of long COVID among those who have had a SARS-CoV-2 infection.

The response to the policy areas is informed by an evidence synthesis considering three elements:

1. A systematic review of evidence on the epidemiology and clinical burden of long COVID internationally.
2. A systematic review among those who have had a SARS-CoV-2 infection, of the evidence of associations between risk or protective factors and development of long COVID.
3. Input from HIQA's COVID-19 Expert Advisory Group.

The key points of this evidence synthesis, which informed HIQA's advice, are as follows:

Review of evidence on the epidemiology and clinical burden of long COVID and of the associations between risk/protective factors and development of long COVID among those who have had a SARS-CoV-2 infection.

- Following acute COVID-19, prolonged and residual symptoms may occur. These symptoms may come and go over time. Novel symptoms and clinical manifestations may appear related to the acute SARS-CoV-2 infection. This condition may be called post-acute COVID-19, post-acute sequelae of SARS-CoV-2 infection (PASC), long-term effects of COVID, chronic COVID or long COVID. In this review, the term long COVID is used.
- Sixty-five primary research studies (51 cohort studies, 12 cross-sectional studies and two cross-sectional cohort studies) and five international registry documents (US: Centers for Disease Control and Prevention (CDC), National Centre for Health Statistics; UK: Office of National Statistics (ONS)) were identified. Following the quality appraisal, 51 primary research studies (comprising approximately 1.1 million participants with a history of COVID-19) were deemed to be of fair or good quality and included in the final data set. The four most recent versions of the international registry documents were included.

- Four sub-groups of interest were considered: general population; age (those aged less than 18 years and those 65 years or older); those classified by the HSE as medically vulnerable, and those with a history of severe COVID-19 illness (as indicated by hospitalisation due to COVID-19).
- Long COVID epidemiology in the general population:
  - Prevalence estimates were reported in seven studies and ranged from 15.2% to 53.1% in studies based on self-report data, and from 1.8% to 8.3% in studies considering those with a diagnosis of or referral for long COVID. Within international registry documents, it was estimated that 3.3% of the UK population (January 2023) and 5.9% of all adults in the US (January 2023) were experiencing long COVID.
  - Symptoms with the highest prevalence estimates were fatigue (ranging from 2.9% to 69%), brain fog, memory loss and or confusion (ranging from 0.2% to 45.7%), anosmia (ranging from 1.6% to 43.7%), and shortness of breath (ranging from 3.4% to 39.7%). These findings are broadly consistent with UK ONS estimates which indicated that the most commonly reported symptoms were fatigue (71%), difficulty concentrating (49%), shortness of breath (47%) and muscle ache (46%).
  - Limited evidence was identified for quality of life (QoL) related to long COVID. Estimates related to returning to work ranged from 6.3% of participants reporting an inability to work, to 47.1% of participants reporting their work capacity had not fully recovered. UK ONS data reported that (as of January 2023) long COVID symptoms adversely affected the day-to-day activities of 1.6 million people.
  - Older age was significantly associated with an increased odds of developing long COVID (or similar) in four studies (adjusted odds ratios (aORs) ranging from 1.05 to 2.10). Female sex was significantly associated with an increased odds of developing long COVID (or similar) in three studies (aORs ranging from 1.23 to 1.95).
- Long COVID epidemiology in those aged less than 18 years:
  - Prevalence estimates reported in 11 studies ranged from 4% to 65.7% in studies based on self-report data and from 0.1% to 57.9% in studies considering those with a long COVID diagnosis.
  - Symptoms with the highest prevalence estimates were fatigue (ranging from 1.1% to 22%), headache (ranging from 0.2% to 18%), mood swings

(ranging from 8.1% to 10.9%) and muscle pain (ranging from 0.2% to 10%).

- Two studies identified that long COVID impacted the day-to-day activities of children with a history of COVID-19. There were mixed findings with respect to the impact of COVID-19 on emotional functioning and health-related QoL.
- Within children, older age was associated with the development of long COVID (or similar) in five studies, with higher odds ratios seen in older age groups relative to younger age groups.

- Long COVID epidemiology in those aged 65 years or older:
  - Prevalence estimates ranged from 18.3% to 80.8% based on self-report data reported in four studies and from 5.6% to 8.6% in one study considering those with a long COVID diagnosis.
  - Symptoms with the highest prevalence estimates were fatigue (ranging from 4.9% to 38.7%), shortness of breath (ranging from 5% to 29.9%), sweating or hot flushes (ranging from 3.0% to 24.0%) and memory or concentration impairment (ranging from 1.4% to 23.2%).
  - Two studies reported factors associated with the development of long COVID in older adults. One study identified female sex and obesity as factors associated with fatigue and dyspnoea. The other identified older age and a history of severe acute COVID-19 as being factors associated with a greater impact of chronic obstructive pulmonary disease (COPD) symptoms on overall health and well-being.
- Long COVID epidemiology in those identified as medically vulnerable:
  - Prevalence estimates were reported in two studies, with 17.7% of patients on dialysis and 12.4% to 29.7% (depending on the follow-up time point) of those with multiple sclerosis (MS) self-reporting long-lasting symptoms.
  - In patients on dialysis, symptoms with the highest prevalence estimates were muscle or weight loss greater than 5% (52.8%), extreme fatigue (31.5%), respiratory symptoms or chest pain (14.8%), and post-traumatic stress disorder (PTSD), depression or anxiety (13%). In those with MS, the highest prevalence estimates were for new or worse fatigue (63.2% to 68.3%), lower respiratory tract symptoms (such as having a cough and shortness of breath) (48.4% to 58.3%), new muscle pain (35.8% to 45%) and gastrointestinal symptoms (such as nausea and diarrhoea) (34.7% to 41.7%).

- None of the studies that recruited those identified as medically vulnerable reported on QoL, return to work or physical activity.
- Pre-acute COVID-19 variables and comorbidities were associated with the development of long COVID in two studies. In patients on dialysis, the odds of reporting symptoms of long COVID increased with each year the patient had spent on dialysis, and in those with diabetes, or who were living with overweight or obesity compared with those who were not. In those with MS, pre–COVID-19 anxiety and or depression or having a high disability score were found to decrease the probability of recovery from COVID-19.

- Long COVID epidemiology in those under 18 years with a history of severe COVID-19 illness:
  - Prevalence estimates for long COVID reported in two studies ranged from 9.8% to 20%, based on self-report data.
  - The symptom with the highest prevalence estimate was fatigue (ranging from 1.6% to 9.4%), and the symptom clusters with the highest prevalence estimates were dermatologic (ranging from 0.2% to 4.7%), neurologic (0.9% to 4.2%) and gastrointestinal (2.0% to 3.9%).
- Long COVID epidemiology in those 18 years and older with a history of severe COVID-19 illness:
  - Prevalence estimates for long COVID in those 18 years and older was reported in 19 studies based on self-report data and ranged from 30.8% to 94.6%.
  - Symptoms with the highest prevalence estimates in those 18 years and older were fatigue (ranging from 8.2% to 91.1%), dyspnoea (shortness of breath) (ranging from 3.9% to 83.1%), cough (ranging from 2.0% to 78.2%) and arthralgia and or myalgia (ranging from 7.0% to 73%).
  - Prevalence estimates reported for return to work ranged from 11% to 34% unable to return to work. Eight studies reported severe limitations in physical activity levels ranging from 1.8% to 36%.
- Risk factors for the development of long COVID were identified across all age groups for those with a history of severe COVID-19 illness. Female sex was associated with the development of long COVID in seven studies, with aORs ranging from 1.27 to 2.54. Obesity was also associated with the development of long COVID in three studies, with aORs ranging from 1.02 to 2.24. The

presence of, or number of, comorbidities were associated with an increased odds of developing long COVID or similar in four studies, with diabetes, hypertension, asthma and chronic kidney disease specifically identified.

- Six new onset conditions following acute COVID-19 were identified among individuals reporting symptoms of long COVID in this review: venous thromboembolism, diabetes mellitus, chronic renal failure, chronic fatigue syndrome, fibromyalgia and post-traumatic stress disorder.
- However, due to the study designs included within the review there is a potential under-reporting of new onset conditions.
- Only eight of the 51 studies included within the review investigated the prevalence of long COVID and or long COVID symptoms in matched cohorts. Generally, long COVID prevalence was increased in studies that compared those with a history of COVID-19, to those without. However, this lack of an appropriate comparison group may limit understanding of the baseline estimation of symptoms within sub-groups.
- When investigating symptom prevalence over time, generally, prevalence estimates were observed to decline over time in those with MS, and those under 18 years with a history of severe COVID-19 illness. Mixed trends were observed over time for paediatric populations and those 18 years and older with a history of severe COVID-19 illness. Prevalence estimates over time were not identified for the general population, those aged 65 years and older and patients on dialysis.
- While the review outlines evidence published up to January 2023, of the epidemiology of long COVID internationally, heterogeneity of study designs, long COVID definitions used, outcome assessment methods and follow-up time points are likely to have contributed to the wide range of prevalence estimates observed. While only studies deemed to be of fair and good quality were included in the final analysis, the majority of studies were based on self-report of long COVID and long COVID symptoms and therefore bias may be inherent throughout.
- Long COVID is a complex condition potentially involving a wide range of symptoms and which may result in sustained, significant reductions in quality of life and functioning in some individuals and a substantial burden on healthcare systems as well as having a broader economic impact. In planning healthcare delivery for this population, a focus on multi-disciplinary holistic care will likely be necessary.

COVID-19 Expert Advisory Group

- A meeting of the COVID-19 Expert Advisory Group (EAG) was convened for clinical and technical interpretation of the evidence provided.
- The COVID-19 EAG identified additional factors which should be considered to inform this policy question. These are recorded within the meeting minutes and included:
    - Patient representatives reported that existing services are oversubscribed and that although it is important to establish prevalence it could be a distraction from the provision of care, with many patients experiencing relapsing, remitting and fluctuating symptoms.
    - Initial COVID-19 conversations focused on respiratory symptoms; we now know that long COVID covers a much wider range of symptoms. In addition, many people with pre-existing chronic conditions experienced an exacerbation of their symptoms following SARS-CoV-2 infection, while others developed new-onset chronic conditions.
    - Long COVID as an emerging phenomenon is still poorly understood, highlighting the requirement for additional research. It is important nevertheless to document what is currently known about the biological processes underscoring long COVID symptoms as this may help inform development of treatment interventions.
    - There are certain symptoms that are considered to be part of long COVID, for example fatigue. However, there is also currently an increase in symptomology being dealt with in other services outside the specific long COVID clinics. For example, an activation or flare up of disease for patients with autoimmune conditions may not be identified as 'long COVID'; however exacerbation of underlying conditions may be a morbid consequence of COVID-19. This involves a distinct and potentially uncaptured group (in the literature at least). Their additional care needs potentially represent a huge burden for the HSE. It is important therefore to ensure that existing services are adequately resourced.
    - Those with new onset chronic conditions or deterioration of existing chronic conditions post-COVID are unlikely to need new treatment pathways. Rather, the issue is one of recording the additional burden on existing services to ensure that they are adequately resourced for the increase in patient numbers and or the increase in the intensity of care required. For example, the National Renal Office has identified an increase in the number of new patients with chronic kidney disease (CKD). As with

other patients with CKD, patients who develop CKD post-acute COVID-19 may also require dialysis. It was noted that Ireland experienced much lower mortality rates among dialysis patients than other countries throughout the pandemic.

- It was highlighted that many of the services struggle to cater for the diverse range of symptoms that people with long COVID may present with. It was also suggested that a biopsychosocial model is needed which considers biomedical issues along with potential psychological and neuropsychological issues that may be associated with the condition. This model needs a true multidisciplinary approach with access to a range of specialities including, but not limited to, neurology; infectious diseases; physiotherapy; clinical psychology; occupational therapy; speech and language therapy; pain management; respiratory; cardiology and rehabilitation. Ideally there should be input from physicians with experience in managing post viral illness.
- It is important to highlight the impact of barriers to accessing care for vulnerable and underserved groups such as the geographic accessibility of services and access for vulnerable populations, such as the Traveller community in Ireland. These barriers to accessing care are not specific to the management of long COVID, but should nonetheless be considered in planning long COVID services.
- There is a need to consider the impact of long COVID on vulnerable groups, particularly those who experience an increase in memory problems, as it raises issues in relation to safeguarding with the potential that some may require additional assistance in decision-making.
- The implication of poverty as a risk factor raises an important social issue. However, it is a difficult issue to capture and may ultimately depend on the definition of long COVID. In some groups, there is considerable disparity between chronological and biological age where those from a disadvantaged or underserved background may experience symptoms and conditions at a younger age than is observed for the general population.
- The historical context of ME and other post-viral illnesses needs to be acknowledged. There has been a dominating belief that these conditions are primarily psychological in nature; long COVID patients are very concerned about this incorrect narrative being applied to long COVID, which may result in patients not being offered appropriate treatments and investigations.

- The nature of some of the symptoms and how they are managed was raised. For example, the management of fatigue, brain fog, and sleep disturbance may require diagnostic imaging or pathology to investigate the symptoms observed. However, where diagnostic techniques are currently unavailable other approaches may be needed to quantify both the burden of symptoms and the response to care.
- Patient representatives noted that the long COVID prevalence rates they see within their community would suggest a median range of 20% to 40%. The potential for very prolonged symptoms was also highlighted with some individuals continuing to experience symptoms three years following their initial COVID episode. As a community, patients with long COVID are finding it difficult to access services, with the lack of informed support contributing to trauma and potentially increasing the risk of physical deterioration and psychological impact of this condition.
- Despite lower prevalence rates, long COVID does occur in children, thus it is important to remember the paediatric population in planning services.
- The best way to prevent long COVID is to prevent COVID-19. Patient groups report a worsening of symptoms with each additional infection, so measures to prevent reinfection and further episodes of COVID-19 continue to be important for those with long COVID. The report also notes the high prevalence of long COVID symptoms in those with a history of severe COVID. This emphasises the importance of protecting the entire population, regardless of age, sex or health status prior to SARS-CoV-2 infection and particularly those at risk of severe disease following SARS-CoV-2 infection.
- Vaccination is an important factor in preventing COVID-19 and in particular severe COVID-19 and therefore has a plausible role in the prevention of long COVID. It was noted that a limited number of studies provided data relevant to vaccination with evidence that partial or complete vaccination reduces the risk of long COVID. Many of the studies included individuals whose COVID-19 episode occurred prior to or coincided with the roll out and widespread access to COVID-19 vaccination and it was noted that this along with changes in the circulating variants adds complexity to the analyses. The uniquely comprehensive access to SARS-CoV-2 testing in Ireland during the pandemic in addition to the well-established vaccine programme should support future research. It was agreed that there is an ongoing need to provide clear, concise and

accurate information for members of the public to support decision-making and to counter potential misinformation.

- As the pandemic continued, other acute viral infections reasserted themselves in the community. As such, there is a risk that there was an underdiagnosis of other acute viral infections such as Respiratory Syncytial Virus (RSV) and influenza including potential underdiagnosis of co-infections. This may have led to some of the burden associated with these other viral infections (both the acute viral episode and or the post-acute sequelae) being misattributed to COVID-19 and long COVID.
- Not all post-COVID care needs are due to long COVID. Due to the pandemic there was widespread delayed access to diagnostic and therapeutic services amplifying and contributing to unmet need in health and care services.
- Considering the potential for COVID-19 to aggravate pre-existing conditions and the association between severe COVID-19 and long COVID, researching the prevalence of long COVID in subgroups who were previously 'healthy' may yield interesting data, that is, in populations with a low burden of pre-existing conditions and or who were at low risk of severe COVID-19. An example to consider i research in teenagers, with the potential also to compare prevalence of long COVID with prevalence of other post viral conditions in this cohort.

2.1 Advice

Arising from the findings above, HIQA's advice to the Health Service Executive is as follows:

- This systematic review identified 51 primary research studies (containing approximately 1.1 million participants with a history of COVID-19) and four international registry documents. Four sub-groups were considered: general population, age (those aged less than 18 years and those 65 years or older); those classified by the HSE as medically vulnerable, and those with a history of severe COVID-19 illness.
- When investigating the epidemiology and clinical burden of long COVID internationally:
  - there is uncertainty regarding the prevalence of long COVID. While prevalence estimates were highest in those with a history of severe COVID-

19 illness, long COVID was reported across all populations and age groups indicating a possible substantial burden.

  - long COVID was identified as a complex condition, impacting multiple organ systems, with a wide-range of symptoms. The most common symptoms observed include fatigue, brain fog, memory loss and or confusion, anosmia and shortness of breath. Studies with a maximum follow-up of up to two years observed that symptoms may be long lasting.
  - in general, decreased physical activity levels were reported in those with a history of COVID-19, with more substantial impairments noted in those with a history of severe COVID-19 illness.
  - factors such as reporting methods and population demographics within the identified studies may have contributed to the large variation in prevalence estimates observed.

- When investigating the association between risk and protective factors and the development of long COVID:
  - female sex, increased age and the presence of comorbidities (asthma and or respiratory conditions in particular) were generally associated with an increased risk of developing of long COVID
  - COVID-19 vaccination and increased household income were identified as potential protective factors for long COVID development; however, evidence was limited
  - concurrent exposure to both SARS-CoV-2 infection and COVID-19 vaccine distribution at population level may have contributed to the limited evidence identified regarding vaccine impact.
- The mechanisms underlying the pathogenesis of long COVID are still unclear. The burden of long COVID may include a continuation of symptoms experienced during acute COVID-19, an exacerbation of a pre-existing condition, or the onset of new symptoms and conditions.
- Considerations when planning healthcare delivery for long COVID should include:
  - resourcing multi-disciplinary long COVID services that treat those experiencing a continuation of acute COVID-19 symptoms and or the onset of new symptoms with expertise and skill sets targeted to the management of the most common symptoms
  - additional resourcing for existing services, given the additional burden associated with the management of those experiencing an exacerbation of their pre-existing condition and or new-onset conditions

- equity of access to services including the geographic distribution of services and access for vulnerable populations
- the continuation of public health advice to minimise risk of infection or reinfection and promotion of the COVID-19 vaccination programme to reduce the severity of COVID-19 cases, and potentially the incidence of long COVID.

- This systematic review did not identify evidence of the prevalence of long COVID in Ireland. Given this, and the uncertainty regarding the burden of long COVID internationally, further research relevant to the Irish population may help to inform the delivery of healthcare services for those with long COVID in Ireland.

3 Background

In April 2023, the World Health Organization (WHO) reported that over 762 million individuals have been infected with SARS-CoV-2 worldwide since the identification of COVID-19 in late 2019, leading to over 6.8 million deaths.[1] Typical signs and symptoms of COVID-19 include fever, cough, sore throat, nasal congestion, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, gastrointestinal issues and new loss of taste or smell.[2] Acute COVID-19 is characterised by signs and symptoms of COVID-19 lasting up to four weeks. Symptom severity can range from asymptomatic to very serious,[3] with severe COVID-19 defined as oxygen saturation levels of less than 90% in room air, severe pneumonia, or signs of severe respiratory distress.[2]

Following acute COVID-19, prolonged and residual symptoms may occur; these symptoms may come and go over time, and novel symptoms and clinical manifestations may appear related to the acute SARS-CoV-2 infection. These prolonged and residual symptoms may be referred to by a number of terms, including long COVID,[4] post-acute COVID-19, post-acute sequelae of SARS-CoV-2 infection (PASC), long-term effects of COVID, or chronic COVID. In this report, the term long COVID is used. There are differences also in the minimum time period, ranging, for example, to symptoms occurring four weeks or more after the initial SARS-CoV-2 infection to 12 weeks after the initial infection.[5] The UK's National Institute for Health and Care Excellence (NICE) defines long COVID as both ongoing symptomatic COVID-19 (that is, signs and symptoms of COVID-19 from 4 to 12 weeks after the initial SARS-CoV-2 infection) and post-COVID-19 syndrome (that is, signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and which cannot be explained by an alternative diagnosis).[6] NICE highlights that post-COVID-19 syndrome usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time. They also report that it can affect any system in the body and may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.[6]

The mechanisms underlying the pathogenesis of long COVID are still unclear. A systematic review looking at hypotheses on the pathophysiology of long COVID found that while organ damage from the acute phase likely accounts for symptoms, specific long-lasting inflammatory mechanisms have also been proposed.[7] The clinical spectrum of long COVID comprises a wide range of symptoms and existing studies indicate that long COVID populations are highly heterogeneous. It is therefore recommended that a holistic view is taken when considering patient care. The biopsychosocial model, a dynamic model which recognises the complex interaction of biological, psychological and social constructs of illness[8] is suggested

as an underpinning philosophy in managing patients with long COVID. This model may also align with the heterogeneity observed in long COVID populations, with long COVID possibly presenting in multiple forms. For example, the most common manifestation of long COVID is the continuation of symptoms which commenced during acute COVID-19 infection.[9] However, the onset of new symptoms and or conditions not experienced during acute COVID-19 is also observed. Additionally, while not classically considered long COVID,[9] the exacerbation of a previous condition or conditions, may be a morbid consequence of COVID-19 and must also be considered within the biopsychosocial model.

Reports suggest that the burden associated with long COVID is substantial. A global systematic analysis that included 54 cohort studies and two medical record databases, with data for 1.2 million individuals from 22 countries,[10] estimated that 6.2% of individuals who contracted COVID-19 in 2020 and 2021 experienced at least one of three long COVID symptom clusters (namely, persistent fatigue with bodily pain or mood swings; cognitive problems; or ongoing respiratory problems) at three months post-infection. Of those individuals with long COVID, an estimated 15.1% continued to experience symptoms at 12 months following infection.[10] January 2023 prevalence estimates from the UK Office of National Statistics (ONS) indicate that approximately 3.3% of the UK population living in private households (which equates to approximately 2.1 million individuals) self-reported experiencing long COVID (defined as symptoms continuing for more than four weeks after the first suspected SARS-CoV-2 infection).[11] Of those with self-reported long COVID, 87% reported ongoing symptoms at least 12 weeks post-infection, with 57% and 30% reporting ongoing symptoms at least one year and two years, respectively following a COVID-19 diagnosis. Furthermore, 76% of those with self-reported long COVID reported that their symptoms adversely affected their day-to-day activities, with the most commonly reported symptoms being fatigue, difficulty concentrating, shortness of breath and muscle ache.[11] A 2023 systematic review also documented that COVID-19 survivors reported reduced levels of physical function, activities of daily living, and health-related quality of life at one to six months post SARS-CoV-2 infection,[12] which highlights the potential life-altering impact long COVID can have.

Investigations into the risk of developing long COVID have also been conducted. Risk factors identified to date include older age, a number of pre-existing comorbidities, initial COVID-19 disease severity and female sex.[13] A large cohort study published in 2023 from Israel, based on electronic medical healthcare records, assessed the risk of experiencing long COVID up to 12 months post-COVID-19. They reported that approximately 7.8% of individuals who developed COVID-19 went on to experience long COVID, with greater risk observed with older age, female sex, smoking, and the presence of symptoms such as muscle pain and cough during the acute illness. The study noted that hospitalisation during the acute phase

significantly increased the risk of experiencing several adverse health outcomes after COVID-19, such as respiratory, cardiovascular, dermatological, psychiatric, and neurological complications. Similarly, hospitalisation rates during the follow-up timeframe were substantially higher for individuals with long COVID compared to those who did not experience long COVID.[14]

The risk of developing long COVID may also vary according to the variant of SARS-CoV-2. Differences in the prevalence of self-reported long COVID were noted in the UK ONS data according to the time period in which the individual was infected with SARS-COV-2. For example, 30% reported having COVID-19 prior to November 2020, 12% reported having COVID-19 during the Alpha period (from November 2020 to April 2021), 18% reported having COVID-19 during the Delta period (from May 2021 to November 2021), and 37% reported having COVID-19 during the Omicron period (from November 2021 to present).

The evidence base for long COVID is evolving rapidly. Given its burden, understanding the epidemiology of long COVID is necessary to inform service delivery and the allocation of healthcare resources. Therefore, at the request of the Health Service Executive (HSE), the Health Information and Quality Authority (HIQA) agreed to undertake an international review of the epidemiology (including prevalence, incidence, risk factors and mitigating factors) of long COVID.

The aim of this review is to address the following two research questions:

1. What is the epidemiology and clinical burden of long COVID internationally?

2. Among those who have had a SARS-CoV-2 infection, what are the associations between risk/protective factors and development of long COVID?

4 Methods

The detailed methods used for this review are provided in the protocol: available here. In brief, a systematic electronic literature search was constructed to identify primary research studies and national and international disease registry documents relevant to either research question.[15] Only documents published from 1 November 2021 up to 6 December 2022 were included. A grey literature search for the same time period was also conducted. Additionally, public health guidance documents identified within an evidence synthesis conducted by HIQA titled 'International review of clinical guidelines and models of care for long COVID', available here, were manually searched for primary research studies and relevant data relating to the epidemiology and clinical burden of long COVID.

No language restrictions were applied. All potentially eligible documents were exported to Covidence (www.covidence.org) for independent screening of titles,

abstracts, and full texts by two reviewers for relevance based on inclusion and exclusion criteria detailed in the protocol. The inclusion criteria contained reviews and primary research studies with greater than or equal to 300 participants. However, following screening of 2,688 studies, and based on the large volume of studies included for data extraction at this point (n=208), a protocol deviation was introduced. The exclusion criteria were updated to exclude reviews and primary research studies with less than or equal to 10,000 participants and to exclude studies focusing on a previously outlined subgroup with less than or equal to 300 participants. All documents identified for inclusion prior to the protocol deviation (n=208) were reassessed against these criteria. While the final inclusion and exclusion criteria are outlined for each research question in the protocol, of note, for the epidemiology and clinical burden review question:

- any outcomes related to the epidemiology or clinical burden of long COVID were considered eligible for inclusion.

For review question on risk and or mitigating factors:

- any pre-existing or clinical risk factors (such as being unvaccinated, female sex, and number of symptoms during the acute phase of COVID-19) were eligible for inclusion
- mitigating factors which were eligible for inclusion included vaccination status, physical activity level (prior to COVID-19 onset) and use of pharmaceuticals licensed for the treatment of COVID-19 during the acute phase.

For both review questions:

- the study population included individuals of any age with a history of probable or confirmed SARS-CoV-2 (as defined by the study authors)
- subgroups of interest included those aged under 18 years, those aged 65 years or older, those aged under 65 years who are medically vulnerable (as outlined by the HSE)[16] and those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19)
- prospective / retrospective community / population and hospital based original research studies with ≥ 10,000 participants (or ≥ 300 participants for studies focused on the outlined subgroups) were included
- data relating to the epidemiology and clinical burden of long COVID reported within public health guidance and policy documents identified as relevant within the international *Review of clinical guidelines and models of care for long COVID*[17] conducted by HIQA were included
- national and international disease registries containing data on those with a history of probable or confirmed SARS-CoV-2 were included.

Following application of the inclusion/exclusion criteria, manual forward citation searching was performed on any HTA and national and international disease registry documents identified. Forward citation searching of all included primary research studies was not possible given the volume of included studies. Prior to data extraction, articles excluded as preprints were investigated for updated publication status, while articles excluded as protocols were investigated for associated publications.

For each review question, data extraction and quality appraisal of included original research studies was completed by a single reviewer and checked for accuracy and omissions by a second reviewer. The Newcastle-Ottawa Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used for the appraisal of cohort and case-control studies.[18] An adapted version of this tool, see Appendix 1, was used for cross-sectional studies. The criteria outlined in a cross-sectional survey of multicentre clinical databases in the UK, was used for assessing the attributes of included registries.[19]

5 Results

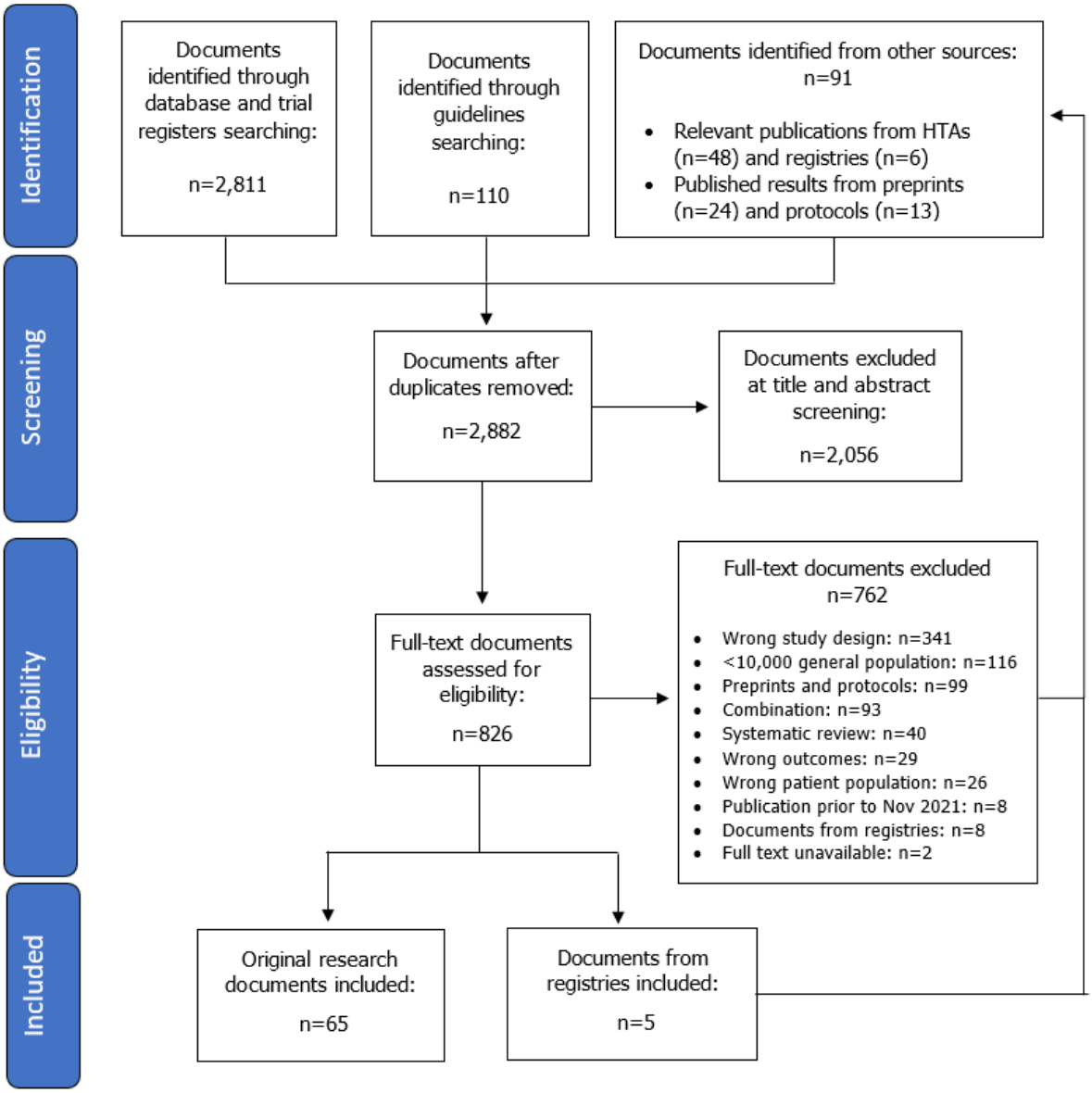
The results are presented in three main sections as follows:

- **Section 5.1 Search results**: a descriptive summary of the range of relevant documents identified.
- **Section 5.2. Methodological quality of included studies:** a quality appraisal of the documents included.
- **Section 5.3 Evidence underpinning:** a summary of the evidence provided within the documents.

5.1 Search results

The collective search up until 9 December 2022 resulted in 3,012 citations. Following removal of duplicates 2,882 citations were screened for relevance, with 826 full-texts assessed for eligibility and 762 subsequently excluded. See Figure 1 for a PRISMA flow diagram of the primary research studies and national and international disease registry documents included in this systematic review.

Figure 1. PRISMA flow diagram of included primary research studies and international and national disease registry documents.



5.1.1 Primary research studies

Using the inclusion and exclusion criteria for identification of primary research studies, 65 studies (published between November 2021 and December 2022) were included in this systematic review. Of the studies included, nine were conducted in Spain,[20-28] eight were conducted in Italy,[29-36] six were conducted in Brazil[37-42] and six were conducted in the UK.[43-48] The majority of the studies were cohort design (51 out of 65, 78%), followed by cross-sectional (12 out of 65, 18%) and cross-sectional cohort designs (where a source population is cross-sectionally sampled and subjects' histories of exposures and outcomes are retrospectively assessed over a

specified time period)[49] (2 out of 65, 3%).[24, 26] Forty-eight of the 65 studies recruited only those with a previous (or suspected) COVID-19 diagnosis, 14 studies recruited both those with a previous (or suspected) COVID-19 diagnosis and those with no previous COVID-19 diagnosis or a negative SARS-CoV-2 test result, and two studies did not have a requirement for either a negative test result or prior COVID-19 diagnosis at recruitment.[50, 51] Follow-up assessment time ranged from one month following COVID-19 diagnosis[43] to 685 days (approximately 98 weeks) after COVID-19 symptom onset.[52] A further overview of the characteristics of the primary research studies is presented below by sub-group and in Appendix 2.

General population

Ten of the 65 (15%) included primary research studies recruited 10,000 or more people representative of the general population with a previous (or suspected) COVID-19 diagnosis.[43, 48, 53-62] The majority of these studies (nine of ten) recruited adults 16 years or older or 18 years or older; one study recruited adolescents and adults aged 15 years or older.[56] The number of participants with a previous (or suspected) COVID-19 diagnosis ranged from 11,710[63] to 416,505[48] across the ten studies.

All studies investigated the presence of long COVID and or long COVID symptoms. Seven out of ten studies administered questionnaires or surveys as the follow-up mode of assessment, with the remaining three studies using registry data.[48, 58, 60] Three further studies (n ≥ 10,000) specifically related to children and adolescents under 18 years of age, and therefore are analysed within that age sub-group.[55, 59, 64]

Age (those aged under 18 years, those aged 65 years or older)

Twenty-one of the 65 (32%) included primary research studies either recruited participants in age groups of interest to the current review, or reported disaggregated results for age groups of interest. Eleven studies recruited children under 18 years of age with a previous (or suspected) COVID-19 diagnosis and two studies recruited children under 17 years of age (with no prior COVID-19 diagnosis required). One study recruited adults over 60 years old who were previously hospitalised with COVID-19.[65] Seven studies reported disaggregated results by age, with two studies investigating children under 18 years old[56, 66] and five studies investigating adults over 60[58] and over 65 years of age.[55] For the subgroup populations of interest, the number of participants with a previous (or suspected) COVID-19 diagnosis ranged from 360[67] to 74,611[67] across the 21 studies.

Presence of long COVID symptoms and or the risk factors associated with long COVID development were investigated in the majority of the studies (15 out of 21

studies), with three studies investigating specific adverse outcomes after COVID-19,[55] that is, development of fatigue and dyspnoea (shortness of breath)[67] and development of anosmia (loss of smell).[33] Fifteen of the 21 studies solely administered a questionnaire/survey or interview online, via telephone/app or in-person. Two studies did not provide sufficient information regarding the follow-up assessment mode.[68] Three of the studies used registry data[55, 58, 69] and one study completed a multi-branched or multidisciplinary assessment involving five different medical departments (general internal medicine, infectious disease, pulmonary disease, public health, and geriatric medicine) who performed assessments and gathered clinical data.[70]

Medically vulnerable

Three of the 65 (5%) included primary research studies recruited populations identified as medically vulnerable (those aged under 65 years who are medically vulnerable (as outlined by the HSE)) in the UK,[46] Turkey[71] and France.[71] The populations recruited were patients on dialysis,[72] those with multiple sclerosis[46] and kidney transplant recipients.[72] While multiple sclerosis (MS) is not identified by the HSE as a condition that puts people at higher risk of severe COVID-19 outcomes, the HSE does identify that individuals may be at higher risk if treated with certain drugs (such as, rituximab, cyclophosphamide, alemtuzumab, cladribine or ocrelizumab in the last six months). Participants with MS within the Garjani et al.[46] study were treated with these drugs, and so the study is relevant to this subgroup analysis.

The number of participants with a previous (or suspected) COVID-19 diagnosis ranged from 523[72] to 1,217[72] across the three studies. The presence of long COVID symptoms,[46, 71] and specifically ongoing respiratory symptoms,[72] were investigated via questionnaire and national registry data.[46, 71] One study[72] did not outline the follow-up assessment mode used.

Those with a history of severe COVID-19 illness

Forty-one of the 65 (63%) primary research studies included those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19). One of the 41 studies specifically included those previously hospitalised with COVID-19 pneumonia.[35] Thirty-four of the studies specifically recruited those previously hospitalised (and for comparison non-hospitalised individuals); four studies recruited those attending outpatient clinics for long COVID (of which some or all were previously hospitalised).[32, 33, 37, 47]

Four studies also recruited broader cohorts of those with a previous (or suspected) COVID-19 diagnosis (children under 18 years old and general population) with

analysis then disaggregated by hospitalisation or lack thereof. Two studies recruited based on the severity of acute COVID-19 illness at hospitalisation, with Gonzalez-Islas[73] recruiting those with moderate to severe acute COVID-19, and Nakayama[42] recruiting those with severe or critical acute COVID-19 illness. Within these studies definitions for the severity of COVID-19 disease varied. Moderate to severe acute, and severe to critical COVID-19 were defined as those hospitalised with COVID-19 and "blood oxygen saturation ≤ 93% on room air, PaO2/FiO2 ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 who required hospitalization"[73] or "dyspnoea, respiratory frequency higher than 30/min, blood oxygen saturation lower than 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio lower than 300, more than 50% of lung infiltrates, and critical infection associated with respiratory failure, septic shock, or multiple organ dysfunction".[42]

One study recruited only those admitted to the intensive care unit (ICU) with COVID-19,[21] with two further studies disaggregating hospitalised data into those admitted to ICU and those hospitalised more generally.[37, 74] The number of participants with a history of severe COVID-19 illness ranged from 351[35] to 9,665[75] across the 41 studies.

Presence of long COVID symptoms and or the risk factors associated with long COVID development were investigated in the majority of the studies (29 out of 41 studies). Twenty-two of the 41 studies solely administered a questionnaire or interview online, via telephone/app or in-person. Thirteen of the studies completed a multi-branched/multidisciplinary assessment and three of the studies extracted data from data registers. Three of the 41 studies did not provide sufficient information regarding the follow-up assessment mode.[21, 76, 77]

5.1.2 National and international disease registries

Five national and international disease registry documents were identified.[78-82] Three of these documents were produced in the US. Two of the US documents were Morbidity and Mortality Weekly Reports by the Centers for Disease Control and Prevention (CDC) and were based on national electronic health record data.[77, 78] The third document was from the National Center for Health Statistics (NCHS) in the US and was based on data from the Household Pulse Survey.[80] Two UK documents were statistical bulletins from the ONS (published in September and November 2022) using UK Coronavirus (COVID-19) Infection Survey data.[81, 82]

However, it was noted that these data are available as monthly updated reports, so a decision was taken to use only the most recent report of the survey data (January 2023).[11] This resulted in a final dataset of four registry documents.[11, 78-80] Publication dates for the four registry documents ranged from May 2022 to January

2023. Two of the four included registry documents recruited adults aged 18 years or older[79, 80] one recruited members of the general population aged two years or older[11] and one recruited children and adolescents aged 18 years or younger.[78]

Thirty-one national or international disease registries and or study databases[21-24, 34, 35, 40, 45, 46, 48, 50, 51, 53, 54, 56-58, 60, 61, 63, 64, 66, 69, 71, 74-77, 83-87] were identified from the 65 included primary research studies. Seven disease registries and or study databases were identified from the UK,[45, 46, 48, 51, 54, 61, 86] four from Germany,[53, 58, 60, 63, 69] three from Spain,[21-24] three from the US,[57, 74, 87] three from Denmark,[56, 64, 75, 88] two were international registries and or study databases,[76, 77] and the remaining registries were from Italy,[89] Brazil,[40] Canada,[85] France,[71] The Russian Federation,[66] South Africa,[84] Switzerland,[50] and the Netherlands.[83] Seventeen disease registries and or study databases related to adult populations,[21-24, 34, 35, 40, 45, 46, 48, 50, 51, 53, 54, 56-58, 60, 61, 63, 64, 66, 71, 74-77, 83-87] six related to paediatric populations,[34, 50, 64, 69, 77, 86] five comprised data from both paediatric and adult populations[51, 56, 60, 66, 71] and three did not specify the included population.[23, 24, 46]

5.1.3 Public health guidance and policy documents

Twenty-four public health guidance and policy documents were reviewed for relevant epidemiological and clinical burden data.[90-113] Twenty-two of the 24 documents were clinical guidelines,[90, 92-98, 100-113] with two documents identified as models of care.[91, 99] Seventeen guidelines[92, 93, 95-98, 100, 101, 103, 104, 106, 108-115] and one model of care[99] were national-level documents, three guidelines[90, 94, 102] and one model of care[91] were regional-level documents and two guidelines[105, 107] were international-level documents. Two guidelines[92, 95] were specific to paediatric populations and one guideline was specific to rehabilitation of older adults post-COVID.[105] No epidemiological and clinical burden data relevant to the research questions were identified in any of the 24 documents.

5.2 Methodological quality of included studies

All 65 primary research studies included within this systematic review were subject to quality appraisal using the Newcastle-Ottawa Assessment Tool. Additionally, one retrospective cohort study by Nakayama et al.,[42] which was at first deemed of fair quality using the Newcastle-Ottawa Assessment Tool was subsequently downgraded to poor quality due to data inconsistencies identified during data extraction. This resulted in, 33 of the 51 included cohort studies deemed to be of good quality (65%), four of fair quality (8%) and 14 of poor quality (27%). Of the 14 included cross-sectional or cross-sectional cohort studies, 11 were deemed to be good quality (79%) and three of fair quality (21%).

Issues were identified relating to the methodological quality of the 65 primary research studies included in this review. Firstly, all primary studies included are observational studies, meaning they are particularly vulnerable to biases and may not incorporate important confounding factors. This is supported by the quality appraisal results, with 14 of the 65 studies (22%) failing to control for factors beyond age, sex and comorbidities. Additionally, 22 of the 51 cohort studies (43%) did not control for the number of times participants may have had COVID-19, the presence of long COVID and or the presence of long COVID symptoms prior to study enrolment. It was also noted that in 36 of the 51 cohort studies (71%), it was not possible to assign a quality appraisal score for the reporting of outcomes. This was mainly due to studies using self-report as the assessment mode for long COVID and or long COVID symptoms. Studies may have used this mode of assessment to allow for a number of long COVID case definitions to be investigated (for example, the prevalence of individual symptoms, lack of recovery from acute COVID-19 and so on).

Additionally, self-report of long COVID and or long COVID symptoms does not rely on the identification of long COVID ICD codes, which were not introduced until October 2021,[116] and may capture information from those who have not attended a physician for a long COVID diagnosis.

All four international registry documents included in this analysis were subject to quality appraisal. The quality of the data in the documents was measured against five criteria: completeness of recruitment, completeness of data, use of explicit definitions of variables, independence of observations of primary outcomes, and extent of data validation.[19] Two of the documents included recruited less than 80% of eligible people[11, 80] and the remaining two documents did not specify the database recruitment proportion.[78, 79] In two of the documents, the level of completeness of the data was not known or not specified.[11, 80] Of the two documents that specified data completeness, Clinical Modification (ICD-10-CM) codes were used to identify COVID-19 case-patients and their electronic health records were monitored for long COVID.[78, 79] All of the documents used explicit definitions for long COVID. Of the four included documents, two included objective outcomes (that is, electronic health records)[78, 79] and two relied on outcomes being self-reported by participants.[11, 80] The data in each of the four registry documents were subjected to range and consistency checks.

Following quality appraisal, due to the large number of primary research studies included within this analysis, only those identified as good and fair quality, that is 51 of the 65 (79%), will be further discussed. All four registry documents were also included.

5.3 Evidence underpinning

The evidence has been partitioned into four sections: long COVID symptoms; new onset conditions; quality of life (QoL), return to work and physical activity or functioning and factors associated with the development of long COVID. New onset conditions represent any finding reported by the included primary research studies and registry documents that cannot be classified as symptoms and may be more directly related to a formal diagnosis. Terms such as anxiety and depression, which may be reported as either a symptom or diagnosis, were retained within the long COVID symptom section. The evidence within each section is then further presented according to the sub-group of interest (general population, age (those aged under 18 years and those aged 65 years or older), medically vulnerable and those with a history of severe COVID-19 illness).

5.3.1 Long COVID symptoms

Due to the breadth of symptoms reported across studies, reporting of symptoms was clustered primarily by the bodily system affected in accordance with the approach used in guidelines jointly published by NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP).[108] These symptom clusters were:

- general
- cardiovascular
- neurological
- respiratory
- psychological and or psychiatric
- ear, nose and throat
- musculoskeletal
- gastrointestinal and dermatologic.

When additional symptoms beyond those outlined were identified, these were assigned to a cluster by the research team which included physician review. Due to the identification of additional symptoms an additional cluster, titled the autonomic nervous system cluster, was added (see Table 4.1 for symptom clusters). Additionally, throughout Section 4.3.1 participants are identified as those with a history of COVID-19 or those with long COVID, with this categorisation based on how the population was identified within the underpinning primary research studies. Prevalence range estimates are reported for each symptom cluster. In studies with multiple time points the highest prevalence estimate value was selected to inform prevalence estimate ranges, for both long COVID prevalence and individual symptom prevalence. In studies with multiple symptoms and or multiple time points the

highest prevalence estimate value was selected to inform prevalence estimate ranges for the symptom cluster.

Table 4.1. Long COVID symptom clusters

General	Cardiovascular	Neurologic	Respiratory	Psychological/psychiatric	Ear, nose and throat	MSK	Gastrointestinal	Autonomic Nervous System	Dermatologic
Fatigue	**Chest tightness**	**Cognitive impairment**	**Breathlessness**	**Symptoms of depression**	**Tinnitus**	**Joint pain**	**Abdominal pain**	Exercise intolerance	**Skin rashes**
Fever	**Chest pain**	**Headache**	**Cough**	**Symptoms of anxiety**	**Earache**	**Muscle pain**	**Nausea and vomiting**	Sweating	**Hair loss**
Pain	**Palpitations**	**Sleep disturbance**	Excess sputum	**Symptoms of post-traumatic stress disorder**	**Sore throat**	**Mobility impairment**	**Diarrhoea**	Orthostatic intolerance	**Conjunctivitis**
Muscle weakness	**Oedema**	**Peripheral neuropathy symptoms (pins and needles and numbness)**	Oxygen desaturation	Behaviour disorders	**Loss of taste and/or smell**		**Weight loss**		
Weakness (if myalgia also listed)	Bleeding	**Dizziness**	Phlegm		**Nasal congestion**		**Reduced appetite**		
Nocturia /incontinence		**Delirium (in older populations)**	Haemoptysis				Stool problems		
Loss of libido		**Visual disturbance**					Dysphagia		
		Paraesthesia					Restricted oral intake		
		Sensory overload							

Key: MSK – musculoskeletal.

Note: Symptoms in bold are clustered primarily by bodily system affected in accordance with the approach used in the guidelines jointly published by NICE, SIGN and RCGP.[108]

General population

Following quality appraisal nine of the ten included primary research studies which recruited 10,000 or more people from the general population, with a previous (or suspected) COVID-19 diagnosis, were retained for analysis. Six of the nine studies included a definition of long COVID or post-COVID condition,[43, 48, 53, 54, 57, 63] with symptoms beginning a minimum of four weeks post-acute COVID-19. Two studies defined long COVID on ICD-10 codes.[58, 60]

Long COVID prevalence estimates were reported in seven studies of populations with a history of COVID-19 (confirmed or suspected) and ranged from 15.2%[57] to 53.1%[56] in studies based on self-report data, and from 1.8%[58] to 8.3%[58] in studies considering those with a diagnosis of or referral for long COVID (see Table 4.2). One study reported increased symptom prevalence in a SARS-CoV-2 test-positive cohort[56] compared with a time-matched SARS-CoV-2 test-negative cohort, six to 12 months following SARS-CoV-2 testing. Donnachie et al.[60] also reported a long COVID incidence estimate of 14.2% (95% CI: 13.9% to 14.5%) in those aged zero to 110 years, which when stratified by age-group in adults ranged from 12.1% (95% CI: 11.7% to 12.5%) in those aged 18 to 39 years, to 19.0% (95% CI: 18.6% to 19.5%) in those aged 40 to 59 years. Within registry documents, ONS data estimated that 2.1 million people living in private households in the UK (3.3% of the population) were experiencing self-reported long COVID as of 4 December 2022.[11] US CDC data estimated that 5.9% of all adults in the US, and 11% of adults who ever had COVID-19 were experiencing long COVID as of 16 January 2023.[80]

Table 4.2. Long COVID prevalence estimates in the general population

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
ONS[11] UK	Self-report via questionnaire	2.1 million of those living in private households in the UK **(3.3% of the population)** were experiencing self-reported long COVID as of 4 December 2022.
CDC[80] US	Self-report via survey	**5.9%** of all adults in the US, and **11%** of adults who ever had COVID-19 were experiencing long COVID as of 16 January 2023.
Ayoubkhani et al.[43] UK	Self-report via questionnaire (Single assessment time point)	6,729 **(23.7%)** at least 12 weeks after COVID-19 infection.
Kostev et al.[58] Germany	Diagnosis (ICD-10: U09.9) (Single assessment time point)	4,285 **(8.3%)** of total sample, 91 to 365 days after first COVID-19 diagnosis.
Meza-Torres et al.[48] England	Diagnosis (long COVID phenotype applied to EHR) (Single assessment time point)	7,623 of 416,505 **(1.8%)** of the population who had been exposed to COVID-19 infection, up to 6 months post-infection.
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	2,359 of 16,091 **(14.7%)** who tested positive at least 2 months prior to reporting continued symptoms. 1,843 of 12,441 **(14.8%)** who tested positive at least 6 months prior to reporting continued symptoms. 1,135 of 7,462 **(15.2%)** who tested positive at least 12 months prior to reporting continued symptoms.
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	3,289 of 11,536 **(28.5%)** when considering those with new symptoms with at least moderate impairment of daily life and ≤80% recovered general health or working capacity. **6.5%** of the infected adult population (assuming that non-responders had completely recovered) 6 – 12 months post-acute COVID-19.
Sørensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Positive SARS-CoV-2 test* **29.6%** reported at least 1 symptom, 6 – 12 months after a positive SARS-CoV-2 test. **53.1%** reported at least 1 of the following problems with new onset within the first 6, 9, or 12 months after a positive SARS-CoV-2 test: difficulties concentrating; memory issues; mental exhaustion; physical exhaustion or sleep problems. *Negative SARS-CoV-2 test (time-matched control group)* **13.0%** reported at least 1 symptom, 6 – 12 months after a negative SARS-CoV-2 test. **11.5%** reported at least 1 of the following problems with new onset within the first 6, 9, or 12 months after a negative SARS-CoV-2 test: difficulties concentrating; memory issues; mental exhaustion; physical exhaustion or sleep problems.

Whitaker et al.[54] England	Self-report via questionnaire (2 assessment time points, different populations at each time point)	**37.7%** reported 1 or more symptoms at least 12 weeks after a positive SARS-CoV-2 test and symptomatic COVID-19 (in main analysis). **21.6%** reported 1 or more symptoms at least 12 weeks after a positive SARS-CoV-2 test and symptomatic COVID-19 (in replication study).

Key: CDC, Centers for Disease Control and Prevention; EHR, electronic health record; ONS, Office for National Statistics; UK, United Kingdom; US, United States.

General Symptom Cluster

Seven studies reported general symptoms,[48, 53, 54, 56-58, 63] with prevalence estimates for this cluster ranging from 16.8%[56] to 45.5%[56] in those with a history of COVID-19 and from 12.5%[48] to 69%[58] in those identified as having long COVID (see Table 4.3). Fatigue and or exhaustion, and fever and or chills were the most commonly reported symptoms across general population studies. Fatigue and or exhaustion prevalence estimates ranged from 2.9% (for severe fatigue)[54] to 69%.[58] The most common symptom identified by those self-reporting long COVID in the ONS statistical bulletin was also fatigue (71%).[11] Prevalence estimates for fever and or chills ranged from 1.7%[54] to 2.3%[56] for fever, from 1.2%[54] to 1.6%[56] for chills and 2.4% when reported as a single outcome (fever or chills).[63] One study also reported an increased prevalence for the general symptom cluster in a SARS-CoV-2 test-positive cohort,[56] compared to a time-matched SARS-CoV-2 test-negative cohort, six to 12 months following SARS-CoV-2 testing (risk differences (RDs) ranging from 0.34 to 40.45).

Table 4.3. General symptom cluster prevalence estimates in the general population

Author or Organisation Country	Long COVID assessment mode	General symptom cluster prevalence estimates
ONS[11] UK	Self-report via questionnaire	*Long COVID* Fatigue **(71%)** was the most common symptom reported in the ONS statistical bulletin.
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of fatigue, % [95%CI]* 3 months post-infection: **28.1** [26.3 to 30.0] 6 months post-infection: **29.3** [28.4 to 30.3] 9 months post-infection: **29.2** [27.9 to 30.5] 12 months post-infection: **27.7** [26.3 to 29.1] 15 months post-infection: **25.0** [23.1 to 27.0]
Kostev et al.[58] Germany	Diagnosis (ICD-10: R53, G93.3) (Single assessment time point)	*Long COVID (n = approximately 4,285)* *Prevalence 91 to 365 days after first COVID-19 diagnosis, n (%)* Malaise and fatigue: 2,957 (**69.0**)
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Weakness and tiredness: 786 (**12.5**) Fever: 105 (**1.7**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Long COVID (n = 2,359)* *Persistent fatigue at least 2 months after diagnosis, n (%)* Total: 1,232/2,359 (**52.2**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection* *Fatigue, % [95%CI]* Total: **37.2** [36.4 to 38.1] *Substantial fatigue (FAS>21), n (%), [95%CI]* Total: 11,141 (**41.9**), [41.0 to 42.8] *Extreme fatigue (FAS>34), n (%), [95%CI]* Total: 11,141 (**11.2**), [10.6 to 11.8] *Chills or fever, % [95%CI]* Total: **2.4** [2.1 to 2.7]

Author or Organisation Country	Long COVID assessment mode	General symptom cluster prevalence estimates
Sørensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 61,002)* *Symptoms 6-12 months after test, n (%)* Fatigue/exhaustion: 6,799 (**11.1**) Chills: 966 (**1.6**) Fever: 1,362 (**2.2**) Red runny eyes: 822 (**1.3)** *Self-reported health problems with new onset between the test date and until 6-12 months after, n (%)* Physical exhaustion: 25,492 (**45.5**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)* *Symptoms 6-12 months after test, n (%)* Fatigue/exhaustion: 2,868 (**3.1**) Chills: 980 (**1.1**) Fever: 1,584 (**1.7**) Red runny eyes: 748 (**0.8)** *Self-reported health problems with new onset between the test date and until 6-12 months after, n (%)* Physical exhaustion: 5, 879 (**7.3**) *6 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 22,541)* Chills: 117 (**1.6**); 134 (**0.9**) Fever: 172 (**2.3**); 206 (**1.4**) Red runny eyes: 92 (**1.2**); 97 **(0.6)** *9 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 106,611)* Chills: 702 (**1.6**); 666 (**1.1**) Fever: 978 (**2.2**); 1,120 (**1.8**) Red runny eyes: 583 (**1.3**); 512 (**0.8**) *12 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 23,728)* Chills: 147 (**1.5**); 180 (**1.3**) Fever: 212 (**2.2**); 258 (**1.9**) Red runny eyes: 147 (**1.5**); 139 (**1.0**)
Whitaker et al.[54] England	Self-report via questionnaire	*History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]*

Author or Organisation Country	Long COVID assessment mode	General symptom cluster prevalence estimates
	(2 assessment time points, different populations at each time point)	*Main analysis (n = 76,155)* Sore eyes: 2,154 (**3**), [2.8 to 3.1] Fever: 897 (**1.2**), [1.2 to 1.3] Severe fatigue: 2,098 (**2.9**), [2.8 to 3.0] Chills: 906 (**1.2**), [1.2 to 1.3] Heavy arms/legs: 2,331 (**3.2**), [3.1 to 3.3] Tiredness: 12,214 (**16.8**), [16.5 to 17.1] *History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Replication study (3 – 8 months after main analysis) (n = 13,170)* Sore eyes: 117 (**1.2**), [1.0 to 1.5] Fever: 55 (**0.6**), [0.4 to 0.8] Severe fatigue: 234 (**2.5**), [2.2 to 2.8] Tiredness: 759 (**8**), [7.5 to 8.6]

Key: ONS, Office for National Statistics; UK, United Kingdom; US, United States.

Cardiovascular Symptom Cluster

Five studies reported symptoms related to the cardiovascular cluster,[48, 53, 54, 56, 63] with chest pain and palpitations the most commonly reported symptoms within this cluster. Prevalence estimates for chest pain ranged from 1.7%[53] to 4.2%[54] in those with a history of COVID-19. In those identified as having long COVID, 5.9%[48] reported chest pain. Prevalence estimates for palpitations in one study ranged from 2.9% to 3.6% in those with a history of COVID-19,[53] while 2.0% of those identified as having long COVID reported palpitations.[48] Additionally, one study reported a chest symptom cluster (containing chest pain, wheezing and shortness of breath) with a prevalence of 30.2% (see Table 4.4).[63] One study also reported an increased prevalence of chest pain in a SARS-CoV-2 test-positive cohort[56] compared with a time-matched SARS-CoV-2 test-negative cohort (RD: 2.01; 95% CI: 1.85 to 2.16), six to 12 months following SARS-CoV-2 testing.

Table 4.4. Cardiovascular symptom cluster prevalence estimates in the general population.

Author or Organisation Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of chest pain, % [95%CI]* 3 months post-infection: **1.7** [1.3 to 2.3] 6 months post-infection: **1.7** [1.4 to 2.0] 9 months post-infection: **1.6** [1.3 to 1.9] 12 months post-infection: **1.4** [1.1 to 1.8] 15 months post-infection: **1.2** [0.8 to 1.8] *Daily prevalence of palpitation, % [95%CI]* 3 months post-infection: **2.9** [2.3 to 3.7] 6 months post-infection: **3.3** [2.9 to 3.7] 9 months post-infection: **3.5** [3.0 to 4.1] 12 months post-infection: **3.6** [3.0 to 4.2] 15 months post-infection: **3.4** [2.7 to 4.4]
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Palpitations: 128 (**2.0**) Chest pain: 371(**5.9**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection, (%) [95%CI]* Chest symptoms†: **30.2** [29.4 to 31.0]
Sørensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 61,002)* *Symptoms 6-12 months after test, n (%)* Chest pain: 1,695 (**2.8%**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)* *Symptoms 6-12 months after test, n (%)* Chest pain: 780 (**0.8**)

Author or Organisation Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
		6 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 22,541) Chest pain: 234 (**3.1**); 90 (**0.6**) *9 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 106,611)* Chest pain: 1,195 (**2.7**); 538 (**0.9**) *12 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 23,728)* Chest pain: 266 (**2.7**); 152 (**1.1**)
Whitaker et al.[54] England	Self-report via questionnaire (Two assessment time points, different populations at each time point)	*History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Main analysis (n = 76,155)* Tight chest: 4,234 (**5.8**), [5.7 to 6.0] Chest pain: 1,854 (**2.5**), [2.4 to 2.7] Heart issues: **0%** *History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Replication study (3 – 8 months after main analysis) (n = 13,170)* Tight chest or chest pain*: 398 (**4.2**), [3.8 to 4.6] Heart issues: 287 (**3**), [2.7 to 3.4] *tight chest and chest pain grouped in the replication study

†Chest symptoms includes chest pain, wheezing and shortness of breath.

Neurological Symptom Cluster

Seven studies reported symptoms related to the neurological cluster.[48, 53, 54, 56-58, 63] Prevalence estimates ranged from 11.0%[53] to 37.7%[56] in those with a history of COVID-19 and from 4.0%[58] to 45.7%[57] in those identified as having long COVID (see Table 4.5). Headaches; difficulties with concentration; brain fog, memory loss and or confusion; sleep-related issues and vertigo and or dizziness were the most commonly reported symptoms across general population studies.

Prevalence estimates ranged from 5.2%[54] to 33.6%[57] for headaches, from 0.6%[48] to 29.7%[56] for difficulties with concentration, from 0.2%[48] to 45.7%[57] for brain fog, memory loss and or confusion and from 0.7%[48] to 30%[57] for sleep-related issues. One study also reported an increased prevalence of new onset neurological symptoms and neurological health problems in a SARS-CoV-2 test-positive cohort[56] compared with a time-matched SARS-CoV-2 test-negative cohort (RDs ranging from 2.38 to 32.58), six to 12 months following SARS-CoV-2 testing. The ONS reported a prevalence estimate of 49% for difficulty concentrating in those with self-reported long COVID.[11]

Table 4.5. Neurologic symptom cluster prevalence estimates in the general population.

Author or Organisation Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
ONS[11] UK	Self-report via questionnaire	*Long COVID* A prevalence estimate of **49%** was reported for difficulty concentrating.
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of disturbance of memory, % [95%CI]* 3 months post-infection: **6.4** [5.5 to 7.5] 6 months post-infection: **6.7** [6.2 to 7.2] 9 months post-infection: **6.8** [6.1 to 7.5] 12 months post-infection: **6.5** [5.8 to 7.3] 15 months post-infection: **6.4** [5.4 to 7.6] *Daily prevalence of headache, % [95%CI]* 3 months post-infection: **5.6** [4.7 to 6.6] 6 months post-infection: **6.0** [5.5 to 6.6] 9 months post-infection: **5.8** [5.2 to 6.5] 12 months post-infection: **5.1** [4.4 to 5.8] 15 months post-infection: **3.9** [3.1 to 4.9] *Daily prevalence of loss of concentration, % [95%CI]* 3 months post-infection: **9.0** [7.9 to 10.2] 6 months post-infection: **9.4** [8.8 to 10.1] 9 months post-infection: **9.7** [8.9 to 10.6] 12 months post-infection: **9.8** [8.9 to 10.8] 15 months post-infection: **9.7** [8.5 to 11.1] *Daily prevalence of sleep disorders, % [95%CI]* 3 months post-infection: **10.8** [9.6 to 12.1] 6 months post-infection: **11.0** [10.4 to 11.7] 9 months post-infection: **10.9** [10.0 to 11.8] 12 months post-infection: **10.3** [9.4 to 11.3] 15 months post-infection: **9.4** [8.2 to 10.8] *Daily prevalence of vertigo, % [95%CI]* 3 months post-infection: **2.1** [1.6 to 2.7] 6 months post-infection: **2.4** [2.1 to 2.7] 9 months post-infection: **2.5** [2.1 to 3.0]

Author or Organisation Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		12 months post-infection: **2.4** [2.0 to 3.0] 15 months post-infection: **2.2** [1.6 to 2.9]
Kostev et al.[58] Germany	Diagnosis (ICD-10: R41.8) (Single assessment time point)	*Long COVID (n = approximately 4,285)* *Prevalence 91 to 365 days after first COVID-19 diagnosis, n (%)* Symptoms involving cognitive functions and awareness: 171 (**4.0**)
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Memory loss and confusion: 14 (**0.2**) Difficulty concentrating: 35 (**0.6**) Trouble sleeping: 46 (**0.7**) Headache: 306 (**4.9**) Vertigo and dizziness: 137 (**2.2**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Long COVID (n = 2,359)* *Persistent headache at least 2 months after diagnosis, n (%)* Total (n=2,359): 793 (**33.6**) *Persistent brain fog at least 2 months after diagnosis, n (%)* Total (n=2,359): 952 (**40.4**) *Persistent poor memory at least 2 months after diagnosis, n (%)* Total (n=2,359): 664 (**28.1**) *Persistent either brain fog or poor memory at least 2 months after diagnosis, n (%)* Total (n=2,359): 1079 (**45.7**) *Persistent dizziness at least 2 months after diagnosis, n (%)* Total (n=2,359): 485 (**20.6**) *Persistent sleep disruption at least 2 months after diagnosis, n (%)* Total (n=2,359): 708 (**30.0**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection (%) [95%CI]* Neurocognitive impairment: **31.3** [30.5 to 32.2] Headache or dizziness: **19.9** [19.2 to 20.6]
Sørensen et al.[56] Denmark	Self-report via questionnaire	*History of COVID-19 (n = 61,002)* *Symptoms 6-12 months after test, n (%)*

Author or Organisation Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
	(Single assessment time point)	Sleeping legs/arms: 2,841 (**4.7**) Headache: 3,740 (**6.1**) Dizziness: 2,430 (**4.0**) *Self-reported new diagnoses received between the test date and until 6-12 months after, n (%)* Mental exhaustion: 20,810 (**37.7**) Difficulties concentrating: 16,720 (**29.7**) Memory issues: 16,149 (**28.7**) Sleep problems: 11,850 (**22.9**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)* *Symptoms 6-12 months after test, n (%)* Sleeping legs/arms: 1,236 (**1.3**) Headache: 2,868 (**3.1)** Dizziness: 1,495 (**1.6**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)* *Self-reported health problems with new onset between the test date and until 6-12 months after, n (%)* Mental exhaustion: 5,879 (**7.3**) Difficulties concentrating: 2,812 (**3.4**) Memory issues: 3,057 (**3.7**) Sleep problems: 4,936 (**6.5**) *6 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 22,541)* Sleeping legs/arms: 355 (**4.7**); 174 (**1.2**) Headache: 502 (**6.7**); 413 (**2.7**) Dizziness: 322 (**4.3**); 210 (**1.4**) *9 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 106,611)* Sleeping legs/arms: 2,053 (**4.7**); 859 (**1.4**) Headache: 2,657 (**6.1**); 2,003 (**3.2**) Dizziness: 1,754 (**4.0**); 1,049 (**1.7**) *12 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 23,728)* Sleeping legs/arms: 433 (**4.4**); 203 (**1.5**) Headache: 581 (**5.9**); 452 (**3.2**)

Author or Organisation Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Dizziness: 354 (**3.6**); 236 (**1.7**)
Whitaker et al.[54] England	Self-report via questionnaire (2 assessment time points, different populations at each time point)	*History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Main analysis (n = 76,155)* Headache: 3,792 (**5.2**), [5.1 to 5.4] Difficulty sleeping: 5,427 (**7.5**), [7.3 to 7.7] Numbness/tingling: 1,511 (**2.1**), [2 to 2.2] *History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Replication study (3 – 8 months after main analysis) (n = 13,170)* Headache: 311 (**3.3**), [3 to 3.7] Difficulty sleeping: 438 (**4.6**), [4.2 to 5.1] Numbness/tingling: 202 (**2.1**), [1.9 to 2.5] Confusion/brain fog/forgetfulness: 590 (**6.2**), [5.8 to 6.8] Vision issues: 182 (**1.9**), [1.7 to 2.2]

Key: ONS, Office for National Statistics; UK, United Kingdom; US, United States.

Respiratory Symptom Cluster

Seven studies reported symptoms related to the respiratory cluster,[48, 53, 54, 56-58, 63] with prevalence estimates ranging from 3.4%[53] to 13.9%[63] in those with a history of COVID-19 and from 11.3%[48] to 39.7%[57] in those identified as having long COVID (see Table 4.6).[63] The ONS reported a prevalence estimate of 47% for respiratory symptoms in those with self-reported long COVID.[11] Dyspnoea (shortness of breath) and cough were the most commonly reported symptoms across general population studies. Dyspnoea prevalence estimates ranged from 3.4%[53] to 39.7%.[57] Prevalence estimates for cough ranged from 2.9%[53] to 8.6%.[48] One study also reported increased dyspnoea prevalence in a SARS-CoV-2 test-positive cohort (RD: 4.87; 95% CI: 4.64 to 5.07),[56] compared to a time-matched SARS-CoV-2 test-negative cohort, six to 12 months following SARS-CoV-2 testing; however, the prevalence of cough was similar across the groups (RD: -0.01; 95% CI: -0.23 to 0.22). Whitaker et al.[54] also reported sneezing prevalence estimates of 0.7% to 2.1%.

Table 4.6. Respiratory symptom cluster prevalence estimates in the general population.

Author or Organisation Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
ONS[11] UK	Self-report via questionnaire	*Long COVID* A prevalence estimate of **47%** was reported for respiratory symptoms.
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of cough, % [95%CI]* 3 months post-infection: **2.9** [2.3 to 3.7] 6 months post-infection: **2.6** [2.3 to 3.0] 9 months post-infection: **2.5** [2.1 to 2.9] 12 months post-infection: **2.5** [2.1 to 3.0] 15 months post-infection: **2.8** [2.1 to 3.6] *Daily prevalence of dyspnoea, % [95%CI]* 3 months post-infection: **3.0** [2.4 to 3.7] 6 months post-infection: **3.2** [2.8 to 3.6] 9 months post-infection: **3.3** [2.9 to 3.9] 12 months post-infection: **3.4** [2.9 to 4.0] 15 months post-infection: **3.4** [2.7 to 4.3]
Kostev et al.[58] Germany	Diagnosis (ICD-10: R53 and G93.3) (Single assessment time point)	*Long COVID (n = approximately 4,285)* *Prevalence 91 to 365 days after first COVID-19 diagnosis, n (%)* Abnormalities of breathing: 900 (**21**)
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Shortness of breath: 714 (**11.3**) Cough: 544 (**8.6**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Long COVID (n = 2,359)* *Persistent shortness of breath at least 2 months after diagnosis, n (%)* Total (n=2,359): 937 (**39.7**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection (%) [95%CI]* Upper respiratory symptoms: **13.9** [13.3 to 14.6]
Sørensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 61,002)* *Symptoms 6-12 months after test, n (%)* Dyspnoea: 3,277 (**5.4**) Cough: 2,956 (**4.8**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)*

Author or Organisation Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		Symptoms 6-12 months after test, n (%) Dyspnoea: 813 (**0.9**) Cough: 4,007 (**4.4**) *6 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 22,541)* Dyspnoea: 450 (**6.0**); 122 (**0.8**) Cough: 349 (**4.6**); 592 (**3.9**) *9 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 106,611)* Dyspnoea: 2,361 (**5.4**); 556 (**0.9**) Cough: 2,097 (**4.8**); 2,789 (**4.4**) *12 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 23,728)* Dyspnoea: 466 (**4.8**); 135 (**1.0**) Cough: 510 (**5.2**); 696 (**5.0**)
Whitaker et al.[54] England	Self-report via questionnaire (2 assessment time points, different populations at each time point)	*History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Main analysis (n = 76,155)* Sneezing: 1,512 (**2.1**), [2.0 to 2.2] Shortness of breath: 7,166 (**9.8**), [9.6 to 10.1] New persistent cough: 3,073 (**4.2**), [4.1-4.4] *History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Replication study (3 – 8 months after main analysis) (n = 13,170)* Sneezing: 64 (**0.7**), [0.5-0.9] Shortness of breath: 750 (**7.9**), [7.4-8.5]. New persistent cough: 361 (**3.8**), [3.5-4.2]

Key: ONS, Office for National Statistics; UK, United Kingdom; US, United States.

Autonomic Nervous System Symptom Cluster

Two studies reported symptoms related to the autonomic nervous cluster.[56, 57] In those with a history of COVID-19, 3.4%[56] reported hot flushes and or sweating six to 12 months post-acute COVID-19. In those identified as having long COVID, 29%[57] reported exercise intolerance two months post-acute COVID-19. One study also reported an increased prevalence of hot flushes and or sweating in a SARS-CoV-2 test-positive cohort[56] compared with a time-matched SARS-CoV-2 test-negative cohort (RD: 1.66; 95% CI: 1.48 to 1.84), six to 12 months following SARS-CoV-2 testing.

Psychological and or Psychiatric Symptom Cluster

Five studies reported symptoms related to the psychological and or psychiatric cluster (see Table 4.7).[48, 53, 56, 57, 63] Prevalence estimates ranged from 3.5%[56] to 21.1%[63] in those with a history of COVID-19, and from 6.4%[48] to 28.7%[57] in those identified as having long COVID. Anxiety and or depression (low mood) were the most commonly reported symptoms across general population studies. Prevalence (estimated at six to 12 months post-acute COVID-19 infection) for anxiety and depression (or low mood) ranged from 3.4%[56] to 28.7%[57] and 3.5%[56] to 23.3%,[57] respectively. One study reported an increased prevalence of both diagnosed anxiety and depression in a SARS-CoV-2 test-positive cohort,[56] compared to a time-matched SARS-CoV-2 test-negative cohort (RDs of 1.00 and 1.15), six to 12 months following SARS-CoV-2 testing.

Table 4.7. Psychological and or psychiatric symptom cluster prevalence estimates in the general population

Author or Organisation Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of anxiety, % [95%CI]* 3 months post-infection: **9.8** [8.6 to 11.0] 6 months post-infection: **10.0** [9.4 to 10.7] 9 months post-infection: **9.8** [9.0 to 10.7] 12 months post-infection: **9.1** [8.3 to 10.1] 15 months post-infection: **8.1** [7.0 to 9.4] *Daily prevalence of depression, % [95%CI]* 3 months post-infection: **6.8** [5.9 to 8.0] 6 months post-infection: **6.5** [6.0 to 7.1] 9 months post-infection: **6.4** [65.8 to 7.2] 12 months post-infection: **6.5** [5.8 to 7.3] 15 months post-infection: **6.7** [5.7 to 7.9]
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Worry and anxiety: 407 (**6.4**) Low mood and not enjoying anything: 389 (**6.2**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Long COVID (n = 2,359)* *Persistent depressed mood at least 2 months after diagnosis, n (%)* Total (n=2,359): 550 (**23.3**) *Persistent anxious mood at least 2 months after diagnosis, n (%)* Total (n=2,359): 678 (**28.7**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection (%) [95%CI]* Anxiety or depression: **21.1** (20.4 to 21.9)
Sørensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 61,002)* *Self-reported new diagnoses received between the test date and until 6 - 12 months after test, n (%)* Anxiety: 1,900 (**3.4**) Depression: 1,883 (**3.5**) *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)* *Self-reported new diagnoses received between the test date and until 6 - 12 months after test, n (%)* Anxiety: 1,783 (**2.1**) Depression: 1,870 (**2.3)**

Key: US, United States.

Ear, Nose and Throat (ENT) Symptom Cluster

Seven studies reported symptoms related to the ear, nose and throat cluster.[48, 53, 54, 56-58, 63] Prevalence estimates ranged from 4.8%[54] to 23.6%[63] in those with a history of COVID-19 and from 1.6%[48] to 43.7%[57] in those identified as having long COVID (see Table 4.8). Anosmia and ageusia (loss of taste) were the most commonly reported symptoms across general population studies, with specific prevalence estimates ranging from 1.6%[48] to 43.7%[57] for anosmia or dysosmia; 0.7%[63] to 4.0%[54] for ageusia or dysgeusia and 6%[58] to 23.6%[54] for the combined symptoms (anosmia and or ageusia).

Sore throat was also reported in four studies,[48, 53, 54, 56] with prevalence estimates ranging from 0.9%[53] to 4.1%.[56] One study also reported an increased prevalence of dysmosia (change in smell) and of dysguesia (change in taste) in a SARS-CoV-2 test-positive cohort (RDs of 10.92 and 8.68),[56] compared with a time-matched SARS-CoV-2 test-negative cohort, six to 12 months following SARS-CoV-2 testing; however, the prevalence of runny nose and of sore throat were similar across the two cohorts (RDs of -0.22 and -0.65).

Table 4.8. Ear nose and throat symptom cluster prevalence estimates in the general population

Author or Organisation Country	Long COVID assessment Mode	Ear, Nose and Throat symptom cluster prevalence estimates
Bernas et al.[53] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 12,609)* *Daily prevalence of sore throat, % [95%CI]* 3 months post-infection: **0.9** [0.6 to 1.4] 6 months post-infection: **0.8** [0.6 to 1.0] 9 months post-infection: **0.8** [0.6 to 1.0] 12 months post-infection: **0.7** [0.5 to 1.0] 15 months post-infection: **0.7** [0.4 to 1.1] *Daily prevalence of anosmia/ageusia, % [95%CI]* 3 months post-infection: **7.7** [6.7 to 8.9] 6 months post-infection: **9.1** [8.5 to 9.7] 9 months post-infection: **9.4** [8.6 to 10.3] 12 months post-infection: **8.6** [7.7 to 9.5] 15 months post-infection: **6.8** [5.8 to 8.1]
Kostev et al.[58] Germany	Diagnosis (ICD-10: R43) (Single assessment time point)	*Long COVID (n = approximately 4,285)* *Prevalence 91 to 365 days after first COVID-19 diagnosis, n (%)* Disturbances of smell and taste: 257 (**6**)
Meza-Torres et al.[48] England	Diagnosis (SNODMED CT codes) (Single assessment time point)	*Long COVID (Community) (n = 6,315)* *Prevalence at 1-6 months post-infection, n (%)* Loss of smell: 103 (**1.6**) Loss of taste: 43 (**0.7**) Sore throat: 77 (**1.2**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Long COVID (n = 2,359)* *Persistent loss of smell at least 2 months after diagnosis, n (%)* Total (n=2,359): 1,031 (**43.7**)
Peter et al.[63] Germany	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 11,536)* *Prevalence of symptom clusters 6-12 months after acute infection (%) [95%CI]* Smell or taste disorder: **23.6** [22.9 to 24.4]
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 61,002)* *Symptoms 6-12 months after test, n (%)* Dysosmia: 6,674 (**10.9**) Dysgeusia: 5,365 (**8.8**) Runny nose: 2,376 (**3.9**) Sore throat: 2,285 (**3.7)** *Negative SARS-CoV-2 test (time-matched control group) (n = 91,878)*

Author or Organisation Country	Long COVID assessment Mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Symptoms 6-12 months after test, n (%) Dysosmia: 604 (**0.7**) Dysgeusia: 551 (**0.6**) Runny nose: 3,474 (**3.8**) Sore throat: 3,690 (**4.0**) *6 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 22,541)* Dysosmia: 702 (**9.4**); 70 (**0.5**) Dysgeusia: 587 (**7.8**); 59 (**0.4**) Runny nose: 267 (**3.6**); 527 (**3.5**) Sore throat: 276 (**3.7**); 519 (**3.5**) *9 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 106,611)* Dysosmia: 5,044 (**11.5**); 422 (**0.7**) Dysgeusia: 4,008 (**9.2**); 391 (**0.6**) Runny nose: 1,710 (**3.9**); 2,373 (**3.8**) Sore throat: 1,602 (**3.7**); 2,583 (**4.1**) *12 months after test (n %) (positive SARS-CoV-2 test; negative SARS-CoV-2 test) (n = 23,728)* Dysosmia: 928 (**9.5**); 112 (**0.8**) Dysgeusia: 770 (**7.9**); 101 (**0.7**) Runny nose: 399 (**4.1**); 574 (**4.1**) Sore throat: 404 (**4.1**); 588 (**4.2**)
Whitaker et al.[54] England	Self-report via questionnaire (2 assessment time points, different populations at each time point)	*History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Main analysis (n = 76,155)* Runny nose: 1,882 (**2.6**), [2.5 to 2.7] Blocked nose: 2,102 (**2.9**), [2.8 to 3.0] Loss or change to sense of smell: 3,510 (**4.8**), [4.7 to 5.0] Loss or change to sense of taste: 2,927 (**4.0**), [3.9 to 4.2] Sore throat: 2,212 (**3.0**), [2.9 to 3.2] Hoarse voice: 1,572 (**2.2**), [2.1 to 2.3] Dizziness: 2,224 (**3.1**), [2.9 to 3.2] *History of symptomatic COVID-19* *Prevalence at least 12 weeks after a positive SARS-CoV-2 test n (%), [95%CI]* *Replication study (3 – 8 months after main analysis) (n = 13,170)*

Author or Organisation Country	Long COVID assessment Mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Runny nose or blocked nose*: 154 (**1.6**), [1.4 to 1.9] Loss or change to sense of smell: 404 (**4.3**), [3.9 to 4.7] Loss or change to sense of taste: 364 (**3.9**), [3.5 to 4.3] Sore throat or hoarse voice**: 172 (**1.8**), [1.6 to 2.1] Dizziness: 244 (**2.6**), [2.3 to 2.9] Hearing issues: 196 (**2.1**), [1.8 to 2.4] *runny nose and blocked nose grouped in replication study **sore throat and hoarse voice grouped in replication study

Key: US, United States.

Musculoskeletal Symptom Cluster

Five studies reported symptoms related to the musculoskeletal cluster,[48, 53, 54, 56, 63] with prevalence estimates ranging from 5.7%[56] to 16.8%[63] in those with a history of COVID-19, while one study including those identified as having long COVID reported a prevalence of 1.9%[48] for muscle aches (see Appendix 6 General Population, Table 2). Myalgia[48, 53, 54, 63] and arthralgia[53, 54] were the most commonly reported symptoms across general population studies, with myalgia prevalence estimates ranging from 1.9%[48] to 7.2%[54] and arthralgia prevalence estimates ranging from 4.8[54] to 7.3%.[53] One study also reported that 16.8% of participants reported musculoskeletal pain.[63] One study also reported increased prevalence of musculoskeletal symptoms in a SARS-CoV-2 test-positive cohort,[56] compared with a time-matched SARS-CoV-2 test-negative cohort (RDs of 4.68 and 3.50), six to 12 months following SARS-CoV-2 testing. The ONS reported a prevalence estimate of 46% for myalgia in those with self-reported long COVID.[11]

Gastrointestinal Symptom Cluster

Five studies reported symptoms related to the gastrointestinal (GI) cluster,[48, 53, 54, 56, 63] with prevalence estimates ranging from 1.8%[53] to 5.6%[63] in those with a history of COVID-19 and from 0.6%[48] to 2.8%[48] in those identified as having long COVID (see Appendix 6 General Population, Table 2). Abdominal pain or symptoms, and nausea or vomiting were the most commonly reported GI symptoms across general population studies. Prevalence estimates for abdominal pain ranged from 1.6%[53] to 2.1%.[56] Nausea or vomiting prevalence estimates ranged from 0.4%[53] to 3.5%.[63] Loss or lack of appetite and diarrhoea were also reported in four studies with prevalence estimates ranging from 0.6%[48] to 2.9%[56] and 1.7%[54] to 1.9%[56] respectively. One study also reported increased GI symptom prevalence in a SARS-CoV-2 test-positive cohort,[56] compared with a time-matched SARS-CoV-2 test-negative cohort (RDs ranging from 0.34 to 1.15), six to 12 months following SARS-CoV-2 testing.

Dermatologic Symptom Cluster

Two studies reported symptoms related to the dermatologic cluster,[54, 63] with prevalence reported at 12 weeks or more[54] and at six to 12 months[63] post-acute COVID-19 (see Appendix 6 General Population, Table 2). Prevalence estimates ranged from 1.9%[54] to 10.1%[63] in those with a history of COVID-19. Both Whitaker et al.[54] and Peter et al.[63] reported hair loss as a symptom of long COVID, with hair loss prevalence estimates of 1.4% and 7.0%, respectively. Peter et al.[63] also reported a rash or paresthesia prevalence estimate of 10.1%, with Whitaker et al.[54] reporting prevalence estimates ranging from 0.1% to 1.9% for some related

symptoms (itchy areas on the skin, sudden swelling to face or lips and sores or blisters on feet).

Age (those aged under 18 years, those aged 65 years or older)

Following quality appraisal, 18 of the 21 primary research studies which reported data on specific age groups were retained for analysis. Fourteen of the 21 studies reported a definition of long COVID or post-COVID condition,[34, 36, 51, 55, 58, 64, 66, 67, 69, 77, 86] with time frames from four weeks[34] to one-year post-infection.[55, 58, 69] Three studies defined long COVID on ICD-10 codes.[55, 58, 69] Eleven studies reported prevalence estimates for those aged under 18 years and seven studies reported prevalence of long COVID or long COVID symptoms for those aged 60 or 65 years and older.

Those aged under 18 years

In paediatric populations with a history of COVID-19 (confirmed or suspected), across 11 studies prevalence estimates for long COVID ranged from 4%[34] to 65.7%[88] in studies based on self-report data and from 0.1%[55] to 57.9%[69] in studies considering those with a long COVID diagnosis (see Table 4.9). Four studies reported increased prevalence of long COVID in SARS-CoV-2 test-positive cohorts,[55, 64, 86, 88] compared with matched SARS-CoV-2 test-negative cohorts (or those who never had a positive SARS-CoV-2 test result). Of the two studies that collected and reported prevalence estimates using repeated assessments for paediatric populations, the prevalence of long COVID or long COVID symptoms decreased over time. Buonsenso et al.[34] reported a reduction in the proportion of children classified as having poor recovery following acute COVID-19 (score of 1 to 4 on full recovery scale) over time, from 4% at one to five months post-COVID-19, to 1.3% at six to nine months and 0.7% at 12 months or greater following COVID-19. Similarly, Pazukhina et al.[66] reported prevalence estimates of long COVID or symptoms of long COVID of 20% and 11.1% at six months and 12 months following COVID-19, respectively.

Table 4.9. Long COVID prevalence estimates in those aged under 18 years

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
Buonsenso et al.[34] Italy	Self-report via interview (3 assessment time points, same population)	*Children ≤ 18 years* *Recovery rate over time (full recovery scale – 1: not recovered, 10: fully recovered)* *All observations, n (%) (n = 679)* 1-4: 17 (**2.6**) 5-7: 73 (**11**) 8-10: 576 (**86**) *1–5 months, n (%) (n = 355)* 1-4: 14 (**4**) 5-7: 46 (**13**) 8-10: 288 (**83**) *6–9 months, n (%) (n = 157)* 1-4: 2 (**1.3**) 5-7: 7 (**4.6**) 8-10: 144 (**94**) *≥12 months, n (%) (n = 154)* 1-4: 1 (**0.7**) 5-7: 15 (**9.9**) 8-10: 136 (**89**)
Dumont et al.[50] Switzerland	Self-report via questionnaire (completed by parents) (Single assessment time point)	*Persistent symptoms, n (%):* Symptoms lasting over 4 weeks: 102 (**18**) Symptoms lasting 4–6 weeks: 30 (**5**) Symptoms lasting 6–8 weeks: 14 (**2**) Symptoms lasting 8–12 weeks: 4 (**1**) Symptoms lasting over 12 weeks: 54 (**9**) *Prevalence of symptoms lasting >12 weeks by age, n (95% CI):* Age 0–5: 8.0 (1.8 to 14.2) Age 6–11: 5.3 (2.6 to 8.1) Age 12–17: 13.6 (9.3 to 18.1) All ages: 9.1 (6.7 to 11.8)
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay,	Self-report via caregivers	*Children < 18 years* *Persistent, new or recurring health problem 90 days Following the Index ED Visit for SARS-CoV-2 test positive patients, n (%), [95%CI]*

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
Singapore, Spain, and the United States	(Single assessment time point)	All children (n=1,884): 110 (**5.8**), [4.8 to 7.0] Not hospitalised (n=1,437): 66 (**4.6**) [3.6 to 5.8] Hospitalised (n=447): 44 (**9.8**) [7.2 to 13.0]
Kikkenborg Berg et al.[64] Denmark	Self-report via questionnaire (Single assessment time point)	*Children ≤ 14 years* *Those with long COVID (at least 1 new onset symptom not known before the positive SARS-CoV-2 test and present 8 weeks after the positive test)* 0-3 years (n=1,368): 427 (**31.2**) 4-11 years (n=5,684): 1,505 (**26.5**) 12-14 years (n=3,316): 1,077 (**32.5**) *Those reporting at least 1 symptom lasting at least 2 months in the SARS-CoV-2 positive cohort (n %)* 0-3 years (n=1,194): 478 (**40.0**) 4-11 years (n=5,023): 1,912 (**38.1**) 12-14 years (n=2,857): 1,313 (**46.0**) *Those reporting at least 1 symptom lasting at least 2 months in those who never had a positive SARS-CoV-2 test (n %)* 0-3 years (n=3,855): 1,049 (**27.2**) 4-11 years (n=18,372): 6,189 (**33.7**) 12-14 years (n=10,789): 14,454(**41.3**)
Kikkenborg Berg et al.[88] Denmark	Self-report via questionnaire (Single assessment time point)	*Children 15 – 18 years* *Those with at least 1 new onset symptom not known before the positive SARS-CoV-2 test and present 4 weeks after the positive test* 15-18 years (n=6,630): 4,353 **(65.7)** *Those with long COVID (at least 1 new onset symptom not known before the positive SARS-CoV-2 test and present 8 weeks after the positive test)* 15 – 18 years: 2,997 (**47.8%)** *Those reporting at least 1 symptom lasting more than 2 months (irrespective of whether symptoms were present before the SARS-CoV-2 positive test) in the SARS-CoV-2 test positive cohort (n %)* 15 -18 years: 3,159 (**61.9**) *Those reporting at least 1 symptom lasting more than 2 months in those who never had a positive SARS-CoV-2 test (n %) (age and sex matched)* 15 -18 years: 12,340 (**57.0**)

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
Kildegaard et al.[55] Denmark	Diagnosis (ICD-10: B948A and Z038Q) (Single assessment time point)	*At 1-6 months follow-up the prevalence of long COVID in children and adolescents (<18 years)* SARS-CoV-2 positive cohort, n, Risk (%): 58 (**0.12**, 0.09 to 0.15) Reference cohort (time-matched) who had not previously tested positive for SARS-CoV-2, n, Risk (%): 32 (**0.01** (0.00 to 0.01)
Kostev et al.[69] Germany	Diagnosis (ICD-10: U09.9) (Single assessment time point)	*Children < 18 years* *Patients with post-COVID-19 condition (defined using the ICD-10 code U09.9) (stratified by age and sex)* Total: 114 (**1.7**) *Age, n (%)* ≤5 years: 14 (**12.3**) 6–9 years: 12 (**10.5**) 10–12 years: 22 (**19.3**) 13–17 years: 66 (**57.9**)
Miller et al.[51] England and Wales	Self-report via survey (Single assessment time point in participants who answered the survey question on persistent symptoms and three assessment time points in participants whose household had participated in three weekly surveys over five weeks).	*Children ≤ 17 years* *Persistent symptoms for ≥4 weeks, n (%), [95%CI]* Overall: 129 (**2.6**), [2.1 to 3.0] Children with a history of SARS-CoV-2 infection: 43 (**4.1**), [2.9 to 5.4]
Nugawela et al.[86] England	Self-report via questionnaire (Single assessment time point)	*Children 11 – 17 years (Data is matched for test, age, sex and geographical area)* *Long COVID 3 months after a PCR test, (%)* Total population (n=7,139): 1,536 (**21.5**) SARS-CoV-2 negative (n=3,893): 719 (**18.5**) SARS-CoV-2 positive (n=3,246): 817 (**25.2**) *Number of symptoms = 0* Total population (n=7,139): 2,968 (**41.6**) SARS-CoV-2 negative (n=3,893): 1,848 (**47.5**) SARS-CoV-2 positive (n=3,246): 1,120 (**34.5**) *Number of symptoms = 1-4*

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
		Total population (n=7,139): 3,496 (**49.0**) SARS-CoV-2 negative (n=3,893): 1,798 (**46.2**) SARS-CoV-2 positive (n=3,246): 1,698 (**52.3**) *Number of symptoms = 5+* Total population (n=7,139): 675 (**9.5**) SARS-CoV-2 negative (n=3,893): 247 (**6.3**) SARS-CoV-2 positive (n=3,246): 428 (**13.2**)
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population).	*Children ≤ 18 years* *Post-COVID-19 symptoms which started no later than 3 months after hospital discharge and lasted for at least 2 months* *6-month follow-up, n (%), [95%CI]* Children (n=360): 72 (**20**), [15.8 to 24.2] *12-month follow-up, n (%), [95%CI]* Children (n=360): 40 (**11.1**), [8.1 to 14.4]
Trapani et al.[36] Italy	Self-report via questionnaire (completed by parents, filled in by paediatrician) (Single assessment time point)	*Children ≤ 16 years* *Long COVID-19 defined as symptoms reported 8–36 weeks after recovery from acute COVID-19* *Primary care (n=629)* At least one symptom, n (%), [95%CI]: 153 (**24.3**), [21.0 to 27.9] Cumulative incidence of long COVID after 2-3 months, % [95%CI]: **20.5** [14.3 to 27.4] Cumulative incidence of long COVID after 4-5 months, % [95%CI]: **26.9** [21.1 to 33.3] p=0.338 (2-3 months vs 4-5 months) *At least 1 symptom, n (%):* 0-5 years (n=202): 37 (**18.3**) 6-10 years (n=235): 50 (**21.3**) 11-16 years (n=192): 66 (**34.3**) p=0.001 (comparing the three age groups) Incidence of long COVID in children in primary care, n (%) Children with pre-existing diseases (n=59): 19 (**32.2**) Children without pre-existing diseases (n=570): 134 (**23.5**) p=0.152 Cumulative incidence of abnormal fatigue in children in primary care, n (%) Children with pre-existing diseases (n=59): 8 (**13.6**)

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
		Children without pre-existing diseases (n=570): 36 (**6.3**) Symptomatic acute COVID-19, n (%) At least 1 symptom (n=230): 107 (**46.5**) Non-symptomatic acute COVID-19, n (%) At least 1 symptom (n=399): 46 (**11.5**) p<0.001

Key: US, United States.

General Symptom Cluster

Seven studies reported symptoms related to the general symptom cluster, in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77, 88] Studies reported either an overall prevalence of general symptoms or of 'other' symptoms or they reported the prevalence of specific symptoms within this cluster, with differences in prevalence noted between studies.

General symptoms included fatigue, fever, cold hands and or feet, discoloured fingers and or toes, 'general symptoms' and 'other symptoms'. Prevalence estimates for 'general' symptoms was reported as 31.2%[51] by one study. Prevalence estimates for fatigue ranged from 1.1%[77] to 22%.[34] Two studies reported prevalence of 'other' symptoms as 0.6%[66] and 8.3%,[51] respectively. Funk et al.[77] reported prevalence estimates of 1.1% for fatigue and 0.5% for fever.

Across studies, differences were reported in prevalence over time, when stratified by age, and by whether or not participants had a prior diagnosis of COVID-19. Of the two studies that collected and reported prevalence estimates for fatigue using repeated assessments for paediatric populations, mixed trends were observed. Buonsenso et al.[34] reported prevalence estimates of 22% at one to five months, 15% from six to nine months and 16% at 12 months or greater following COVID-19. Pazukhina et al.[66] reported decreasing prevalence estimates of long COVID or symptoms of long COVID of 9.4% at six months and 3.6% at 12 months following COVID-19.

Trapani et al.[36] found that while 7% and 0.6% of children reported fatigue and 'other' symptoms, respectively, the prevalence of fatigue significantly differed depending on whether the child had a history of symptomatic or asymptomatic acute COVID-19 (16.5% compared to 5%, respectively). Two studies compared the prevalence of general symptoms (lasting at least two months and lasting at least six months) in a SARS-CoV-2 test positive cohort (cases) to prevalence in an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Mixed trends for prevalence estimates were observed, depending on the age group and symptom. Kikkenborg Berg et al.[64] found that in children aged under three years, the prevalence of fever, lasting at least two and at least six months, was significantly higher in cases compared to controls, with a similar difference found for the prevalence of fatigue in this age group. The prevalence of fever for these time intervals was not significantly different between cases and controls in those aged between four and 11 years,[64] between 12 and 14 years,[64] and between 15 and 18 years.[88] The prevalence of fatigue lasting at least 6 months was significantly higher in cases aged between 12 and 14 years[64] and in those aged between 15 and 18 years,[88] compared to controls.

Neurological Symptom Cluster

Seven studies reported symptoms related to the neurological cluster, in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77, 88] The prevalence of neurological symptoms ranged from 0.9%[77] to 18.0%[34] in those with a history of COVID-19, while in another study 18.4% of those identified as having long COVID reported neurological symptoms.[51] Headache was the most commonly reported symptom among paediatric populations, with prevalence estimates ranging from 0.2%[77] to 18%.[34] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and in the case of headache, whether they had a history of symptomatic or asymptomatic acute COVID-19.

Of the two studies that collected and reported prevalence estimates for neurological symptoms at multiple time points for paediatric populations, mixed trends were observed. Buonsenso et al.[34] reported prevalence estimates of neurological symptoms ranging from 0.3% to 14% at one to five months, 0.6% to 8.9% at six to nine months and 0.6% to 11% at 12 months or more following COVID-19. Pazukhina et al.[66] reported prevalence estimates of 4.2% for both neurological and sleep problems at six months, and estimates of 1.7% and 0.6% for neurological and sleep problems, respectively at 12 months following COVID-19. Trapani et al.[88] found that while 6.8% of children reported neurological symptoms, the prevalence was significantly higher in children who had a history of symptomatic compared with asymptomatic acute COVID-19 (14.4% versus 2.5%).

Two studies compared neurological symptoms (lasting at least two months and lasting at least six months) in a SARS-CoV-2 test positive cohort (cases) to an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Mixed trends were observed, depending on the age group and symptom. Kikkenborg Berg et al.[64, 88] found the prevalence of headaches in children aged between four and 18 years was significantly higher in cases compared to controls for both time intervals (lasting at least two months and lasting at least six months). Considering concentration issues and trouble remembering, the prevalence of this symptom (lasting at least six months) was significantly higher in cases that in controls for those aged between 12 and 14 years, but no difference in prevalence was noted for those aged between four and 11 years, and between 15 and 18 years for either time interval. Compared with controls, the prevalence of dizziness was significantly higher in cases for those aged between 12 and 14 years[64] and for those aged 15 and 18 years[88] at both time intervals. The prevalence of light sensitivity was not significantly different between cases and controls for those aged between four and 11 years[64] and those aged between 12 and 14 years,[64] but a

significantly lower prevalence was seen in cases for those aged between 15 and 18 years.[88]

Cardiovascular Symptom Cluster

Seven studies reported symptoms related to the cardiovascular cluster, in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77, 88] The prevalence of cardiovascular symptoms ranged from 1.1%[77] to 6.4%,[34] in those with a history of COVID-19, while in another study 10.1% of those identified as having long COVID reported cardiovascular symptoms.[51] Chest pain was the most commonly reported cardiovascular symptom among paediatric populations, with prevalence estimates ranging from 0.2%[77] to 6.4%.[34] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

There were inconsistent findings in the two studies that collected and reported prevalence estimates using repeated assessments, with no obvious trend in one study[34] and decreasing prevalence over time in the other study.[66] Specifically, Buonsenso et al.[34] reported prevalence estimates of cardiovascular symptoms of 3.4% at one to five months, 6.4% at six to nine months, and 0% at 12 months or more following COVID-19, while Pazukhina et al.[66] reported prevalence estimates of 1.1% at six months and 0.3% at 12 months following COVID-19. Trapani et al.[36] found that 0.8% of children who attended primary care reported cardiovascular symptoms, with no significant difference between children with a history of symptomatic or asymptomatic acute COVID-19 (1.7% versus 0.3%). Two studies compared the prevalence of cardiovascular symptoms (lasting at least two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) to the prevalence in an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Mixed trends for prevalence estimates were observed, depending on the age group and symptom. Kikkenborg Berg et al.[88] found that the prevalence of chest pain in adolescents aged between 12 and 14 years, and in adolescents aged between 15 and 18 years was significantly higher in cases compared with controls. However, no difference in prevalence between cases and controls was observed in those aged between four and 11 years.[64] The prevalence of palpitations did not differ between cases and controls for those aged between four and 11 years, and between 15 and 18 years; however, a significantly higher prevalence of palpitations was found in cases, for adolescents aged between 12 and 14 years, when considering symptoms that lasted at least six months.[88]

Respiratory Symptom Cluster

Seven studies reported symptoms related to the respiratory cluster, in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77, 88] The prevalence of respiratory symptoms ranged from 0.7%[77] to 11.4%[36] in those with a history of COVID-19, while 22% of those identified as having long COVID reported respiratory symptoms.[51] Cough was the most commonly reported respiratory symptom among paediatric populations with prevalence estimates ranging from 0.6%[77] to 6.4%.[64] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Two studies collected and reported prevalence estimates for respiratory symptoms using repeated assessments in paediatric populations. Buonsenso et al.[34] reported prevalence estimates of respiratory symptoms at one to five months, six to nine months and 12 months or more following COVID-19. Prevalence declined over time for some symptoms in this cluster, although it was not consistent for all symptoms (for example, difficulty breathing chest tightness: 3.9% versus 1.9% versus 0%, persistent cough: 5.6% versus 3.2% versus 3.2%). Similarly, Pazukhina et al.[66] noted a decline in prevalence over time (1.9% versus 1.1% at six months and 12 months post COVID-19, respectively). Trapani et al.[66] found that while 6% of children reported respiratory symptoms, the prevalence was significantly higher for children who had a history of symptomatic compared with asymptomatic acute COVID-19 (8.7% versus 4.5%). Two studies compared prevalence of respiratory symptoms (lasting at least two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) with prevalence in an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Mixed trends for prevalence estimates were observed, depending on the age group and symptom. Kikkenborg Berg et al.[64] found that the prevalence of coughing and trouble breathing was significantly higher in cases compared to controls for children aged three years and under. For those aged between four and 11 years, a significantly higher prevalence of coughing and trouble breathing was observed among cases when considering symptoms lasting at least two months, although no difference was observed at six months. The prevalence of coughing and trouble breathing was significantly higher in cases for adolescents aged between 12 and 14 years and those aged between 15 and 18 years.[88]

Psychological and or Psychiatric Symptom Cluster

Five studies reported reported symptoms related to the psychological or psychiatric cluster, in paediatric populations.[36, 51, 64, 77, 88] Prevalence estimates ranged from 0.9%[77] to 10.9%[88] in those with a history of COVID-19, while in another study 10.1% of those identified as having long COVID reported psychological symptoms

(see Appendix 7 Age, Table 2).[51] Mood swings was the most commonly reported psychological and or psychiatric symptom among paediatric populations, with prevalence estimates ranging from 8.1%[64] to 10.1%.[88] Prevalence estimates were noted to vary depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Trapani et al.[36] found that while 4.9% of children reported psychological and or psychiatric symptoms, the prevalence significantly differed depending on whether the child had a history of symptomatic or asymptomatic acute COVID-19 (8.7% versus 2.8%). Two studies compared the prevalence of mood swings (lasting two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) to an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Considering symptoms that lasted at least two months, a significantly higher prevalence of mood swings was reported for controls aged between four and 11 years,[64] 11 and 14 years[88] and 15 and 18 years,[88] compared to their comparative case age-groups. Considering symptoms that lasted at least six months, no significant difference in the prevalence of mood swings was observed between cases and controls for any age group.

Dermatologic Symptom Cluster

Seven studies reported symptoms related to the dermatologic cluster, in paediatric populations.[34, 36, 51, 64, 66, 77, 88] Prevalence estimates ranged from 0.6%[77] to 8.8%[88] in those with a history of COVID-19, and 12.8% of those identified as having long COVID reported dermatologic symptoms[51] (see Appendix 7 Age, Table 2). Dark circles under eyes and skin rash were the most commonly reported symptom among paediatric populations, with prevalence estimates ranging from 2.2%[64] to 8.8%[88] and 0.6%[77] to 7.7%[34] respectively. Prevalence estimates were noted to vary depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Trapani et al.[36] found that while 1.9% of children reported dermatological symptoms, the prevalence differed significantly depending on whether the child had a history of symptomatic or asymptomatic acute COVID-19 (3.9% versus 0.8%). Prevalence estimates varied over time for skin rash with one study reporting estimates of 4.5% at one to five months post-acute COVID-19, 7.7% six to nine months post-acute COVID-19 and 2.6% 12 months or more post-acute COVID-19.[34] A similar trend was observed for bilateral conjunctivitis with prevalence estimates of 0%, 0.7% and 0% for the same time intervals.[34] Two studies compared neurological symptoms (lasting at least two months and at least six months) in a

SARS-CoV-2 test positive cohort (cases) compared with an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Mixed trends for prevalence estimates were observed, depending on the age group and symptom. Symptoms identified included rash, dark circles under eyes, extreme paleness and chapped lips. No obvious trend was observed with mixed findings as to whether the prevalence of individual symptoms among cases were higher, lower, or the same as those seen in the control group depending on the symptom duration and age group considered.

Musculoskeletal Symptom Cluster

Seven studies reported symptoms related to the musculoskeletal cluster, in paediatric populations.[34, 36, 51, 64, 66, 77, 88] The prevalence of musculoskeletal symptoms ranged from 0.2%[77] to 10.0%[34] in those with a history of COVID-19, and 11.9% of those identified as having long COVID reported musculoskeletal symptoms (see Appendix 7 Age, Table 2).[51] Myalgia was the most commonly reported symptom among paediatric populations, with prevalence estimates ranging from 0.2%[77] to 10.0%.[34] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Of the two studies that collected and reported prevalence estimates for musculoskeletal symptoms using repeated assessments, there were inconsistent findings. Buonsenso et al.[34] reported prevalence estimates of musculoskeletal symptoms at one to five months, six to nine months and 12 months or more following COVID-19. Over the same time intervals, no obvious trends were observed over time for persistent muscle pain (10% versus 3.2% versus 3.2%) and joint pain or swelling (5.6% versus 2.5% versus 2.6%). Pazukhina et al.[66] reported a decrease in the prevalence of musculoskeletal symptoms from 1.7% at six months to 0.8% at 12 months following COVID-19. Trapani et al.[36] found that while 4.9% of children reported muscle and or joint pain, the prevalence was significantly higher in those with a history of symptomatic compared with asymptomatic acute COVID-19 (9.6% versus 2.3%). Two studies compared musculoskeletal symptoms (lasting at least two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) to an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] In those aged between 12 and 14 years the prevalence of pain in muscles or joints lasting at least six months was significantly higher in cases compared to controls.[64] Similar prevalence estimates were reported in cases and controls in the remaining age groups (under three years, between four and 11 years, and between 15 and 18 years) for both time intervals.

Ear, Nose and Throat Symptom Cluster

Seven studies reported symptoms related to the ear, nose and throat (ENT) cluster in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77] Prevalence estimates of symptoms in the ENT cluster ranged from 0.5%[77] to 8.7%[36] in those with a history of COVID-19, and 21.1% of those identified as having long COVID reported ENT symptoms.[51] Smell and or taste disorders such as anosmia and ageusia were the most commonly reported symptoms, with prevalence estimates ranging from 0.5%[77] to 8.7%.[36] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Of the two studies that collected and reported prevalence estimates for ENT-related symptoms using repeated assessments, no clear trend was evident. Buonsenso et al.[34] reported prevalence estimates of ENT symptoms at one to five months, six to nine months and 12 months or more following COVID-19. A decline in the prevalence of altered taste was observed over time (3.1% versus 2.5% versus 1.3%), with all remaining symptoms displaying mixed trends (for example, loss of smell: 1.4% versus 1.3% versus 1.9%). Pazukhina et al.[66] reported prevalence estimates of sensory symptoms of 0.8% at six months and 0.3% at 12 months following COVID-19.

Trapani et al.[36] found that while 3.3% of children reported ENT-related symptoms, the prevalence was significantly higher in those with a history of symptomatic compared with asymptomatic acute COVID-19 (8.7% versus 0.3%). Two studies compared the prevalence of sore throat (lasting at least two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) to an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Prevalence of sore throat was significantly higher in cases compared to controls for all age groups four years and older, for both time intervals.[64, 88]

Gastrointestinal Symptom Cluster

Seven studies reported symptoms related to the gastrointestinal cluster, in paediatric populations (see Appendix 7 Age, Table 2).[34, 36, 51, 64, 66, 77, 88] The prevalence of gastrointestinal symptoms ranged between 1.8%[77] to 8.9%[34] in those with a history of COVID-19, and 13.8% of those identified as having long COVID reported gastrointestinal symptoms.[51] The most common symptom reported among paediatric populations was stomach ache, with prevalence estimates ranging from 2.3%[88] to 8.2%.[34] Prevalence estimates were noted to vary over time and also varied depending on whether or not the child and or adolescent had a documented

previous SARS-CoV-2 infection, and whether they had a history of symptomatic or asymptomatic acute COVID-19.

Of the studies that collected and reported prevalence estimates for gastrointestinal symptoms using repeated assessments, the prevalence of some symptoms was noted to decrease over time. However, for other symptoms no obvious trends were observed. Buonsenso et al.[34] reported prevalence estimates of gastrointestinal symptoms at one to five months, six to nine months and 12 months or more following COVID-19. A decline in the prevalence of weight loss and nausea was observed over time (weight loss: 4.2% versus 3.5% versus 2.6%; nausea: 3.9% versus 1.9% versus 0.6%), with all remaining symptoms displaying mixed trends (for example poor appetite: 6.2% versus 8.9% versus 4.5%). Pazukhina et al.[66] reported prevalence estimates of gastrointestinal symptoms of 3.9% at six months and 0.6% at 12 months following COVID-19.

Trapani et al.[77] found that while 3% of children reported gastrointestinal issues, prevalence was significantly higher in those with a history of symptomatic compared with asymptomatic acute COVID-19 (5.2% versus 1.8%). Two studies compared gastrointestinal symptoms (lasting at least two months and at least six months) in a SARS-CoV-2 test positive cohort (cases) to an age and sex matched cohort who had never tested positive for SARS-CoV-2 (controls).[64, 88] Symptoms considered included nausea, loss of appetite, and stomach ache. No significant difference in the prevalence of nausea was observed between cases and controls, across all age groups. When considering loss of appetite, prevalence estimates were significantly higher in COVID-19 cases compared to controls, for those aged three years and under, and those aged between 15 and 18 years for both time intervals, with no difference observed for other age groups. There were mixed findings as to whether the prevalence of stomach ache among cases was higher, lower, or the same as that seen in the control group depending on the symptom duration and age group considered.

Those aged 65 years and older

Five of seven studies reported long COVID prevalence data for adults aged 60 or 65 years and older with a previous (or suspected) COVID-19 diagnosis (see Table 4.10).[54, 57, 58, 65, 67] Prevalence estimates ranged from 18.3%[57] to 80.8%[54] in studies based on self-report data. Additionally, 8.6% and 5.6% of those aged 60 to 70 years and those aged over 70 years, respectively were diagnosed with long COVID for the time interval 91 to 365 days post-acute COVID-19.[58]

Table 4.10. Long COVID prevalence estimates in those aged 65 years and older

Author or Organisation Country	Long COVID assessment mode	Long COVID prevalence estimates
Daitch et al.[67] Israel, Switzerland, Spain, and Italy	Self-report via interview (Single assessment time point)	*For each symptom, individuals who reported symptoms of moderate to severe intensity were counted as positive, n (%) (5 months post-acute COVID-19)* *Any symptom, n (%)* >65 years (n=410): 328 (**80.0**) *≥3 symptoms (high burden of long COVID), n (%)* > 65 years (n=255): 87 (**34.1**)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*Adults > 60 years* *Any long COVID post-sequelae 1 year post hospital discharge, n (%)* Total patients: 630 (**51.1**) Severe: 252 (**57.5**) Non-severe: 378 (**47.5**)
Kostev et al.[58] Germany	Diagnosis (ICD-10: U09.9) (Single assessment time point)	*Prevalence 91 to 365 days after first COVID-19 diagnosis, n (%)* 61–70 years: 4,440 (**8.6**) >70 years: 2,891 (**5.6**)
Perlis et al.[57] US	Self-report via survey (Single assessment time point)	*Point prevalence of long COVID in those who tested positive for SARS-CoV-2 (Estimate % 95% CI)* 60 – 69 years: **18.3** (16.1 to 20.7) 70 + years: **14.3** (11.6 to 17.4)
Whitaker et al.[54] England	Self-report via questionnaire (Single assessment time point)	65 – 74 years 3,615 out of 7,811 (**80.8%**) reported one or more symptoms at least 12 weeks after symptomatic COVID-19 (in main analysis) 74+ years 1,229 out of 2,326 (**52.8%**) reported one or more symptoms at 12 weeks after symptomatic COVID-19 (not required to have tested positive for SARS-CoV-2) (in main analysis)

General Symptom Cluster

Four studies reported symptoms related to the general cluster, in adults aged 60 or 65 years and older (see Appendix 7 Age, Table 2).[56, 65, 67, 70] Prevalence estimates ranged from 10.4%[56] to 38.7%[67] in those with a history of COVID-19. Fatigue was the most commonly reported symptom, with prevalence estimates ranging from 4.9%[56] in males aged 70 years or older to 38.7%[67] in those aged 65 years or older.

One study reported general symptoms stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] Generally, higher prevalence of symptoms in this cluster were observed in females, compared to males for those aged 60 to 69 years, and 70 years or older. Additionally, a higher prevalence of symptoms in this cluster were reported in cases compared with controls.

Neurological Symptom Cluster

Four studies reported symptoms related to the neurological cluster, in adults aged 60 or 65 years and older (see Appendix 7 Age, Table 2).[56, 65, 67, 70] Prevalence estimates ranged from 1.4%[65] to 23.2% in those with a history of COVID-19.[67] Memory and or concentration impairment were the most commonly reported symptoms, with prevalence estimates ranging from 1.4%[70] to 23.2%.[67] One study reported neurological symptoms stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] Generally, higher prevalence of symptoms in this cluster were observed in females, compared to males for those aged 60 to 69 years, and 70 years or older. Additionally a higher prevalence of symptoms in this cluster were reported in cases compared to controls.

Cardiovascular Symptom Cluster

Four studies reported symptoms related to the cardiovascular cluster, in adults aged 60 or 65 years and older (see Appendix 7 Age, Table 2).[56, 65, 67, 70] Prevalence estimates for cardiovascular symptoms ranged from 2.1%[56] to 21.5%[65] in those with a history of COVID-19. Chest pain or chest tightness was the most commonly reported symptom, with prevalence estimates ranging from 2.1%[56] to 21.5%.[65] One study reported chest pain stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] A higher prevalence of chest pain was reported in both males and female aged 60 to 69 years in cases, compared to controls (female: 2.1% versus 0.6%; male: 1.9% versus 0.6%).

Respiratory Symptom Cluster

Four studies reported symptoms related to the respiratory cluster, in adults aged 60 or 65 years and older (see Appendix 7 Age, Table 2).[56, 65, 67, 70] Prevalence estimates for respiratory symptoms ranged from 6.0%[56] to 29.9%[67] in those with a history of COVID-19. Shortness of breath and cough were the most commonly reported symptoms, with prevalence estimates ranging from 5.0%[65] to 29.9%[67] and 4.0%[56] to 14.2%.[67] One study reported dyspnoea and cough stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] Generally, higher prevalence of both dyspnoea and cough were observed in females, compared to males for those aged 60 to 69 years, and 70 years or older. Additionally, a higher prevalence of respiratory symptoms was observed in cases compared to controls.

Psychological and or Psychiatric Symptom Cluster

Two studies reported symptoms related to the psychological and or psychiatric symptom cluster, in adults aged 60 or 65 years and older.[65, 67] In those with a history of COVID-19, the prevalence of symptoms in this cluster ranged from 12.8%[67] to 16.9% (see Appendix 7 Age, Table 2).[65] One study reported a prevalence estimate of 16.9% for emotional distress,[67] and 10.7% to 12.8% of participants reported anxiety in the other study.[65]

Dermatologic Symptom Cluster

One study[67] reported symptoms related to the dermatologic cluster, in adults over 65 years, with 4.8% of survey participants with a history of COVID-19 experiencing hair loss (see Appendix 7 Age, Table 2).[67]

Musculoskeletal Symptom Cluster

Three studies reported symptoms related to the musculoskeletal cluster, in adults aged 60 or 65 years and older.[56, 65, 67] Prevalence estimates of musculoskeletal symptoms ranged from 6.2%[56] to 22.4%[64] in those with a history of COVID-19 (see Appendix 7 Age, Table 2). Myalgia was the most commonly reported symptom, with prevalence estimates ranging from 4.8%[56] to 22.4%.[67] One study reported muscle and or joint pain, and reduced strength in arms or legs stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] Generally, higher prevalence estimates in this cluster were observed in females, compared to males for those aged 60 to 69 years old. Additionally, a higher prevalence of musculoskeletal symptoms was reported in cases, compared to controls.

Ear, Nose and Throat Symptom Cluster

Three studies reported symptoms related to the ear, nose and throat (ENT) cluster, in adults 60 or 65 years and older.[56, 65, 67] Prevalence estimates for ENT symptoms ranged from 2.7%[65] to 13.2%[67] in those with a history of COVID-19 (see Appendix 7 Age, Table 2).[67] A smell or taste disorder such as anosmia and or ageusia were the most commonly reported symptoms, with prevalence estimates ranging from 2.7%[65] to 13.2%.[67] One study reported ENT symptoms stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[67] Generally, higher prevalence estimates of symptoms in this cluster were observed in females compared to males for those aged 60 to 69 years old, and 70 years or older. Additionally, a higher prevalence of ENT symptoms was reported in cases, compared to controls.

Gastrointestinal Symptom Cluster

Three studies reported symptoms related to the gastrointestinal cluster, in older adults aged 60 or 65 years and older.[56, 65, 70] Prevalence estimates of gastrointestinal symptoms ranged from 1.4%[65] to 5.7%[70] in those with a history of COVID-19 (see Appendix 7 Age, Table 2). Diarrhoea was the most commonly reported symptom with prevalence estimates ranging from 0.8%[65] to 5.7%.[70] One study reported gastrointestinal symptoms stratified by sex and age, in time matched SARS-CoV-2 test positive (cases) and test negative (controls) cohorts.[56] Generally, higher prevalence estimates of symptoms in this cluster were observed in females, compared to males for those aged 60 to 69 years old, and those 70 years or older. Additionally, higher prevalence estimates of symptoms in this clusters were observed in cases compared to controls.

Autonomic Nervous System Symptom Cluster

Two studies reported symptoms related to the autonomic nervous system cluster in adults aged 60 or 65 years and older.[56, 65] Sweating and or hot flushes was reported in both studies, with prevalence estimates ranging from 3.0%[56] to 24.0%[65] (see Appendix 7 Age, Table 2). Fang et al.[65] found that at one year post-acute COVID-19, up to 24% of adults aged 65 years or older reported sweating as a symptom. Sorensen et al.[56] reported a higher prevalence of hot flushes and or sweating in females compared to males for those aged 60 to 69 years old, and those 70 years or older. Additionally, Sorensen et al.[56] reported a higher prevalence of autonomic nervous system symptoms in a SARS-CoV-2 test positive cohort compared to test negative controls.

Medically vulnerable (those aged under 65 years who are medically vulnerable (as outlined by the HSE))

Following quality appraisal, two of the three studies which recruited populations identified as medically vulnerable were retained for analysis (see Appendix 8 Medically vulnerable, Table 1).[46, 71] Belkacemi et al.[71] recruited patients on dialysis with previous COVID-19 diagnosis, while Garjani et al.[46] recruited those with MS and previous confirmed or suspected COVID-19. Results from these studies are reported separately.

Patients on dialysis

Belkacemi et al.[71] did not include a definition of long COVID or post-COVID condition, but identified that 17.7% of patients on dialysis self-reported having some long-lasting clinical symptoms, at six months post-acute COVID-19. The four symptoms with the highest prevalence estimates were reported in four different symptom clusters (gastrointestinal; general; cardiovascular or respiratory; and psychological and or psychiatric symptoms).

Gastrointestinal, General, Cardiovascular, Respiratory and Psychological and or Psychiatric Symptom Clusters

Belkacemi et al.[71] reported that of patients on dialysis identified as having long COVID (long lasting symptoms), 52.8% reported muscle or weight loss greater than 5%; 31.5% reported extreme fatigue; 14.8% reported respiratory symptoms or chest pain and 13.0% reported PTSD, depression and or anxiety.

Remaining clusters

Further symptoms identified in patients on dialysis identified as having long COVID were joint or muscle pain (9.3%), headache (8.8%), diarrhoea (6.0%), tachycardia (2.8%) and anosmia or ageusia (2.3%).[71]

Those with multiple sclerosis (MS)

Garjani et al.[46] did not include a definition of long COVID or post-COVID condition, but identified that 29.7% of people with MS self-reported long-standing COVID-19 symptoms for four weeks or more, while 12.4% self-reported long-standing COVID-19 symptoms for 12 weeks or more. The four symptoms with the highest prevalence estimates were reported in three different symptom clusters (general; respiratory; gastrointestinal and musculoskeletal symptom clusters).

General, Respiratory, Musculoskeletal and Gastrointestinal Symptom Clusters

Garjani et al.[46] observed that 63.2% to 68.3% of people with MS identified as having long COVID (long lasting symptoms) reported new or worse fatigue at four and 12 weeks or more post-acute COVID-19. This was followed by 48% to 58.3% reporting lower respiratory tract symptoms (such as cough and shortness of breath);

35.8% to 45% reporting new muscle pain and 34.7% to 41.7% reporting gastrointestinal symptoms (such as nausea or vomiting) (see Appendix 8 Medically vulnerable, Table 2).

Remaining clusters

Further symptoms identified in those with MS identified as having long COVID were change in smell or taste (28.3% to 29.5%); upper respiratory tract symptoms (such as sore throat, nasal congestion, or sneezing) (22.1% to 25.0%); headache (21.1% to 21.7%) and fever (3.2% to 5%).

Those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19)

Following quality appraisal, 33 of the 42 studies focused on those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19) were retained for analysis. Twelve of the 33 studies included a definition of long COVID or post-COVID condition,[23, 40, 48, 52, 55, 66, 73-75, 77, 85, 117, 118] with the time frame varying from four weeks[40, 48, 117] to two years post-acute COVID-19.[23] Of the 22 studies that reported prevalence data for those hospitalised with COVID-19,[22, 23, 30-32, 37, 38, 40, 41, 45, 47, 48, 52, 55, 65, 66, 74, 85, 117, 118] two studies included data for those admitted to intensive care.[37, 74]

Those aged under 18 years

Two studies reported long COVID prevalence estimates based on self-report data in children with a history of severe COVID-19 illness.[66, 77] Overall prevalence estimates for these studies are reported first followed by estimates for the different symptom clusters below.

Funk et al.[77] found that 9.8% of children had symptoms of long COVID at 90 days follow-up. Prevalence of long COVID symptoms was noted to be higher when comparing hospitalised SARS-CoV-2 test positive and test negative cohorts (10.2% versus 5.0%), frequency matched by hospitalisation status, country and recruitment date. Also based on self-report data, Pazukhina et al.[66] found that the prevalence of long COVID symptoms declined over time, with estimates of 20% and 11.1% at six and 12 month follow-up, respectively (see Table 4.10).

General Symptom Cluster

Both studies reported symptoms related to the general symptom cluster, in children with a history of severe COVID-19 illness.[66, 77] Fatigue was reported in both studies with one study reporting prevalence estimates of 1.6% at 90 days follow-up,[77] and the other reporting declining prevalence estimates from a six month follow-up

(9.4%) to 12 month follow-up (3.6%).[66] Funk et al.[77] also reported 0.5% of participants had fever at 90 days follow-up, and similar prevalence estimates for general symptoms for frequency matched hospitalised SARS-CoV-2 test positive and test negative cohorts (see Table 4.11).

Neurological Symptom Cluster

Both studies reported symptoms related to the neurological symptom cluster in children with a history of severe COVID-19 illness.[66, 77] Prevalence estimates ranged from 0.9%[77] to 4.2%.[66] No difference in prevalence estimates for neurological symptoms was noted between frequency matched hospitalised SARS-CoV-2 test positive and test negative cohorts. Pazukhina et al.[66] reported that prevalence of neurological symptoms and sleep problems declined over time, with estimates of 4.2% and 1.7% for neurological problems, and 4.2% and 0.6% for sleep problems, at six month and 12 month follow-up respectively (see Table 4.12).

Cardiovascular Symptom Cluster

Both studies also reported prevalence estimates for cardiovascular symptoms in children with a history of severe COVID-19 illness,[66, 77] with prevalence estimates ranging from 1.1%[66] to 2.0%[77](see Table 4.13). Prevalence was estimated at 2.0% at 90 days follow-up in one study,[77] with a significantly higher prevalence noted in a hospitalised SARS-CoV-2 test positive cohort (1.5%) compared to a frequency matched hospitalised SARS-CoV-2 test negative cohort (0%). Pazukhina et al.[66] reported that the prevalence of cardiovascular symptoms declined over time, with estimates of 1.1% and 0.3% at six month and 12 month follow-up respectively.[66]

Respiratory Symptom Cluster

Both studies reported symptoms related to the respiratory symptom cluster in children with a history of severe COVID-19 illness,[66, 77] with prevalence estimates ranging from 1.6%[77] to 1.9%[66](see Table 4.14). Prevalence estimates in one study were 0.2%, 0.7%, 0.9% and 1.6% for wheezing, cough, difficulty breathing and other respiratory symptoms at 90 days follow-up.[77] No difference in prevalence estimates were reported between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts.[77] Pazukhina et al.[66] reported that prevalence estimates for respiratory symptoms declined over time, with estimates of 1.9% and 1.1% at six and 12 month follow-up respectively.

Psychological and or Psychiatric Symptom Cluster

One study reported symptoms related to the psychological and or psychiatric cluster in children with a history of severe COVID-19 illness,[77] with prevalence estimates

for depression (0.9%) and anxiety (0.7%) reported at 90 days follow-up (see Table 4.15). This study also reported no difference in prevalence estimates for psychological symptoms between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts.[77]

Ear, Nose, and Throat Symptom Cluster

Both studies reported symptoms related to the ear, nose and throat (ENT) cluster in children with a history of severe COVID-19 illness,[66, 77] with prevalence estimates ranging from 0.5%[77] to 0.8%[66](see Table 4.16). Prevalence estimates in one study were 0.5%[77] for general ophthalmologic and or otolaryngologic symptoms, and specifically runny nose and or congestion, and loss of smell or taste at 90 days follow-up. This study also reported no difference in prevalence estimates for ENT symptoms between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts. Pazukhina et al.[66] reported that prevalence estimates for sensory symptoms declined over time, with estimates of 0.8% and 0.3% at six and 12 month follow-up, respectively.

Musculoskeletal Symptom Cluster

Both studies reported symptoms related to the musculoskeletal symptom cluster in children with a history of severe COVID-19 illness,[66, 77] with prevalence estimates ranging from 0.3%[77] to 1.7%[66] (see Table 4.17). One study reported no difference in prevalence estimates reported for musculoskeletal symptoms between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts.[77] Pazukhina et al.[66] reported that prevalence estimates for musculoskeletal symptoms declined over time, with estimates of 1.7% and 0.8% at six and 12 month follow-up, respectively.

Gastrointestinal Symptom Cluster

Both studies reported prevalence estimates for gastrointestinal symptoms in children with a history of severe COVID-19 illness,[66, 77] with prevalence estimates ranging from 2.0%[77] to 3.9%.[66] Prevalence estimates were 1.8% at 90 days follow-up in one study, with no difference in prevalence estimates for gastrointestinal symptoms reported between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts.[77] Pazukhina et al.[66] reported that prevalence estimates declined over time, with estimates of 3.9% and 0.6% at six and 12 month follow-up, respectively (see Table 4.18).[66]

Dermatologic Symptom Cluster

Both studies reported prevalence estimates for dermatological symptoms (or skin conditions) in children with a history of severe COVID-19 illness,[66, 77] with

prevalence estimates ranging from 0.3%[77] to 4.7%[66] (see Table 4.19). One study reported no difference in prevalence estimates for dermatologic symptoms reported between frequency matched, hospitalised SARS-CoV-2 test positive and test negative cohorts.[77] Pazukhina et al.[66] reported that prevalence estimates declined over time, with estimates of 4.7% and 1.9% at six and 12 month follow-up, respectively.

Those aged 18 years and older

Nineteen studies reported long COVID prevalence estimates in adults with a history of severe COVID-19 illness.[22, 27, 30-32, 37, 38, 40, 41, 44, 45, 47, 52, 65, 66, 74, 85, 117, 118] Prevalence estimates ranged from 30.8%[74] to 94.6%[45] in studies based on self-report data (see Table 4.10).

Table 4.10. Long COVID prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Long COVID prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n=4,681)* *Prevalence of symptoms that the patients did not experience before their COVID-19 diagnosis, but have had persistently had during the 7 days prior to follow-up, n (%)* Total over both time periods: 2,915 **(62.3)** 3-6 month follow-up: 1,774 **(66.0)** 6-12 month follow-up: 1,141 **(57.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	All participants were recruited as long COVID
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	Post-COVID-19 Functional Status scale results revealed that, out of 800 participants, 567 **(70.9%)** reported limitations in daily activities, which were severe for 45 **(5.62%)** of them.
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*Prevalence of persistent post-COVID syndrome reported, n (%)* 30 days follow-up (n=449): 322 **(71.7)** 180 days follow-up (n=435): 206 **(45.9)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	The population all had (self-reported) long COVID.
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	**91.7%** (418) of patients reported at least 1 persisting symptom/sequelae 12 months after hospital discharge and **69.6%** (317) reported 2 or more symptoms.
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	The persistence of at least 1 physical and/or mental health symptom 4 or more weeks after acute COVID-19 onset. Long COVID was prevalent in **84%** of the participants (369/439).
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	Any symptom at 1-year follow-up, n (%): 773/817 **(94.6)** Symptom count, median (IQR): 10 (4-16) 5 month (paired) data Any symptom, n (%): 580/619 **(93.7)** Symptom count, median (IQR): 9 (4-16) 1 year (paired) data Any symptom, n (%): 584/619 **(94.3)** Symptom count, median (IQR): 9 (4-17)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	Patients were asked to report any sustained, intermittent, and emerging symptoms, respectively. The patient's current symptoms were carefully documented and evaluated by specialists to distinguish from their pre-COVID-19 status or other underlying diseases that were not associated with COVID-19.

Author Country	Long COVID assessment mode	Long COVID prevalence estimates
		Any long COVID post-sequelae, n (%) Total patients: 630 **(51.1)** Severe: 252 **(57.5)** Non-severe: 378 **(47.5)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*Symptoms reported at least 2 months post-COVID-19 hospitalisation in persons who were discharged home, n (%)* Long COVID (troubled by persistent symptoms): 124 **(31.5)** No symptoms whatsoever: 104 **(26.3)** Fully recovered and no longer troubled by symptoms (on average, recovery occurred within 2 months): 270 **(68.5)** The proportion at 12 weeks for those troubled by persisting symptoms: **31.8%** The proportion with any symptom at both 8 weeks and 12 weeks: **73.7%**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	Long COVID patients were those with post–COVID-19 symptoms 2 years after acute COVID-19 *Patients who experience at least 1 symptom post-acute COVID-19, n (%)* Hospitalised: 215 **(59.7)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	618 **(83.0%)** of participants had at least 1 of the 10 symptoms measured with standardised instruments.
Frontera et al.[117] US	Completion of validated scales (2 assessment time points, population could participate in either or both time points)	Post-acute symptoms of COVID-19 defined as new or persistent symptoms occurring ≥4 weeks after SARS-CoV-2 infection. At 6 and 12 months, **90%** and **87%** of patients had abnormalities on at least 1 of the metrics assessed (e.g. functional status and disability, activities of daily living, global cognition, quality of life), respectively.
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the US	Self-report via caregivers (Single assessment time point)	*Children* Post-COVID conditions were present if the caregiver indicated at the 90-day interview that the participant had any persistent, new, or returning symptoms or health problems. *Reported 90-days post–COVID-19 conditions, n (%), [95%CI]* SARS-CoV-2–positive children (n=1884): 110 **(5.8)**, [4.8 to 7.0] Hospitalised SARS-CoV-2–positive children (n=447): 44 **(9.8)**, [7.4 to 13.0] *Reported 90-days post–COVID-19 conditions (frequency matched), n (%), [95%CI]* Hospitalised SARS-CoV-2–positive children: 40 (**10.2%**) [7.4%-13.7%] Hospitalised SARS-CoV-2–negative children: 19 (**5.0%**) [3.0%-7.7%]
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19

Author Country	Long COVID assessment mode	Long COVID prevalence estimates
		(2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547)* Symptoms, median (IQR): 1 (0-2) Time since symptom onset, days (IQR): 69 (51–111)
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population in all 3 time points)	COVID-19 survivors with long COVID symptoms are defined as having at least 1 sequelae symptom (i.e. those that are newly occurring and persistent, or worse than the status before getting COVID-19, and that cannot be explained by an alternative disease) which is largely consistent with the case definition of post-COVID-19 condition. *Any symptoms* *Total (n=1,192), n (%)* 6 months after symptom onset (n=1,149): 777 **(68.0)** 12 months after symptom onset (n=1,188): 583 **(49.0)** 2 years after symptom onset (n=1,190): 650 **(55.0)** *Scale 3 – not requiring supplemental oxygen (n=295), n (%)* 6 months after symptom onset (n=286): 194 **(68.0)** 12 months after symptom onset: 141 **(48.0)** 2 years after symptom onset (n=294): 158 **(54.0)** *Scale 4 – requiring supplemental oxygen (n=806), n (%)* 6 months after symptom onset (n=774): 509 **(66.0)** 12 months after symptom onset (n=802): 395 **(49.0)** 2 years after symptom onset (n=805): 440 **(55.0)** *Scale 5-6 – requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91), n (%)* 6 months after symptom onset (n=89): 74 **(83.0)** 12 months after symptom onset: 47 **(52.0)** 2 years after symptom onset: 52 **(57.0)** *Any prevalent symptom at 2-year follow up (n %) p value* Those with a previous SARS-CoV-2 positive test result(n = 1,127): 736 (**65**) Matched (age, sex and comorbidities) cohort who did not have a previous SARS-CoV-2 test result (n = 1,127): 366 (32) p < 0.0001

Author Country	Long COVID assessment mode	Long COVID prevalence estimates
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	Post-COVID-19 condition was defined as the presence of any symptom which started no later than 3 months after hospital discharge and lasted for at least 2 months as per the WHO case definition. Symptom duration was calculated from the time of the hospital discharge in the absence of reliable objective medical record data regarding date of first symptoms appearance. *6 month follow-up, n (%), [95%CI]* Adults (n=1,013): 508 **(50.2)**, [47.1 to 53.3] Children (n=360): 72 **(20.0)**, [15.8 to 24.2] *12 month follow-up, n (%), [95%CI]* Adults (n=1,013): 345 **(34.1)**, [31.2 to 36.9] Children (n=360): 40 **(11.1)**, 8.1 to 14.4]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. *Prevalence of sequelae or persistent symptoms 12 months after discharge, n (%)* Exposed cohort – hospitalised due to COVID-19, (n=453): 163 **(36.1)** Non-exposed cohort – hospitalised due to other causes and matched by institution and date of admission, (n=453): 160 **(35.3)** p-value: 0.80 *Incidences of sequelae or persistent symptoms after discharge, n (cumulative incidence)* Exposed cohort – hospitalised due to COVID-19, (n=453): 120 (**26.5**) Non-exposed cohort – hospitalised due to other causes and matched by institution and date of admission, (n=453): 105 (**23.2**) Risk ratio [95%CI]: 1.14 (0.9 to 1.4)
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*Patients who reported symptoms 4 to 12 weeks after hospital discharge*, n (%)* ≥1 persistent symptom: 325 **(76.0)** >2 persistent symptoms: 154 **(36.0)** >3 persistent symptoms: 92 **(21.0)** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	Patients were characterised as having PASC if they noted persistent COVID-19 symptoms on the 90-day post-discharge survey (or the 60-day survey if the 90-day survey was incomplete). 309/1,038 patients **(29.8%)** reported persistent symptoms on the follow-up survey at least 60 days after the acute illness.

Author Country	Long COVID assessment mode	Long COVID prevalence estimates
		246/800 patients **(30.8%)** who received treatment for COVID-19 in the hospital, developed PASC. 63/238 **(26.5%)** high-risk outpatients developed PASC. 309/879 **(35.2%)** participants who completed the 60-day or 90-day survey developed PASC (mix of inpatient and outpatient).

Key: PASC, Post-acute sequelae of SARS-CoV-2; UK, United Kingdom, US, United States.

General Symptom Cluster

Twenty-two studies reported symptoms related to the general symptom cluster for adults only [22, 30-32, 37, 38, 40, 41, 45, 47, 56, 65, 74, 85, 117-119] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates for this cluster ranged from 9%[119] to 94.6%[45] in adults with a history of severe COVID-19 (see Table 4.11) and 11%[117] to 91.1%[85] in those identified as having long COVID. Fatigue was the most commonly reported symptom with 23 studies reporting it,[22-27, 30-32, 37, 38, 40, 41, 44, 45, 47, 65, 66, 70, 74, 85, 117-119] seven studies reported on fever.[30, 32, 37, 40, 56, 74, 117] Prevalence estimates for fatigue ranged from 8.2%[22] to 76.4%[28] in those with a history of COVID-19 and from 11%[117] to 91.1%[85] in those identified as having long COVID.

Prevalence estimates were noted to differ in adults by gender and over time in studies reporting prevalence estimates at multiple time points. Barreto et al.[37] noted a significantly higher prevalence of fatigue in females compared to males (70.4% versus 54.8%) in those self-reporting long COVID. Four studies identified that the prevalence of fatigue decreased over time,[25, 30, 66, 119] using repeated measures within the same population. The prevalence of fatigue reduced from 47.9% to 34.7% in a study reporting 30 and 180 days post COVID-19,[30] 38% to 9% in a study reporting three and six month follow-up,[119] and from 72.8% to 45.4% and 24.9% to 12.0% respectively, in studies reporting follow-up at six months and 12 months post COVID-19.[25, 66] One study also identified that the prevalence of fever in adults decreased over time,[30] from 2.9% at 30 days to 0.4% at 180 days post COVID-19.

Prevalence estimates (or prevalence estimates ranges) for a number of other symptoms in adults, related to the general symptom cluster were identified: pain or discomfort (35.8%[27] to 64.5%[38]), weakness (13%[41] to 68.6%[85]), bleeding (4.4% to 4.7% in one study[45]), thyroid dysfunction (20.5% to 16.9% at 30 days and 180 days post COVID-19[30]), and urological symptoms (1.3%[22] to 24%[41]). Rivera-Izguierdo et al.[22] also reported a higher prevalence of fatigue, urological symptoms and ophthalmological symptoms in a cohort hospitalised with a positive SARS-CoV-2 test, compared with a time and institution matched cohort hospitalised for other reasons.

Table 4.11. General symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	General symptom prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up n (%):* Fatigue: 847 **(32%)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up n (%):* Fatigue: 493 **(25%)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* *Long COVID complaints are usually initiated at the acute stage of disease, persisting as residual symptoms* Number of persistent symptoms (median IQR): 4.0 (2.0–6.0) Fatigue: 738/1163 **(63.5%)** Persistent symptoms (≥1 month post the acute phase of infection) by sex and disease severity at the acute phase. *Mild (male n = 89, female n = 262) (N %)* Number of persistent symptoms (median IQR): Male: 3.0 (2.0–5.0) Female: 5.0 (3.0–7.0) Fatigue: Male: 53 **(59.6)** Female: 194 **(74.0)** *Moderate (male n = 155, female n = 183) (N %)* Number of persistent symptoms (median IQR): Male: 3.0 (1.0–5.0) Female: 5.0 (3.0–7.0) Fatigue: Male: 77 **(49.7)** Female: 121 **(66.1)** *Severe (male n = 262, female n = 213) (N %)* Number of persistent symptoms (median IQR): Male: 3.0 (2.0–5.0) Female: 5.0 (3.0–7.0) Fatigue: Male: 143/261 **(54.8)** Female: 150 **(70.4)** *New symptoms after recovery from acute illness (n, N %)* Number of symptoms (Median IQR): 8.0 (6.0 10.0%) Fever: 514/808 **(63.6%)** Fatigue/Muscle weakness: 668/809 **(82.6%)**

Author Country	Long COVID assessment mode	General symptom prevalence estimates
		Clinical presentation of LONG COVID by calendar time according to variant predominance distribution *Ancestral (n = 736) Period August 2020 to January 2021 (n/N %)* Fatigue: 466/735 **(63.4%)** *Gama Variant (n = 249) Period March 2021 to July 2021 (n/N %)* Fatigue: 140 **(56.2%)**
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	*History of COVID-19 (n = 801)* At follow-up (3 to 11 months after hospital discharge): Pain and discomfort: 516/800 **(64.5%)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population in both time points)	*History of COVID-19 (n = 449)* 30 days post-COVID-19 n (%): Fatigue: 215 **(47.9)** Fever: 13 **(2.9)** Thyroid dysfunction: 66 **(20.5)** *History of COVID-19 (n = 435)* 180 days post-COVID-19 n (%): Fatigue: 151 **(34.7)** Fever: 2 **(0.4)** Thyroid dysfunction: 35 **(16.9)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*Long COVID (n = 376)* *Overall reported symptoms - hospitalised (n = 376), n (%)* Fatigue: 345 **(82.7%)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456) 12-month follow-up n (%):* Fatigue: 230 **(54.6%)** *General health status n (%):* <5: 11 **(2.4%)** 5-6: 65 **(14.3%)** 7-8: 234 **(54.5%)** 9-10: 144 **(31.7%)** *Severe medical issues after COVID-19 n (%):* ER admission: 47 **(10.4%)** Hospitalisation: 30 **(6.6%)**

Author Country	Long COVID assessment mode	General symptom prevalence estimates
		Haepatologic problems: 2 **(0.4%)** Other: 15 **(3.3%)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of Long COVID >4 weeks post-COVID-19:* Fatigue: 233 **(63.1%)** Fever: 6 **(1.6%)** Number of symptoms: 1-5: 296 **(80.2%)** 6-10: 73 **(19.8%)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up n (%):* Any symptom: 773/817 **(94.6%)** Symptom count Median (IQ): 10 (4 - 16) Fatigue: 463/770 **(60.1%)** Pain: 359/770 **(46.6%)** Bleeding: 34/781 **(4.4%)** Symptoms measured by VAS 0-10 scale (within the PSQ): Fatigue (n=752) Median IQR: 3.0 (0.0 – 6.0) Pain (n=751) Median IQR: 1.0 (0.0 – 5.0) *5 month (paired) data* Bleeding: 26/551 **(4.7%)** Symptoms measured by VAS 0-10 scale (within the PSQ): Fatigue (n=521) Median IQR: 3.0 (0.0 – 6.0) Pain (n=514) Median IQR: 1.0 (0.0 – 5.0) *1 year (paired) data* Bleeding: 24/551 **(4.4%)** Symptoms measured by VAS 0-10 scale (within the PSQ): Fatigue (n=521) Median IQR: 3.0 (0.0 – 6.0) Pain (n=514) Median IQR: 1.0 (0.0 – 5.0)
Fang et al.[65] China	Self-report via questionnaire	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up n (%):*

Author Country	Long COVID assessment mode	General symptom prevalence estimates
	(Single assessment time point)	Fatigue: 400 **(32.4%)** Chill: 1 **(0.1%)** *Severe patients' n (%):* Fatigue: 166 **(37.9%)** *Non-severe patients' n (%):* Fatigue: 234 **(29.4%)** Chill: 1 **(0.1%)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥2 months following COVID-19 n (%):* Total: n=398 Fatigue: 210 **(53%)** Weakness: 151 **(38.2%)** Long COVID: n=124 Fatigue: 113 **(91.1%)** Weakness: 85 **(68.6%)** Full Recovery: n=270 Fatigue: 96 **(35.6%)** Weakness: 65 **(24.2%)**
Fernández-de-las-Peñas et al.[25] Spain	Self-report via interview (2 assessment time points, same population at both time points)	*Post-COVID fatigue at 6 months (n %):* 300/412 **(72.8%)** *Post-COVID fatigue at 12 months (n %):* 187/412 **(45.4%)**
Fernández-de-las-Peñas et al.[26] Spain	Self-report via interview (Single assessment time point)	*Number of post-COVID-19 symptoms (n %)* None: 212 **(18.5%)** 1 symptom: 238 **(21%)** 2 symptoms: 267 **(23.5%)** 3 or more symptoms: 425 **(37%)** *7 months post-COVID-19 (n %):* Fatigue: 695 **(61%)** No: 447 **(39.1%)** Mild: 342 **(30.0%)**

Author Country	Long COVID assessment mode	General symptom prevalence estimates
		Moderate: 258 **(22.6%)** Severe: 95 **(8.3%)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 668)* No of post-COVID-19 symptoms (mean SD): Hospitalised: 1.3 (1.4) *Symptoms ≥2 Years Post-COVID-19 (n %)* *Hospitalised:* Fatigue: 161 **(44.7%)** Pain symptoms (including headache): 129 **(35.8%)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Number of Post-COVID-19 Symptoms (mean SD):* Wuhan: 2.7 (1.3) Alpha: 1.8 (1.1) Delta: 2.1 (1.5) *Wuhan Post-COVID-19 Symptoms, n (%):* Fatigue: 137 **(68.2%)** *Alpha Post-COVID-19 Symptoms, n (%):* Fatigue: 151 **(71.5%)** *Delta Post-COVID-19 Symptoms, n (%):* Fatigue: 155 **(76.4%)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Median no of symptoms:* 2 (IQR=1-5) *Objective symptoms* (Median IQR, % of total participants with abnormal result, n):* Fatigue, score (0-52) (abnormal if ≤39): 42 (33 47); **38%** (n=285) *Additional symptoms (N %):* Nocturia: 176 **(24%)** Weakness: 96 **(13%)** *Median follow-up was 200 days post-hospital discharge
Frontera et al.[117] US	Completion of validated scales and interview	*History of COVID-19 (6 month follow-up: n = 382)*

Author Country	Long COVID assessment mode	General symptom prevalence estimates
	(2 assessment time points, population could participate in either or both time points)	*Scores on tests of function, cognition, and neurological quality of life at 6 months (Mean SD):* NeuroQoL fatigue, (abnormal T-score ≥ 60): 45.7 (10) *Scores on tests of function, cognition, and neurological quality of life at 12 months (Mean SD):* NeuroQoL fatigue, (abnormal T-score ≥ 60): 45.6 (11) *Abnormal or poor scores at 6 months (n %):* NeuroQoL fatigue: 14/272 **(5%)** *Abnormal or poor scores at 12 months (n %):* NeuroQoL fatigue: 20/223 **(9%)** *Long COVID (n = 239)* *Symptoms at 12 months (n %):* Fatigue: 25 **(11%)** Fever: 5 **(2%)** Difficulty urinating: 7 **(3%)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the US	Self-report via caregivers (Single assessment time point)	*Children: History of COVID-19 (n = 1,884)* **Hospitalised N=447** *Number of persistent, new or recurring health problem (n %):* 1: 28 **(6.3)** 2: 8 **(1.8)** 3+: 8 **(1.8)** *Symptoms (n %):* Fatigue or weakness: 7 **(1.6)** Fever: 2 **(0.5)** *Other symptoms or diagnoses, n (%) [95%CI]:* 6 **(1.3)** [0.5-2.9] *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%) p-value* Fatigue or weakness: 6 (**1.5**); 1 (0.3) p = 0.12 Fever: 2 (**0.5**); 0 (0); p = 0.50 Other symptoms or diagnoses: 5 (**1.3**); 2 (0.5) p = 0.45
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 Hospitalised (n=547); Emergency Dept (n=212)* Fatigue: 187 **(34.2%)**; 98 **(46.2)**

Author Country	Long COVID assessment mode	General symptom prevalence estimates
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406) n (%):* Fatigue: 154 **(38%)** *6 months follow-up (n=406) n (%):* Fatigue: 36 **(9%)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* *6 month follow-up n (%) 95% CI:* Fatigue Adults: 252/1013 **(24.9%)**; 95% CI: 22.21% to 27.54% Children: 34/360 **(9.4%)**; 95% CI: 6.39% to 12.5% *12 month follow-up n (%) 95% CI:* Fatigue Adults: 122/1013 **(12.0%)**; 95% CI: 10.07% to 14.02% Children: 13/360 **(3.6%)**; 95% CI: 1.94% to 5.56%
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* *Exposed cohort (hospitalised due to COVID-19) (n = 453); Non-exposed cohort (hospitalised due to other causes) (n = 453) (matched by institution and date of admission) n (%). P-value* General/systemic symptoms: 68 **(15.0)**; 80 **(17.7)**. 0.281 Fatigue: 37 **(8.2)**; 56 **(12.4)**. 0.038 Haematological symptoms: 7 **(1.5)**; 7 **(1.5)**. 1.000 Thrombotic events: 5 **(1.1)**; 0 **(0.0)**. 0.025 Nephrological symptoms: 5 **(1.1)**; 2 **(0.4)**. 0.162 Urological symptoms: 6 **(1.3)**; 16 **(3.5)**. 0.031 Ophthalmological symptoms: 5 **(1.1)**; 16 **(3.5)**. 0.015 Infection: 7 **(1.5)**; 6 **(1.3)**. 0.898
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No: 58,581 (96) Yes: 2,421 (4)* *Symptoms 6-12 months after test n (%):* Fatigue/exhaustion: 397 **(16.4%)** Chills: 57 **(2.4%)** Fever: 68 **(2.8%)** Red runny eyes: 58 **(2.4%)**

Author Country	Long COVID assessment mode	General symptom prevalence estimates
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Symptoms* Chronic fatigue: **36%** Fever: **3%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	*History of COVID-19 (n = 1,038)* *30 days follow-up n (%):* Fatigue: 169 **(73.2%)** Fever and chills: 119 **(51.5%)** *At least 60 days follow-up (%):* Fatigue: **31.4%** Persistent fever: **1.9%**

Neurological Symptom Cluster

Twenty-two studies reported symptoms related to the neurological cluster for adults only,[22, 24, 27, 28, 30-32, 37-39, 41, 45, 47, 52, 56, 65, 85, 117-119] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates ranged from 3.9[65] to 62.4%[30] in those with a history of COVID-19 and 23%[117] to 69.8%[37] in those identified as having long COVID (see Table 4.12). Headache was the most commonly reported symptom, with prevalence estimates ranging from 2.0%[32] to 69.8%.[37] The prevalence of neurological symptoms was noted to differ by gender and over time in studies reporting prevalence data for multiple time points.

In a study that looked at the prevalence of persistent symptoms by sex and disease severity during the acute phase, in those with self-reported long COVID, Barreto et al.[37] found a higher prevalence of neurological symptoms in females compared to males (memory loss 61% versus 44.2%; headache 37.8% versus 24.6%; insomnia 55.9% versus 45.2%). Five studies investigated the persistence of neurological symptoms in adults over time, using repeated assessments.[30, 45, 52, 66, 119]

One study reported a reduction in the prevalence of memory impairment and brain fog over time from 41.4% to 35.6% for memory impairment and 52.1% to 43.9% for brain fog at 30 and 180 days post-acute COVID-19.[30] Evans et al.[45] reported similar prevalence estimates in confusion and or fuzzy head and difficulty in concentrating at five month and one year follow up. Two studies also reported a reduction in the prevalence of headache over time, with reductions from 11% to 3% in a study reporting three and six month follow-up,[119] and from 28.5% to 15.1% in a study reporting follow-up at 30 and 180 days post-acute COVID-19.[30] In contrast, the prevalence of headache increased over time in one study,[52] with a prevalence of 2%, 5% and 7% at six months, 12 months, and two years, respectively, while it remained stable overtime in another study,[45] with prevalence estimates of 30.5% at a 5 month follow-up and 32.3% at a one year follow-up. Four studies reported a reduction in the prevalence of sleep disturbances over time in adults, with reductions from 10.5% to 3.6% in a study reporting six months and 12 months follow-up,[66] 62.4% to 53.6% in a study reporting 30 days and 180 days follow-up,[30] from 27% to 17% in a study reporting six months, and 12 month follow-up (however with an increase to 25% at two years follow-up),[52] and from 5% to 2%[119] in a study reporting three months and six months follow-up.

Two studies investigated differences in neurological symptoms in matched cohorts. Huang et al.[52] reported significantly higher prevalence of headaches, dizziness and sleep difficulties at two years follow-up in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched

community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izguierdo et al.[22] reported significantly higher prevalence estimates for neurological symptoms and confusion, but not for other symptoms (sensitivity disorders, movement disorders and sleep disturbances), in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons.

Table 4.12 Neurological symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Headache: 316 (**12.0**) Dizziness: 205 (**8.0**) Brain fog: 319 (**12.0**) Sleep difficulty: 453 (**17.0**) *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Headache: 207 (**10.0**) Dizziness: 125 (**6.0**) Brain fog: 161 (**8.0**) Sleep difficulty: 254 (**13.0**)
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Headache: 411/1,112 (**37.0**) Dizziness: 212/602 (**35.2**) Memory loss: 332/603 (**55.1**) Insomnia: 317/603 (**52.6**) Motor disabilities: 193/1,028 (**18.8**) ***Persistent symptoms (≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (male, n=89; female, n=262)** *Headache, n (%)* Male: 32 (**36.0**) Female: 131/260 (**50.4**) Dizziness, n (%) Male: 12/37 (**32.4**) Female: 44/97 (**45.4**) Memory loss, n (%) Male: 16/37 (**43.2**) Female: 60/98 (**61.2**) Insomnia, n (%) Male: 18/37 (**48.6**) Female: 62/98 (**63.3**)

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Motor disabilities, n (%) Male: 5/83 (**6.0**) Female: 37/248 (**14.9**) **Moderate (male, n=155; female, n=183)** Headache, n (%) Male: 36/151 (**23.8**) Female: 77/175 (**44.0**) Dizziness, n (%) Male: 15/84 (**17.9**) Female: 36/93 (**38.7**) Memory loss, n (%) Male: 38/85 (**44.7**) Female: 66/93 (**71**) Insomnia, n (%) Male: 32/84 (**38.1**) Female: 60/93 (**64.5**) Motor disabilities, n (%) Male: 14/138 (**10.1**) Female: 37/158 (**23.4**) **Severe (male, n=262; female, n=213)** Headache, n (%) Male: 58/236 (**24.6**) Female: 76/201 (**37.8**) Dizziness, n (%) Male: 44/155 (**28.4**) Female: 61/136 (**44.9**) Memory loss, n (%) Male: 68/154 (**44.2**) Female: 83/136 (**61**) Insomnia, n (%) Male: 70/155 (**45.2**) Female: 76/136 (**55.9**) Motor disabilities, n (%) Male: 51/222 (**23.0**) Female: 50/179 (**27.9**) ***New symptoms after recovery from acute illness*** Headache, n (%): 565/809 (**69.8**)

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Clinical presentation of long COVID by calendar time according to variant predominance distribution **Ancestral (n=736) Period August 2020 to January 2021, n (%)** Headache: 243/685 (**35.5**) Dizziness: 70/181 (**38.7**) Memory loss: 100/182 (**54.9**) Insomnia: 96/181 (**53.0**) Motor limitation: 107/619 (**17.3**) **Gama Variant (n=249) Period March 2021 to July 2021, n (%)** Headache: 83/248 (**33.5**) Dizziness: 71/244 (**29.1**) Memory loss: 136/244 (**55.7**) Insomnia: 122/245 (**49.8**) Motor limitation: 52/235 (**22.1**)
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	*History of COVID-19 (n = 801)* *At follow-up (3 to 11 months after hospital discharge)* Daytime sleepiness and insomnia evaluations showed subthreshold results. Assessments showed poor handgrip strength (**52.2%**, 379 of 726) and abnormal Timed Up and Go results (mean 13.07s, SD: 6.49).
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19 n (%)* Headache: 128 **(28.5)** Brain fog: 234 **(52.1)** Dizziness: 88 **(19.6)** Memory impairment: 186 **(41.4)** Peripheral neuropathy: 133 **(29.6)** Sleeping disorders: 280 **(62.4)** *History of COVID-19 (n = 435)* *180 days post-COVID-19 n (%)* Headache: 66 **(15.1)** Brain fog: 191 **(43.9)** Dizziness: 13 **(2.9)** Memory impairment: 155 **(35.6)** Peripheral neuropathy: 78 **(17.9)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Sleeping disorders: 233 **(53.6)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was not hospitalised - 105.7 ±55.7 days and hospitalised - 106.8 ±61.5 days.* *Overall reported symptoms – hospitalised (n = 376), n (%)* Problems with mental abilities: 183 **(43.9)** Sleep problems: 179 **(42.9)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up, n (%)* (symptom scale used in the study (o=no symptom, 10=maximum intensity, 5=presence if symptom)) Memory disorder (<5): 15 **(3.5)** Headache: 73 **(17.4)** Sleep difficulties: 147 **(32.4)** Limitations to daily activities (limitations to daily activities + troubled walking): 69 **(16.4)** *Severe medical issues after COVID-19, n (%)* Neurologic problems: 1 **(0.2)**
Damiano et al.[39] Brazil	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 701)* *Cognitive outcomes 6-11 months post-hospitalisation, mean (SD)* Magnitude of cognitive complaints: 5.2 (4.1) Temporal and Spatial Orientation of Mini-Mental State Examination orientation score: 8.3 (3.3) Trail Making Test-A: 65.5 seconds (48.0 seconds) Verbal fluency: 15.6 (5.4) Alcohol Use Disorder Identification Test score: 1.6 (3.5) Digit symbol substitution test: 32.2 (19.3) Impairment in naming ability Boston naming test: 13.2 (2.3) Word list: 15.4 (4.7) Constructional praxis: 8.3 (2.6) Word list recall: 4.9 (2.3) Word list recognition: 7.9 (2.8)
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of Long COVID >4 weeks post-COVID-19, n (%)* Headache: 90 **(24.4)**
Evans et al.[45] UK	Self-report via questionnaire	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Physical slowing down: 429/811 **(52.9)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
	(2 assessment time points, population could participate in either or both time points)	Sleep disturbance: 402/769 **(52.3)** Slowing down in your thinking: 377/808 **(46.7)** Short-term memory loss: 360/808 **(44.6)** Limb weakness: 341/813 **(41.9)** Difficulty with concentration: 337/807 **(41.8)** Tingling feeling/pins and needles: 285/813 **(35.1)** Headache: 253/808 **(31.3)** Confusion/fuzzy head: 250/811 **(30.8)** Dizziness or lightheaded: 243/810 **(30.0)** Difficulty with communication: 168/810 **(20.7)** Problems seeing: 115/807 **(14.3)** Tremor/shakiness: 106/812 **(13.1)** Loss of control of passing urine: 96/807 **(11.9)** Can't fully move or control movement: 83/810 **(10.2)** Loss of control of opening your bowels: 58/807 **(7.2)** Hemiparesis (including facial): 29/811 **(3.6)** Fainting / blackouts: 15/808 **(1.9)** Seizures: <5/808 **(<1)** *5 month (paired) data* Physical slowing down: 313/609 **(51.4)** Sleep disturbance: NA Slowing down in your thinking: 263/602 **(43.7)** Short-term memory loss: 247/595 **(41.5)** Limb weakness: 289/607 **(47.6)** Difficulty with concentration: 242/595 **(40.9)** Tingling feeling/pins and needles: 243/599 **(40.6)** Headache: 184/603 **(30.5)** Confusion/fuzzy head: 181/606 **(29.9)** Dizziness or lightheaded: 175/594 **(29.5)** Difficulty with communication: 106/604 **(17.5)** Problems seeing: 100/590 **(16.9)** Tremor/shakiness: 76/599 **(12.7)** Loss of control of passing urine: 65/605 **(10.7)** Can't fully move or control movement: 57/593 **(9.6)** Loss of control of opening your bowels: 35/600 **(5.8)** Hemiparesis (including facial): 25/597 **(4.2)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Fainting / blackouts: 9/588 **(1.5)** Seizures: <5/592 **(<1)** *1 year (paired) data* Physical slowing down: 314/609 **(51.6)** Sleep disturbance: 275/530 **(51.9)** Slowing down in your thinking:279/602 **(46.3)** Short-term memory loss: 263/595 **(44.2)** Limb weakness: 253/607 **(41.7)** Difficulty with concentration: 243/595 **(41.0)** Tingling feeling/pins and needles: 211/599 **(35.2)** Headache: 195/603 **(32.3)** Confusion/fuzzy head: 186/606 **(30.7)** Dizziness or lightheaded: 182/594 **(30.6)** Difficulty with communication: 124/604 **(20.5)** Problems seeing: 85/590 **(14.4)** Tremor/shakiness: 76/599 **(12.7)** Loss of control of passing urine: 68/605 **(11.2)** Can't fully move or control movement: 56/593 **(9.4)** Loss of control of opening your bowels: 40/600 **(6.7)** Hemiparesis (including facial): 17/597 **(2.8)** Fainting / blackouts: 8/588 **(1.4)** Seizures: <5/592 **(<1)** *Symptoms measured by VAS 0-10 scale (within the Patient Symptom Questionnaire)* Sleep quality (n=754) Median (IQR): 2.0 (0.0–5.0)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Dizziness: 47 **(0.8)** Headache: 31 **(2.5)** *Severe patients, n (%)* Dizziness: 17 **(3.9)** Headache: 16 **(3.7)** *Non-severe patients, n (%)* Dizziness: 30 **(3.8)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Headache: 15 **(1.9)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* ***Symptoms ≥2 months following COVID-19, n (%)*** *Total (n=398)* Sleep disturbance: 109 **(27.5)** Problems with memory: 14 **(3.5)** Concentration: 14 **(3.5)** Headache: 14 **(3.5)** Numbness: 12 **(3.0)** Dizziness: 11 **(2.8)** *Long COVID (n=124)* Sleep disturbance: 71 **(57.3)** *Full recovery (n=270)* Sleep disturbance: 37 **(13.7)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* Symptoms, participants were assessed a mean of 8.4 months after hospital discharge, n (%) Memory loss: 341 **(17.3)** Cognitive blurring/brain fog: 189 **(9.6)** Concentration loss: 140 **(7.1)** Ocular problems: 116 **(5.9)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* ***Symptoms ≥2 Years post-COVID-19, n (%)*** *Hospitalised (n = 360)* Memory loss: 72 **(20.0)** Cognitive blurring/brain fog: 18 **(5.0)** Concentration loss: 6 **(1.7)** Ocular problems: 14 **(3.9)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan post-COVID-19 symptoms (mean follow-up 6.5 months) (n = 201), n (%)* Memory loss: 39 **(19.4)** Brain fog: 21 **(10.4)** Attention Disorders: 14 **(7.0)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Visual Problems: 5 **(2.5)** *Alpha post-COVID-19 symptoms (mean follow-up 6 months) (n = 211), n (%)* Memory loss: 38 **(18.0)** Brain fog: 22 **(10.4)** Attention Disorders: 13 **(6.1)** Visual Problems: 11 **(5.2)** *Delta post-COVID-19 symptoms (mean follow-up 6.3 months) (n = 202), n (%)* Memory loss: 36 **(17.8)** Brain fog: 22 **(10.9)** Attention Disorders: 6 **(3.0)** Visual Problems: 9 **(4.5)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Objective symptoms*, median (IQR); % of total participants with abnormal result (n)* Memory impairment, score (0-14) (abnormal if ≥7): 4 (1-8); **35.0** (262) Insomnia, score (0-28) (abnormal if ≥8): 6 (2-11); **32.0** (240) *Additional symptoms*, n (%)* Dizziness: 264 **(36.0)** Loss of concentration: 208 **(31.0)** Paresthesia: 116 **(15.0**) Gait problems: 83 **(11.0)** Headache: 80 **(11.0)** Loss of consciousness: 27 **(4.0)** *Median follow-up was 200 days post-hospital discharge
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (6 month follow-up: n = 382)* *Scores on tests of function, cognition, and neurological quality of life at 6 months and 12 months, mean (SD)* Modified Rankin Scale (poor=4–6): 3 (2) and 2 (2) Barthel Index (abnormal<100): 85.7 (25) and 87.2 (24) T-MoCA (abnormal≤18): 17.0 (3.5) and 17.5 (3.8) NeuroQoL sleep (abnormal T-score≥60): 46.3 (10) and 46.1 (11) *Abnormal or poor scores at 6 months and 12 months, n (%)* Modified Rankin Scale: 189/381 **(50.0)** and 79/236 **(34.0)** Barthel Index: 134/304 **(44.0)** and 86/236 **(36.0)** T-MoCA: 106/215 **(49.0)** and 69/170 **(41.0)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Long COVID (n = 239) *Symptoms at 12 months, n (%)* Brain fog/confusion/difficulty concentrating/memory loss: 48 **(20.0)** Headache: 54 **(23.0)** Dizziness/lightheadedness: 17 **(7.0)** Vision abnormalities: 8 **(3.0)** Difficulty sleeping: 27 **(11.0)** Fainting/blackouts: 5 **(2.0)** Tremors: 3 **(1.0)** Slowness of movement: 13 **(5.0)** Jerking of the limbs: 2 **(1.0)** Numbness: 8 **(3.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* ***Hospitalised (n=447)*** *Symptoms, 90 days follow-up n (%)* Mental 'fuzziness', loss of focus: 1 **(0.2)** Dizziness or lightheaded: 0 **(0)** Headache: 4 **(0.9)** Seizures: 1 **(0.2)** *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched Hospitalised SARS-CoV-2–negative children), n (%), [95%CI]* Mental 'fuzziness', loss of focus: 1 (**0.3**); 0 (**0**) p >0.99 Dizziness or lightheaded: 0 (**0**); 2 (**0.5**) p = 0.24 Headache: 3 (**0.8**); 3 (**0.8**) p >0.99 Seizures: 1 (**0.3**); 1 (**0.3**) p >0.99
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547)* Headache, n (%): 38 **(6.9)** Brain fog (encompasses problems with memory, cognition and concentration), n (%): 35 **(6.4)** Disturbed sleep, n (%): 25 **(4.6)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Emergency Dept (n=212) Headache, n (%): 29 **(13.7)** Brain fog (encompasses problems with memory, cognition and concentration), n (%): 29 **(13.7)** Disturbed sleep, n (%): 25 **(11.8)**
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population in all 3 time points)	*History of COVID-19 (n = 1,192)* *Scale 3 - not requiring supplemental oxygen n=295* *Scale 4 - requiring supplemental oxygen n=806* *Scale 5-6 - requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation n=91* *6 months after symptom onset, total; scale 3; scale 4; scale 5-6* Sleep difficulties, n (%): 313/1,151 **(27.0)**; 75/286 **(26.0)**; 205/776 **(26.0)**; 33/89 **(37.0)** Dizziness, n (%): 64/1,151 **(6.0)**; 19/286 **(7.0)**; 39/776 **(5.0)**; 6/89 **(7.0)** Headache, n (%): 20/1,147 **(2.0)**; 6/287 **(2.0)**; 11/772 **(1.0)**; 3/88 **(3.0)** *12 months after symptom onset, total; scale 3; scale 4; scale 5-6* Sleep difficulties, n (%): 206/1,188 **(17.0)**; 47 **(16.0)**; 146/802 **(18.0)**; 13 **(14.0)** Dizziness, n (%): 61/1,188 **(5.0)**; 15 **(5.0)**; 38/802 **(5.0)**; 8 **(9.0)** Headache, n (%): 55/1,188 **(5.0)**; 15 **(5.0)**; 36/802 **(4.0)**; 4 **(4.0)** *2 years after symptom onset, total; scale 3; scale 4; scale 5-6* Sleep difficulties, n (%): 298/1,190 **(25.0)**; 70/294 **(24.0)**; 203/805 **(25.0)**; 25 **(27.0)** Dizziness, n (%): 131/1,190 **(11.0)**; 31/294 **(11.0)**; 90/805 **(11.0)**; 10 **(11.0)** Headache, n (%): 81/1,190 **(7.0)**; 23/294 **(8.0)**; 50/805 **(6.0)**; 8 **(9.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); Those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Sleep difficulties: 354 (**31**); 153 (**14**) p < 0.0001 Dizziness: 164 (**15**); 78 (**7**) p < 0.0001 Headache: 110 (**10**); 34 (**3**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Headache: 47 **(11.0)** Sleep difficulties: 20 **(5.0)** *6 months follow-up (n=406)*

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Headache: 12 **(3.0)** Sleep difficulties: 8 **(2.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* ***6 month follow-up, n (%), [95% CI]*** *Neurological* Adults (n=1,013): 192 **(19.0)**, [16.5 to 21.3] Children (n=360): 15 **(4.2)**, [2.2 to 6.4] *Sleep problems* Adults (n=1,013): 106 **(10.5)**, [8.6 to 12.3] Children (n=360): 15 **(4.2)**, [2.2 to 6.4] ***12 month follow-up, n (%), [95% CI]*** *Neurological* Adults (n=1,013): 90 **(8.9)**, [7.2 to 10.6] Children (n=360): 6 **(1.7)**, [0.6 to 3.1] *Sleep problems* Adults (n=1,013): 36 **(3.6)**, [2.5 to 4.7] Children (n=360): 2 **(0.6)**, [0.0 to 1.4]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n=453) vs Non-exposed cohort - hospitalised due to other causes (n=453) (matched by institution and date of admission)* Neurological symptoms, n (%); p value: 44 **(9.7)** vs 28 **(6.2)**; 0.049 Headache, n (%); p value: 13 **(2.9)** vs 12 **(2.6)**; 0.839 Sensitivity disorders, n (%); p value: 9 **(2.0)** vs 8 **(1.8)**; 0.807 Movement disorders, n (%); p value: 5 **(1.1)** vs 1 **(0.2)**; 0.062 Confusion, memory loss, n (%); p value: 16 **(3.5)** vs 8 **(1.8)**; 0.043 Sleep disturbances, n (%); p value: 17 **(3.8)** vs 14 **(3.1)**; 0.584
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No: 58,581 (96) Yes: 2,421 (4)* **Symptoms 6-12 months after test, n (%)** Sleeping legs/arms: 203 **(8.4)**

Author Country	Long COVID assessment mode	Neurologic symptom cluster prevalence estimates
		Headache: 180 **(7.4)** Dizziness: 158 **(6.5)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* *Symptoms*, n (%)* Total n=428 Insomnia: 68 **(16.0)** Visual disorders: 55 **(13.0)** Brain fog: 54 **(13.0)** Tremors/parenthesia: 21 **(5.0)** Headache: 10 **(2.0)** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.

Key: UK, United Kingdom, US, United States.

Cardiovascular Symptom Cluster

Twenty studies reported symptoms related to the cardiovascular cluster for adults only,[22, 24, 26-28, 30-32, 37, 40, 41, 45, 47, 52, 56, 65, 85, 117-119] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates ranged from 0.6%[27] to 39%[119] in those with a history of COVID-19 and from 5.0%[117] to 63.5%[37] in those identified as having long COVID (see Table 4.13). Palpitations or tachycardia, and chest pain or chest tightness were the most commonly reported symptoms, with prevalence estimates ranging from 0.6%[27] to 37.4%[30] and 1.1%[22] to 63.5%,[30] respectively.

At two years post-acute COVID-19, Huang et al.[52] found that 12% of participants reported palpitations and 5% reported chest pain. The prevalence of cardiovascular symptoms was noted to differ by gender and over time. Barreto et al.[37] identified a significantly higher reporting of cardiovascular symptoms in females (45.5%) compared with males (32.2%) in those with self-reported long COVID. Five studies investigated the persistence of cardiovascular symptoms in adults, using repeated assessments over time.[30, 45, 52, 66, 119] Two studies identified that the prevalence of chest pain decreased over time;[30, 119] however one study reported increased chest pain prevalence from six month to 12 month follow-up,[52] and another study reported similar prevalence estimates for chest pain at five month and one year follow-up,[45]. Mixed trends were also observed for the prevalence of palpitations, with decreases,[119] and similar prevalence estimates[52, 118, 119] reported over time. One study reported the prevalence of cardiovascular symptoms decreased over time,[66] with reductions from 6.2% to 1.2% at six and 12 months post-acute COVID-19, respectively. Two studies investigated differences in the prevalence of cardiovascular symptoms in matched cohorts. Huang et al.[52] reported a significantly higher prevalence of palpitations and of chest pain, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izguierdo et al.[22] reported no significant difference in prevalence estimates for chest pain in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.13. Cardiovascular symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Chest pain: 303 **(11.0)** Palpitation: 304 **(11.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Chest pain: 175 **(9.0)** Palpitation: 166 **(8.0)** *Additional (not specified to a follow-up time point)* New-onset hypertension: 11
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Chest pain: 525/1,162 **(45.2%)** ***Persistent symptoms (defined as ≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (Male, n=89; Female, n=262)** Chest pain, n (%) Male: 53 **(59.6)** Female: 149 **(56.9)** **Moderate (Male, n=155; Female, n=183)** Chest pain, n (%) Male: 54 **(34.8)** Female: 88/182 **(48.4)** **Severe (Male, n=262; Female, n=213)** Chest pain, n (%) Male: 84/261 **(32.2)** Female: 97 **(45.5)** **New symptoms after recovery from acute illness** Chest pain, n (%): 514/809 **(63.5)**

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
		Clinical presentation of long COVID by calendar time according to variant predominance distribution **Ancestral (n=736) Period August 2020 to January 2021** Chest pain, n (%): 337/734 **(45.9)** **Gama Variant (n=249) Period March 2021 to July 2021** Chest pain, n (%): 95 **(38.2)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449): 30 days post-COVID-19, n (%)* Chest pain: 129 **(28.7)** Tachyarrhytmias: 168 **(37.4)** Pericarditis/myocarditis: 31 **(6.9)** Hypertension: 116 **(25.8)** *History of COVID-19 (n = 435): 180 days post-COVID-19, n (%)* Chest pain: 89 **(20.4)** Tachyarrhytmias: 91 **(20.9)** Pericarditis/myocarditis: 4 **(0.9)** Hypertension: 61 **(14.0)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *Severe medical issues after COVID-19 at 12 months follow-up, n (%)* Cardiovascular problems: 17 **(3.72)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of long COVID >4 weeks post-COVID-19, n (%)* Chest pain: 129 **(35.0)** Palpitations: 15 **(4.1)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Chest tightness: 198/807 **(24.5)** Palpitations: 165/803 **(20.5)** Chest pain: 124/804 **(15.4)** Leg/ankle swelling: 223/810 **(27.5)** *5 month (paired) data* Chest tightness: 157/599 **(26.2)** Palpitations: 122/588 **(20.7)** Chest pain: 105/600 **(17.5)** Leg/ankle swelling: 156/602 **(25.9)**

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
		1 year (paired) data Chest tightness: 145/599 **(24.2)** Palpitations: 122/588 **(20.7)** Chest pain: 87/600 **(14.5)** Leg/ankle swelling: 160/602 **(26.6)** *Symptoms measured by VAS 0-10 scale (within the PSQ), median IQR* Cough (n=751): 0.0 (0.0–2.0)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Oedema of lower limbs: 24 **(1.9)** Chest tightness: 195 **(15.8)** Palpitations: 66 **(5.4)** *Severe patients, n (%)* Oedema of lower limbs: 13 **(3.0)** Chest tightness: 94 **(21.5)** Palpitations: 29 **(0.6)** *Non-severe patients, n (%):* Oedema of lower limbs: 11 **(1.4)** Chest tightness: 101 **(12.7)** Palpitations: 37 **(4.7)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥2 months following COVID-19, n (%)* *Total, n=398* Palpitations: 61 **(15.4)** *Long COVID, n=124* Palpitations: 46 **(37.1)** *Full recovery, n=270* Palpitations: 14 **(5.2)**
Fernández-de-las-Peñas et al.[24]	Self-report via interview	*History of COVID-19 (n = 1,969)* Palpitations/tachycardia, n (%): 140 **(7.1)**

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
Spain		
Fernández-de-las-Peñas et al.[26] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,142)* *7 months post-COVID-19, n (%)* Chest pain: 80 **(7.0)** Tachycardia-palpitations: 77 **(6.5)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* *Symptoms ≥2 years post-COVID-19* Hospitalised vs non-hospitalised, n (%) Palpitations/tachycardia: 2 **(0.6)** vs 6 **(1.9)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan Post-COVID-19 Symptoms (mean follow-up 6.5 months), n (%)* Tachycardia: 3 **(1.4)** *Alpha Post-COVID-19 Symptoms (mean follow-up 6 months), n (%)* Tachycardia: 7 **(3.3)** *Delta Post-COVID-19 Symptoms mean follow-up 6.3 months), n (%)* Tachycardia: 8 **(4.0)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Additional symptoms*, n (%)* Chest pain: 143 **(20.0)** Oedema: 129 **(18.0)** *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Chest pain: 5 **(2.0)** Irregular heartbeat or racing heart: 11 **(5.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* **Hospitalised (n=447)** Cardiovascular, n (%) [95%CI]: 9 **(2.0)** [0.9-3.8] *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%)* Chest pain: 0 (**0**); 1 (**0.3**) p =0.49 Cardiovascular: 6 (**1.5**); 0 (**0**) p = 0.03

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547); Emergency Dept (n=212)* Chest pain, n (%): 76 **(13.9)**; 53 **(25.0)** Palpitations, n (%): 31 **(5.7)**; 32 **(15.1)**
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population at all 3 time points)	*History of COVID-19 (n = 1,192)* Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91) *6 months after symptom onset, n (%)* Palpitations: 108/1,151 **(9.0)**; 28/286 **(10.0)**; 66/776 **(9.0)**; 14/89 **(16.0)** Chest pain: 53/1,147 (**5.0**); 15/287 **(5.0)**; 34/772 **(4.0)**; 4/88 **(5.0)** *12 months after symptom onset, n (%)* Palpitations: 110/1,188 **(9.0)**; 19 **(6.0)**; 84/802 **(10.0);** 7 **(8.0)** Chest pain: 86/1,188 **(7.0)**; 23 **(8.0)**; 59/802 **(7.0)**; 4 **(4.0)** *2 years after symptom onset, n (%)* Palpitations: 145/1,190 **(12.0)**; 41/294 **(14.0)**; 95/805 **(12.0)**; 9 **(10.0)** Chest pain: 83/1,190 **(7.0)**; 19/294 **(6.0)**; 54/805 **(7.0)**; 10 **(11.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Palpitations: 174 (**15**); 50 (**4**) p < 0.0001 Chest pain: 91 (**8**); 18 (**2**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Chest pain, n (%): 158 **(39.0)** Palpitation, n (%): 126 **(31.0)** *6 months follow-up (n=406)*

Author Country	Long COVID assessment mode	Cardiovascular symptom cluster prevalence estimates
		Chest pain, n (%): 61 **(15.0)** Palpitation, n (%): 41 **(10.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* *6 month follow-up* *Cardiovascular, n (%), [95%CI]* Adults: 63/1,013 **(6.2)**, [4.7 to 7.7] Children: 4/360 **(1.1)**, [0.3 to 2.2] *12 month follow-up* *Cardiovascular, n (%), [95%CI]* Adults: 12/1,013 **(1.2)**, [0.6 to 1.9] Children: 1/360 **(0.3)**, [0.0 to 0.8]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n=453) vs non-exposed cohort - hospitalised due to other causes (n = 453) (matched by institution and date of admission)* Chest pain, n (%); p value: 5 **(1.1)** vs 8 **(1.8)**; 0.578
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No 58,581 (96) Yes 24,21 (4)* **Symptoms 6-12 months after test, n (%)** Chest pain: 121 **(5)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Palpitations, n (%)*: 40 **(9.0)** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.

Key: UK, United Kingdom, US, United States.

Respiratory Symptom Cluster

Twenty-four studies reported symptoms related to the respiratory cluster in adults only,[24-28, 30-32, 37, 38, 40, 41, 45, 47, 48, 52, 56, 65, 74, 85, 117-120] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates ranged from 3.9%[27] to 64.7%[38] in those with a history of COVID-19 and from 31%[117] to 83.1%[37] in those identified as having long COVID (see Table 4.14). Shortness of breath and cough were the most commonly reported symptoms, with prevalence estimates ranging from 3.9%[27] to 83.1%[37], and 2.0%[26] to 78.2%,[37] respectively.

The prevalence of respiratory symptoms was noted to differ by gender and over time. In those self-reporting long COVID, Barreto et al.[37] observed a higher prevalence of shortness of breath in males (71.8%) compared with females (65.3%), while the opposite was found in the reporting of cough (41.8% of adult females versus 38.7% of males).

Six studies investigated the persistence of respiratory symptoms over time.[25, 30, 45, 52, 66, 119] Two studies reported a reduction in the prevalence of shortness of breath over time, from 50.8% to 38.2% in a study reporting 30 and 180 days follow-up,[30] and from 17% to 14% in a study reporting six month and 12 month follow-up post-acute COVID-19.[25] Two studies also reported reductions in the prevalence of cough over time, with reductions from 29.8% to 20% in a study reporting 30 days and 180 days follow-up,[30] and from 18% to 3% in a study reporting follow-up at three months and six months post-acute COVID-19.[119] Two studies investigated differences in the prevalence of respiratory symptoms in matched cohorts. Huang et al.[52] reported a significantly higher prevalence of cough, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izquierdo et al.[22] reported no significant difference in the prevalence of respiratory symptoms in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.14. Respiratory symptom cluster prevalence estimates for those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Shortness of breath: 563 **(21.0)** Cough: 272 **(10.0)** Excess sputum: 171 **(6.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Shortness of breath: 347 **(17.0)** Cough: 139 **(7.0)** Excess sputum: 123 **(6.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Cough: 453/1,163 **(39.0)** Dyspnoea: 790/1,164 **(67.9)** mMRC≥2 (Only applied to patients reporting dyspnoea): 361/744 **(48.5)** Oxygen Saturation (Pulse Oximetry), Median (IQR): 97 (96–98) ***Persistent symptoms (≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (Male n=89; Female n=262)** *Cough, n (%)* Male: 35 **(39.3);** Female: 97 **(37.0)** *Dyspnoea, n (%)* Male: 58 **(65.2);** Female: 178 **(67.9)** *mMRC ≥ 2 (Only applied to patients reporting dyspnoea), n (%)* Male: 22 **(37.9);** Female: 75 **(44.6)** *Oxygen Saturation (Pulse Oximetry), Median (IQR)* Male: 97.0 (97.0–98.0); Female: 98.0 (97.0–99.0) **Moderate (Male n=155; Female n=183)**

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		Cough, n (%) Male: 56 **(36.1);** Female: 75 **(41.0)** *Dyspnoea, n (%)* Male: 98 **(63.2);** Female: 128 **(69.9)** *mMRC ≥ 2 (Only applied to patients reporting dyspnoea), n (%)* Male: 36 **(38.3);** Female: 56 **(46.7)** *Oxygen Saturation (Pulse Oximetry), Median (IQR)* Male: 97.0 (96.0–98.0); Female: 97.0 (96.0–98.0) **Severe (Male n=262; Female n=213)** *Cough, n (%)* Male: 101/261 **(38.7);** Female: 89/213 **(41.8)** *Dyspnoea, n (%)* Male: 188/262 **(71.8);** Female: 139/213 **(65.3)** *mMRC≥2 (Only applied to patients reporting dyspnoea), n (%)* Male: 93/172 **(54.1);** Female: 78/131 **(59.5)** *Oxygen Saturation (Pulse Oximetry), Median (IQR)* Male: 97.0 (96.0–98.0); Female: 97.0 (96.5–98.0) **New symptoms after recovery from acute illness (n, %)** Cough: 633/809 **(78.2)** Dyspnoea: 672/809 **(83.1)** ***Clinical presentation of LONG COVID by calendar time according to variant predominance distribution*** **Ancestral (n=736); Period August 2020 to January 2021, n (%)** Cough: 269/735 **(36.6)** Dyspnoea: 486 **(66.0)** **Gama Variant (n=249); Period March 2021 to July 2021, n (%)** Cough: 106 **(42.6)** Dyspnoea: 165 **(66.3)**

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	*History of COVID-19 (n = 801)* *At follow-up (3 to 11 months after hospital discharge), n (%)* Breathlessness: 514/795 **(64.7)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Dyspnoea/breathlessness: 228 **(50.8)** Cough: 134 **(29.8)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%)* Dyspnoea/breathlessness: 166 **(38.2)** Cough: 87 **(20.0)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was 105.9+53.0 (not hospitalised - 105.7 ±55.7 days and hospitalised - 106.8 ±61.5 days).* *Overall reported symptoms – hospitalised (n = 376), n (%)* Breathing problems: 55 **(13.2)** Cough: 185 **(44.4)** *Overall reported symptoms – non-hospitalised (n = 2,644), n (%)* Breathing problems: 335 **(11.7)** Cough: 1,207 **(42.0)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up, n (%) (symptom scale used in the study (o=no symptom, 10=maximum intensity, 5=presence if symptom))* Dyspnoea at rest (≥5): 57 **(12.5)** Exertional dyspnoea, n (%) mMRC 0: 128 **(28.3)** mMRC≥1: 324 **(71.7)** Cough: 73 **(16.1)** *Severe medical issues after COVID-19, n (%)* Respiratory problems: 5 **(1.1)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of Long COVID >4 weeks post-COVID-19, n (%)*

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		Dyspnoea: 198 **(53.7)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Breathlessness (n=769): 395 **(51.4)** Cough (n=771): 215 **(27.9)** Pain on breathing (n=807): 106 **(13.1)** *5 month (paired) data* Breathlessness: NA Cough: NA Pain on breathing: 65/593 **(11.0)** *1 year (paired) data* Breathlessness: 281/537 **(52.3)** Cough: 148/530 **(27.9)** Pain on breathing: 72/593 **(12.1)** Symptoms measured by VAS 0-10 scale (within the PSQ), Median (IQR) Breathlessness (n=747): 2.0 (0.0 – 5.0)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Dyspnoea: 44 **(3.6)** Cough: 71 **(5.8)** Expectoration: 53 **(4.3)** Haemoptysis: 1 **(0.1)** Shortness of breath: 53 **(4.3)** *Severe patients, n (%)* Dyspnoea: 22 **(5.0)** Cough: 34 **(7.8)** Expectoration: 26 **(5.9)** Shortness of breath: 30 **(6.8)** *Non-severe patients, n (%)* Dyspnoea: 22 **(2.8)** Cough: 37 **(4.7)** Expectoration: 27 **(3.4)** Haemoptysis: 1 **(0.1)**

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		Shortness of breath: 23 **(2.9)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥ 2months following COVID-19, n (%)* *Total (n=398)* Breathlessness: 165 **(41.7)** Cough: 75 **(18.9)** *Long COVID (n=124)* Breathlessness: 98 **(79.0)** Cough: 41 **(33.1.0)** *Full Recover (n=270)* Breathlessness: 66 **(24.4)** Cough: 33 **(12.2)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* Participants were assessed a mean of 8.4 months after hospital discharge. Dyspnoea at rest, n (%): 459 **(23.3)** Dyspnoea at exertion, n (%): 1,054 **(53.5)**
Fernández-de-las-Peñas et al.[25] Spain	Self-report via interview (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 412)* Post-COVID dyspnoea at 6 months, n (%): 71/412 **(17.0)** Post-COVID dyspnoea at 12 months, n (%): 56/412 **(14.0)**
Fernández-de-las-Peñas et al.[26] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,142)* *7 months post-COVID-19, n (%)* Dyspnoea with activity: 627 **(55.0)** No: 608 **(53.2)** Mild: 345 **(30.2)** Moderate 213 **(18.6)** Severe: 69 **(6.0)** Dyspnoea at rest: 268 **(23.5)** No: 874 **(76.5)** Mild: 199 **(17.4)** Moderate: 48 **(4.2)** Severe: 21 **(1.8)** Cough: 24 **(2.0)**

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* *Symptoms ≥2 Years Post-COVID-19, n (%)* *Hospitalised* Dyspnoea at rest: 14 **(3.9)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan Post-COVID-19 Symptoms (mean follow-up 6.5 months), n (%)* Dyspnoea: 59 **(29.4)** Cough: 3 **(1.5)** *Alpha Post-COVID-19 Symptoms (mean follow-up 6 months), n (%)* Dyspnoea: 29 **(13.8)** Cough: 9 **(4.2)** *Delta Post-COVID-19 Symptoms (mean follow-up 6.3 months), n (%)* Dyspnoea: 26 **(12.8)** Cough: 24 **(2.1)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Objective symptoms*, Median (IQR), % of total participants with abnormal result, n* Dyspnoea, score (0-5), (abnormal ≥2): 1 (0-2), **30.0**, 225 *Additional symptoms*, n (%)* Cough: 139 **(19.0)** *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Shortness of breath: 73 **(31.0)** Cough: 18 **(8.0)** Wheezing: 10 **(4.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the US	Self-report via caregivers (Single assessment time point)	*Children* *History of COVID-19 (n = 1,884)* ***Hospitalised (n=447)*** *Symptoms (n %)* Cough: 4 **(0.9)** Difficulty breathing, short of breath: 3 **(0.7)** Wheeze or asthma exacerbation: 1 **(0.2)**

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		Other respiratory symptoms or diagnoses: 7 **(1.6)** *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched Hospitalised SARS-CoV-2–negative children), n (%), [95%CI]* Cough: 4 (**1.0**); 2 (0.5) p =0.69 Difficulty breathing, short of breath: 3 (**0.8**); 0 (0) p =0.25 Wheeze or asthma exacerbation: 1 (**0.3**); 1 (0.3) p >0.99 Other respiratory symptoms or diagnoses: 6 (**1.5**); 3 (0.8) p = 0.51
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547); Emergency Dept (n=212)* Breathlessness: 211 **(38.6)**; 98 **(46.2)** Cough: 106 **(19.4)**; 56 **(26.4)**
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population in all 3 time points)	*History of COVID-19 (n = 1,192)* Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91) *6 months after symptom onset, n (%)* mMRC score 0: 816/1,104 **(74.0)**; 216/288 **(7.0%)**; 551/734 **(75.0)**; 49/82 **(60.0)** mMRC score ≥1: 288/1,104 **(26.0)**; 72/288 **(25.0)**; 183/734 **(25.0)**; 33/82 **(40.0)** *12 months after symptom onset, n (%)* mMRC score 0: 834/1,187 **(70.0)**; 222/294 **(76.0)**; 556/802 **(69.0)**; 56 **(62.0)** mMRC score ≥1: 353/1,187 **(30.0)**; 72/294 **(24.0)**; 246/802 **(31.0)**; 35 **(38.0)** *2 years after symptom onset, n (%)* mMRC score 0: 1,023/1,191 **(86.0)**; 253 **(86.0)**; 694/805 **(86.0)**; 76 **(84.0)** mMRC score ≥1: 168/1,191 **(14.0)**; 42 **(14.0)**; 111/805 **(14.0)**; 15 **(16.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Cough:108 (**10**); 41 (**4**) p < 0.0001

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		mMRC score of 0: 980 (**87**); 919 (**82**) mMRC score of ≥1: 147 (**13**); 208 (**18**) p < 0.0004
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *Three months follow-up (n=406)* Cough, n (%): 73 **(18.0)** *Six months follow-up (n=406)* Cough, n (%): 12 **(3.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* ***6 month follow-up, n (%), [95% CI]*** *Respiratory* Adults: 223/1,013 **(22.0)**, [19.5 to 24.7] Children: 7/360 **(1.9)**, [0.6 to 3.6] **12 month follow-up, *n (%), [95% CI]*** *Respiratory* Adults: 96/1,013 **(9.5)**; [7.7 to 11.3] Children: 4/360 **(1.1)**; [0.3 to 2.2]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n = 453) vs Non-exposed cohort - hospitalised due to other causes (n = 453) (matched by institution and date of admission)* Respiratory symptoms, n (%); p value: 87 **(19.2)** vs 72 **(15.9)**; 0.190 Dyspnoea, n (%); p value: 70 **(15.5)** vs 56 **(12.4)**; 0.179
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No 58,581 (96) Yes 2,421 (4)* **Symptoms 6-12 months after test, n (%)** Dyspnoea: 274 **(11.3)** Cough: 151 **(6.2)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* *Symptoms*, n (%)* Shortness of breath: 158/428 (**37.0**) Cough: 47/428 (**11.0**)

Author Country	Long COVID assessment mode	Respiratory symptom cluster prevalence estimates
		*The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	*History of COVID-19 (n = 1,038)* *30 days follow-up, n (%)* Shortness of breath: 147 **(63.6)** *At least 60 days follow-up, %* Shortness of breath: **13.9** Hospitalised patients. Shortness of breath: **15.4**

Key: UK, United Kingdom, US, United States.

Autonomic Nervous System Symptom Cluster

Five studies reported symptoms related to the autonomic nervous system in adults with a history of severe COVID-19 illness (See Appendix 9 Severe COVID-19, Table 2).[45, 56, 65, 117, 118] Prevalence estimates ranged from 4.5%[56] to 29.3%[45] in those with a history of COVID-19. For those with self-reported long COVID, 8% reported post-exertional malaise.[117] There was a lack of consistency in the symptoms reported relating to autonomic dysfunction across the included studies. Fang et al.[65] found that at one year post-acute COVID-19, 24% of adults reported sweating as a symptom. Sorensen et al.[56] found that at 6-12 month follow-up, 4.5% of participants reported hot flushes and or sweating as a symptom.

Asadi-Pooya et al.[118] found that 2% of adults reported a loss of libido, although this was not specified to a follow-up time point. Evans et al.[45] found that at one year post-acute COVID-19, 29.3% of male adults reported erectile dysfunction as a symptom.

Psychological and or Psychiatric Symptom Cluster

Eighteen studies reported symptoms related to the psychological and or psychiatric cluster in adults with a history of severe COVID-19 illness.[22, 24, 27, 30-32, 38-41, 45, 52, 65, 85, 117-119] Prevalence estimates ranged from 4.0%[118] to 57.3%[38] in those with a history of COVID-19, and from 13%[117] to 56.1%[85] in those identified as having long COVID (see Table 4.15). Anxiety and or depression were the most commonly reported symptoms, with prevalence estimates ranging from 7.3%[22] to 57.3%.[38] Three studies investigated the persistence of psychological and or psychiatric symptoms over time, using repeated assessments.[30, 45, 119] Two studies reported a reduction in the prevalence of anxiety over time, from 51.2% to 33.1% in a study reporting 30 and 180 days follow-up post-acute COVID-19,[30] and from 20% to 3% in a study reporting follow-up at three months and six months post-acute COVID-19.[119] One study reported a decrease in the prevalence of depression over time from 23.4% to 8.9% at 30 and 180 days follow-up post-acute COVID-19,[30] and one study reported similar prevalence estimates for altered personality at 5 months (21.5%) and one year (20.2%) post-acute COVID-19.[45] Rivera-Izquierdo et al.[22] reported significantly higher prevalence of anxiety symptoms, but no difference in the prevalence of general mental health or depressive symptoms in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.15. Psychological and or psychiatric symptom cluster prevalence estimates for those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations at each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Anorexia: 104 **(4.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Anorexia: 65 **(3.0)**
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	*History of COVID-19 (n = 801)* *At follow-up (3 to 11 months after hospital discharge), n (%)* Anxiety and depression: 457/798 **(57.3)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Anxiety: 230 **(51.2)** Major depression: 105 **(23.4)** Psychosis: 51 **(11.3)** Behaviour disorder: 23 **(5.1)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%):* Anxiety: 144 **(33.1)** Major depression: 39 **(8.9)** Psychosis: 9 **(2.0)** Behaviour disorder: 6 **(1.4)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was hospitalised - 106.8 ±61.5 days.* *Overall reported symptoms – hospitalised (n = 376), n (%)* Changes in mood or anxiety or depression: 176 **(42.2)** Nightmares or flashbacks: 53 **(12.7)** PTSD symptoms: 75 **(18)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up, n* (%) *(symptom scale used in the study (o=no symptom, 10=maximum intensity, 5=presence if symptom))*

Author Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
		Anxiety (>5): 104 **(23.2)**
Damiano et al.[39] Brazil	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 701)* ***6-11 months post-hospitalisation*** *Clinical Interview Schedule-Revised (CIS-R)* Depression: **7.5%** Panic disorder: **0.8%** Agoraphobia: **1.5%** Social phobia: **0.8%** Specific phobia: **2.1%** Generalized anxiety disorder: **15.1%** Obsessive–compulsive disorder: **3.1%** Mixed depressive and anxiety disorder: **13.5%** Common mental disorder: **30%** *Psychiatric assessment* PTSD prevalence **13.4**% Last-year suicidal attempt: **2.4%** Last 4 weeks suicidal ideation **10.1%** Hospital Anxiety and Depression Scale anxiety, mean (±SD): 6.0 (5.1) Hospital Anxiety and Depression Scale depression, mean (±SD): 4.8 (4.6)
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of Long COVID >4 weeks post-COVID-19, n (%)* Depression and anxiety (n=361): 199 (**55.1**)
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Altered personality/behaviour ('not the same person'): 171/812 **(21.1)** *5 month (paired) data* Altered personality/behaviour ('not the same person'): 131/608 **(21.5)** *1 year (paired) data* Altered personality/behaviour ('not the same person'): 123/608 **(20.2)**
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Anxiety: 141 **(11.4)** *Severe patients, n (%)*

Author Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
		Anxiety: 56 **(12.8)** *Non-severe patients, n (%)* Anxiety: 85 **(10.7)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥2 months following COVID-19, n (%)* *Total (n=398)* Nightmares or flashbacks: 34 **(8.6)** Low mood: 103 **(26.1)** Anxiety: 112 **(28.4)** *Long COVID (n=124)* Nightmares or flashbacks: 29 **(23.4)** Low mood: 69 **(56.1)** Anxiety: 63 **(50.8)** *Full Recovery (n=270)* Nightmares or flashbacks: 5 **(1.9)** Low mood: 33 **(12.2)** Anxiety: 48 **(17.8)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* Participants were assessed a mean of 8.4 months after hospital discharge. HADSA (0–21), mean (±SD): 4.9 (±5.3) Anxiety (HADSA ≥12 points), n (%): 308 **(15.6)** HADSD (0–21), mean (±SD): 4.7 (±4.8) Depression (HADSD ≥10 points), n (%): 373 **(18.9)** Sleep Quality (0–21) mean (±SD): 6.5 ± 4.0 Poor Sleep Quality (PSQI ≥8 points), n (%): 674 **(34.2)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* ***Symptoms ≥2 Years Post-COVID-19, n (%)*** *Hospitalised, mean (±SD)* HADS-A score (range, 0-21): 1.2 (±1.9) HADS-D score (range, 0-21): 1.7 (±2.4) PSQI score (range, 0-21): 6.5 (±3.7)
Ferreira et al.[41]	Self-report via questionnaire	*History of COVID-19 (n = 749)*

Author Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
Brazil	(Single assessment time point)	*Objective symptoms*, Median (IQR), % of total participants with abnormal result, n* Posttraumatic stress disorder, score (0-85), (abnormal if ≥30): 24 (19-36); **35.0,** 262 Anxiety, points (0-21) (abnormal if >8): 5 (2-9); **26.0,** 195 Depression, points (0-21) (abnormal if >8): 3 (1-7); **22.0,** 165 *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*History of COVID-19* *Scores on tests of function, cognition, and neurological quality of life at 6 months, Mean (±SD)* NeuroQoL anxiety, (abnormal T-score ≥ 60): 48.4 (±9.0) NeuroQoL depression (abnormal T-score ≥ 60): 44.6 (±8.0) *Scores on tests of function, cognition, and neurological quality of life at 12 months, Mean (±SD)* NeuroQoL anxiety, (abnormal T-score ≥ 60): 46.8 (±9) NeuroQoL depression (abnormal T-score ≥ 60): 44.3 (±8.0) *Abnormal or poor scores at 6 months, n (%)* NeuroQoL anxiety: 21/280 **(8.0)** NeuroQoL depression: 8/279 **(3.0)** *Abnormal or poor scores at 12 months, n (%)* NeuroQoL anxiety: 16/225 **(7.0)** NeuroQoL depression: 9/225 **(4.0)** *Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Anxiety: 30 **(13.0)** Depression/sadness: 27 (**11.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* **Hospitalised (n=447)** *Symptoms, n (%)* Anxiety: 4 **(0.9)** Depression: 3 **(0.7)** Other psychological symptoms or diagnoses: 4 **(0.9)** *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%), p value*

Author Country	Long COVID assessment mode	Psychological/Psychiatric symptom cluster prevalence estimates
		Anxiety: 4 (**1.0**); 1 (**0.3**) p =0.37 Depression: 3 (**0.8**); 2 (**0.5**) p >0.99 Other psychological symptoms or diagnoses: 4 (**1.0**); 3 (**0.8**) p >0.99
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population at all 3 time points)	*History of COVID-19 (n = 1,192)* Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91) **2 years after symptom onset** Anxiety symptom (GAD-7≥5): 98/1,187 **(8.0)**; 26/294 **(9.0)**; 66/802 **(8.0)**; 6 **(7.0)** Depression symptom (PHQ-9≥5): 75/1,190 **(6.0)**; 25 **(8.0)**; 45/804 **(6.0)**; 5 **(5.0)** PTSD symptom (PCL-C ≥38): 27/1,189 **(2.0)**; 12 **(4.0)**; 14/803 **(2.0)**; 1 **(1.0)**
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Anxiety, n (%): 81 **(20.0)** *6 months follow-up (n=406)* Anxiety, n (%): 12 **(3.0)**
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n=453) vs Non-exposed cohort - hospitalised due to other causes (n = 453)(matched by institution and date of admission)* Mental health symptoms, n (%); p value: 48 **(10.6)** vs 46 **(10.2)**; 0.828 Depressive symptoms, n (%); p value: 22 **(4.9)** vs 20 **(4.4);** 0.752 Anxiety symptoms, n (%); p value: 33 **(7.3)** vs 19 **(4.2);** 0.046
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Anxiety/depression*: **9.0%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.

Key, PTSD, Post-traumatic stress disorder; UK, United Kingdom; US, United States.

Ear, Nose, and Throat Symptom Cluster

Twenty-three studies reported symptoms related to the ear, nose and throat cluster in adults only,[22, 24, 27, 28, 30-32, 37-41, 45, 47, 52, 56, 65, 70, 74, 85, 117-119] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates for ENT symptoms ranged from 1.7%[39] to 64.4%[30] in those with a history of COVID-19, and from 10.0%[117] to 58.5%[37] in those identified as having long COVID (see Table 4.16). The most commonly reported symptoms were anosmia (loss of smell) and ageusia (loss of taste), with prevalence estimates ranging from 4.1%[24] to 64.4%[30] and 2.7%[24] to 49.8%,[30] respectively.

Differences in prevalence estimates among adults were noted by sex and over time. Barreto et al.[37] found a higher prevalence of loss of smell among females compared with males (13.1% versus 9.1%), in those self-reporting long COVID. Five studies investigated the persistence of ENT symptoms over time.[30, 45, 52, 66, 119] Two studies reported reductions in the prevalence of anosmia over time, with reductions from 64.4% to 53.7% in a study reporting 30 and 180 days follow-up post-acute COVID-19,[30] and from 17% to 14% in a study reporting follow-up at six and 12 months.[119] Prevalence estimates of anosmia reported by Huang et al.[52] reduced significantly from 11% at six months post-acute COVID-19 to 5% at 12 months post-acute COVID-19, but remained stable at two years follow-up. Three studies reported a reduction in the prevalence of ageusia over time, with 3% to 0%,[119] and 8% to 3%[52] at six months and 12 months follow-up post-acute COVID-19, and from 11.6% to 8.7% at five months and one year follow-up,[45] respectively. Finally, Boglione et al.[30] reported a significant increase in the prevalence of ageusia over time from 47.4% to 49.8% from 30 to 180 days post-acute COVID-19.[30]

Two studies used investigated differences in the prevalence of ENT symptoms in matched studies. Huang et al.[52] reported a significantly higher prevalence of sore throat, smell disorder and taste disorder, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izguierdo et al.[22] reported a significantly higher prevalence of pharyngeal, but not otorhinolaryngological symptoms in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.16. Ear nose and throat symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Loss of smell: 123 **(5.0)** Loss of taste: 78 **(3.0)** Sore throat: 124 **(5.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Loss of smell: 92 **(5.0)** Loss of taste: 54 **(3.0)** Sore throat: 74 **(4.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Dysphagia (n=1,143): 55 **(4.8)** Dysphonia (n=1,143): 61 **(5.3)** Olfactory dysfunction (n=1,006): 174 **(17.3)** ***Persistent symptoms (≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (Male n=89; Female n=262)** *Dysphagia, n (%)* Male: 4/88 **(4.5);** Female: 17/259 **(6.6)** Dysphonia, *n (%)* Male: 3/88 **(3.4);** Female: 13/257 **(5.1)** Olfactory dysfunction, *n (%)* Male: 13/82 **(15.9);** Female: 76/245 **(31.0)** **Moderate (Male n=155; Female n=183)** Dysphagia, *n (%)* Male: 7/153 **(4.6);** Female: 7/182 **(3.8)**

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Dysphonia, *n (%)* Male: 6/153 **(3.9);** Female: 6/182 **(3.3)** Olfactory dysfunction, *n (%)* Male: 10/131 **(7.6);** Female: 32/154 **(20.8)** **Severe (Male n=262; Female n=213)** Dysphagia, *n (%)* Male: 4/255 **(1.6);** Female: 16/206 **(7.8)** Dysphonia, *n (%)* Male: 15/257 **(5.8);** Female: 19/206 **(9.2)** Olfactory dysfunction, *n (%)* Male: 20/219 **(9.1);** Female: 23/175 **(13.1)** **New symptoms after recovery from acute illness, n (%)** Olfactory dysfunction (n=808): 473 **(58.5)** **Clinical presentation of long COVID by calendar time according to variant predominance distribution** **Ancestral (n=736); Period August 2020 to January 2021, n (%)** Dysphagia (n=734): 36 **(4.9)** Dysphonia (n=734): 39 **(5.3)** Smell Loss (n=620): 130 **(21.0)** **Gama Variant (n=249) Period March 2021 to July 2021, n (%)** Dysphagia (n=233): 9 **(3.9)** Dysphonia (n=234): 12 **(5.1)** Smell Loss (n=232): 23 **(9.9)**
Battistella et al.[38] Brazil	Functional assessment in-person (Single assessment time point)	*History of COVID-19 (n = 801)* *At follow-up (3 to 11 months after hospital discharge), n (%)* Restricted oral intake (n=783): 56 **(7.2)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Anosmia: 289 **(64.4)**

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Ageusia/dysgeusia: 213 **(47.4)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%)* Anosmia: 234 **(53.7)** Ageusia/dysgeusia: 217 **(49.8)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was hospitalised - 106.8 ±61.5 days).* *Overall reported symptoms – hospitalised (n = 376), n (%)* Anosmia or ageusia: 128 **(31.9)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up, n (%) (symptom scale used in the study (o=no symptom, 10=maximum intensity, 5=presence if symptom))* Smell disorder (<5): 18 **(4.0)** Taste disorder (<5): 13 **(2.9)**
Damiano et al.[39]	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 701)* *6-11 months post-hospitalisation, n (%)* Olfactory hallucinations: 12 (**1.7**) gustatory hallucinations: 9 (**1.3**) Of those with olfactory and gustatory hallucinations, 72.7% and 87.5% reported that these symptoms were not present prior to COVID-19.
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of long COVID >4 weeks post-COVID-19, n (%)* Anosmia: 52 **(14.1)** Dysgeusia: 50 **(13.6)** Both anosmia and dysgeusia: 25 **(6.8)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Problems with balance (n=811): 250 **(30.8)** Loss of sense of smell (n=808): 86 **(10.6)** Loss of taste (n=812): 79 **(9.7)** *5 month (paired) data* Problems with balance: 210/601 (**34.9**)

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Loss of sense of smell: 67/601 (**11.1**) Loss of taste: 70/606 (**11.6**) *1 year (paired) data* Problems with balance: 180/601 (**30.0**) Loss of sense of smell: 60/601 (**10.0**) Loss of taste: 53/606 (**8.7**)
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Sore throat: 12 **(1.0)** Nasal congestion: 2 **(0.2)** Smell reduction: 21 **(1.7)** Taste change: 23 **(1.9)** *Severe patients, n (%)* Sore throat: 7 **(1.6)** Nasal congestion: 1 **(0.2)** Smell reduction: 12 **(2.7)** Taste change: 11 **(2.5)** *Non-severe patients, n (%)* Sore throat: 5 **(0.6)** Nasal congestion: 1 **(0.1)** Smell reduction: 9 **(1.1)** Taste change: 12 **(1.5)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* ***Symptoms ≥2 months following COVID-19, n (%)*** *Total (n=398)* Anosmia: 53 **(13.4)** Ageusia: 52 **(13.2)** *Long COVID (n=124)* Anosmia: 25 **(20.1)** Ageusia: 26 **(21.0)** *Full Recovery (n=270)*

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Anosmia: 28 **(10.4)** Ageusia: 26 **(9.7)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* Participants were assessed a mean of 8.4 months after hospital discharge. Voice Problems, n (%): 35 **(1.8)** Ageusia, n (%): 53 **(2.7)** Anosmia, n (%): 80 **(4.1)** Throat Pain, n (%): 50 **(2.5)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* *Symptoms ≥2 years Post-COVID-19* *Hospitalised, n (%)* Voice problems: 1 **(0.3)** Ageusia: 4 **(1.1)** Anosmia: 16 **(4.4)** Throat pain: 6 **(1.7)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan Post-COVID-19 Symptoms (mean follow-up 6.5 months), n (%)* Ageusia: 10 **(5.0)** Anosmia: 3 **(1.5)** *Alpha Post-COVID-19 Symptoms (mean follow-up 6 months), n (%)* Ageusia: 9 **(4.2)** Anosmia: 12 **(5.7)** *Delta Post-COVID-19 Symptoms (mean follow-up 6.3 months), n (%)* Ageusia: 10 **(5.0)** Anosmia: 12 **(6.0)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Objective symptoms*, Median (IQR), % of total participants with abnormal result, n* Ageusia, VAS (0-100), (abnormal if ≤80): 100 (85-100); **23.0,** 172 Anosmia, VAS (0-100), (abnormal if ≤80): 100 (84-100); **21.0**, 157 *Additional symptoms*, n (%)* Nasal obstruction: 118 **(16.0)**

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Tinnitus: 110 **(15.0)** Hearing loss: 106 **(14.0)** *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Persistent loss of taste/smell: 7 **(3.0)** Difficulty swallowing: 4 **(2.0)** Problems with balance: 24 **(10.0)** Loss of hearing: 3 **(1.0)** Ringing in the ears: 3 **(1.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* **Hospitalised (n=447)** *Symptoms* Runny nose or congestion, n (%): 2 **(0.5)** Loss of smell or taste, n (%): 2 **(0.5)** Ophthalmologic and/or otolaryngologic, n (%), [95%CI]: 2 **(0.5)**, [0.1 to 1.6] *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%), p value* Runny nose or congestion: 2 (**0.5**); 1 (**0.3**) p >0.99 Loss of smell or taste: 2 (**0.5**); 0 (**0**) p =0.5 Ophthalmologic and/or otolaryngologic: 2 (**0.5**); 0 (**0**) p =0.5
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547); Emergency Dept (n=212)* Anosmia, n (%):29 **(5.3)**; **15 (7.1)**
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population at all 3 time points)	*History of COVID-19 (n = 1,192)* *Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91)* *6 months after symptom onset, n (%)*

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Smell disorder: 128/1,151 **(11.0)**; 32/286 **(11.0)**; 82/776 **(11.0)**; 14/89 **(16.0)** Taste disorder: 87/1,151 **(8.0)**; 21/286 **(7.0)**; 58/776 **(7.0);** 8/89 **(9.0)** Sore throat or difficult to swallow: 45/1,151 **(4.0)**; 18/286 **(6.0);** 23/776 **(3.0);** 4/89 **(4.0)** *12 months after symptom onset, n (%)* Smell disorder: 56/1,188 **(5.0)**; 16 **(5.0);** 34/802 **(4.0);** 6 **(7.0)** Taste disorder: 35/1,188 **(3.0)**; 6 **(2.0);** 29/802 **(4.0);** 0 **(0.0)** Sore throat or difficult to swallow: 40/1,188 **(3.0)**; 11 **(4.0);** 26/802 **(3.0);** 3 **(3.0)** *2 years after symptom onset, n (%)* Smell disorder: 67/1,190 **(6.0);** 21/294 **(7.0);** 42/805 **(5.0);** 4 **(4.0)** Taste disorder: 35/1,190 **(3.0);** 11/294 **(4.0);** 20/805 **(2.0);** 4 **(4.0)** Sore throat or difficult to swallow: 64/1,190 **(5.0);** 20/294 **(7.0);** 40/805 **(5.0);** 4 **(4.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Sore throat or difficult to swallow: 94 (**8**); 9 (**1**) p < 0.0001 Smell disorder: 68 (**6**); 4 (**<1**) p < 0.0001 Taste disorder: 33 (**3**); 3 (**<1**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *Three months follow-up (n=406)* Taste disorder, n (%): 12 **(3.0)** Vertigo, n (%): 20 **(5.0)** *Six months follow-up (n=406)* Taste disorder, n (%): 0 **(0.0)** Vertigo, n (%): 4 **(1.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* ***6 month follow-up*** *Sensory, n (%), [95%CI]* Adults (n=1,013): 36 **(3.6),** [2.5 to 4.7] Children (n=360): 3 **(0.8), [**0.0 to 1.9] ***12 month follow-up*** *Sensory, n (%), [95%CI]* Adults (n=1,013): 18 (**1.8**), [1.0 to 2.7]

Author, Country	Long COVID assessment mode	Ear, Nose and Throat symptom cluster prevalence estimates
		Children (n=360): 1 (**0.3**), 0.0 to 0.8]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n= 53) vs Non-exposed cohort - hospitalised due to other causes (n=453)(matched by institution and date of admission)* Pharyngeal symptoms, n (%), p-value: 16 **(3.5)** vs 2 **(0.4)**, <0.001 Otorhinolaryngological symptoms, n (%), p-value: 6 **(1.3)** vs 8 **(1.8),** 0.590
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No 58,581 (96) Yes 2,421 (4)* **Symptoms 6-12 months after test, n (%)** Sore throat: 95 **(3.9)** Runny nose: 92 **(3.8)** Dysgeusia: 184 **(7.6)** Dysomnia: 188 **(7.8)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Anosmia*: **8%** Dysgeusia*: **8%** Impaired hearing*: **4%** Vertigo*: **3%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	*History of COVID-19 (n = 1,038)* *At least 60 days follow-up* Loss of taste or smell: **9.8%** Outpatients. Loss of taste or smell: **15.9%**

Key: UK, United Kingdom; US, United States.

Musculoskeletal Symptom Cluster

Nineteen studies reported symptoms related to the musculoskeletal symptom cluster for adults only,[23, 30-32, 37, 38, 40, 41, 45, 47, 52, 56, 65, 74, 85, 117-120] and one study focused on prevalence estimates for both children and adults (see Table 4.17).[66] Prevalence estimates ranged from 7%[32] to 73%[52] in those with a history of COVID-19 and from 11%[117] to 72.2%[37] in those identified as having long COVID. The most commonly reported symptoms were myalgia and or arthralgia, with prevalence estimates ranging from 7%[32] to 73%.[52]

Barreto et al.[37] found higher reporting of myalgia in females compared to males (46.9% versus 32.6%), in those self-reporting long COVID. Six studies investigated the persistence of musculoskeletal symptoms in adults over time with mixed findings.[30, 45, 52, 66, 118, 119] Three studies reported reductions in the prevalence of myalgia over time, from 21% to 15% in one study with follow-up for the periods three to six months and six to 12 months post-acute COVID-19,[118] from 40.0% to 25.7% in a study with 30 and 180 day follow-up[30] and from 16% to 3% in a study with follow-up at three and six months post-acute COVID-19.[119] In contrast, Huang et al.[52] identified that the prevalence of myalgia increased over time from 3% to 4% to 7% at six month, 12 month and two years follow-up, respectively, and Evans et al.[45] reported similar prevalence estimates for myalgia at 5 months (55.4%) and one year (53.7%). There were mixed findings also with respect to the prevalence of arthralgia over time. Two studies reported a reduction in prevalence over time, from 18% to 15% for the time periods three to six months and six to 12 months post-acute COVID-19,[118] and from 27% to 6% at three months and six months post-acute COVID-19.[119] However, the study by Huang et al.[52] found no significant change in the prevalence of arthralgia over time (prevalence 11%, 12% and 10% at six months, 12 months and two years follow-up, respectively) and Evans et al.[45] reported similar prevalence estimates for arthralgia at 5 months (49.1%) and one year (48.7%).

Two studies investigated differences in the prevalence of neurological symptoms in matched cohorts. Huang et al.[52] reported a significantly higher prevalence of joint pain, myalgia, and fatigue or muscle weakness, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izquierdo et al.[22] reported no difference in the prevalence of muscle or joint pain, or muscle weakness in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.17. Musculoskeletal cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Weakness: 543 **(20.0)** Muscle pain: 562 **(21.0)** Joint pain: 491 **(18.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Weakness: 278 **(14.0)** Muscle pain: 291 **(15.0)** Joint pain: 296 **(15.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Myalgia (excluding Chest pain), n (%): 457/1,163 **(39.3)** ***Persistent symptoms (≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (Male n=89; Female n=262)** Myalgia (excluding Chest pain), n (%) Male: 26 **(29.2);** Female: 106 **(40.5)** **Moderate (Male n=155; Female n=183)** Myalgia (excluding Chest pain), n (%) Male: 44 **(28.4)**; Female: 96 **(52.5)** **Severe (Male n=262; Female n=213)** Myalgia (excluding Chest pain), n (%) Male: 85/261 **(32.6)** Female: 100 **(46.9)** **New symptoms after recovery from acute illness** Myalgia, n (%): 583/807 **(72.2)** ***Clinical presentation of long COVID by calendar time according to variant predominance distribution*** **Ancestral (n=736), Period August 2020 to January 2021, n (%)**

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
		Myalgia: 273/735 **(37.1)** **Gama Variant (n=249), Period March 2021 to July 2021, n (%)** Myalgia: 106 **(42.6)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Myalgias/arthralgias: 181 **(40.0)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%)* Myalgias/arthralgias: 112 **(25.7)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was hospitalised - 106.8 ±61.5 days).* *Overall reported symptoms – hospitalised (n = 376), n (%)* Myalgia or arthralgia: 213 **(51.1)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up (n %)* Myalgia: 94 **(22.3)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of long COVID >4 weeks post-COVID-19, n (%)* Arthralgia: 207 **(56.1)** Myalgia: 189 **(51.2)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Myalgia (n=809): 442 **(54.6)** Arthralgia (n=803): 382 **(47.6)** *5 month (paired) data* Myalgia: 334/603 (55.4) Arthralgia: 289/589 (49.1) *1 year (paired) data* Myalgia: 324/603 (53.7) Arthralgia: 287/589 (48.7)
Fang et al.[65]	Self-report via questionnaire	*History of COVID-19 (n = 1,233)*

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
China	(Single assessment time point)	*Symptoms at 1-year follow-up, n (%)* Myalgia: 111 **(9.0)** *Severe patients, n (%)* Myalgia: 52 **(11.9)** *Non-severe patients, n (%)* Myalgia: 59 **(7.4)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥2 months following COVID-19* *Total (n=398)* Myalgia, n (%): 114 **(28.9)** *Long COVID (n=124)* Myalgia, n (%): 74 **(59.7)** *Full recovery (n=270)* Myalgia, n (%): 39 **(14.5)**
Fernández-de-las-Peñas et al.[23] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* The prevalence of new-onset post-COVID musculoskeletal pain in the total sample was up to 74.9%. Follow-up was 8.4 months (SD 1.5, range 6 to 10 months) after hospital discharge. Musculoskeletal pain symptoms post-COVID, n (%): 887 **(45.1)** No musculoskeletal pain symptoms post-COVID, n (%): 1,082 **(54.9)** 442/887 **(49.8%)** of patients reporting musculoskeletal pain post-COVID also reported musculoskeletal pain symptoms before infection. 445/887 **(50.1%)** of patients reporting musculoskeletal pain post-COVID, reported new-onset musculoskeletal pain post-COVID. 220/442 **(24.8%)** individuals experiencing previous symptoms, reported that post-COVID pain symptoms were different from previous symptomatology (new-onset musculoskeletal pain post-COVID). 222/442 **(25.1%)** patients experienced an increase in the previous symptoms (exacerbated musculoskeletal pain post-COVID) on their:

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
		intensity, n (%): 89 **(40.1)** extension, n (%): 42 **(18.9)** frequency, n (%): 55 **(24.8)** intensity and extension, n (%): 36 **(16.2)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Objective symptoms*, Median (IQR), % of total participants with abnormal result, n* Muscle/joint pain, VAS (0-100) (abnormal if ≥65): 40 (10-65), **41.0,** 307 *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Joint pain/ache: 20 **(8.0)** Stiffness of muscles: 17 **(7.0)** Weakness of arms or legs: 25 **(11.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* ***Hospitalised (n=447)*** *Symptoms, n (%)* Muscle, joint, or body pain: 1 **(0.2)** *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%), p value* Muscle, joint, or body pain: 1 (**0.3**); 2(0.5) p =0.62
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547); Emergency Dept (n=212)* Arthralgia, n (%):40 **(7.3);** 20 **(9.4)** Postural symptoms, n (%):14 **(2.6);** 17 **(8.0)** Myalgia, n (%):57 **(10.4);** 26 **(12.3)**
Huang et al.[52] China	Self-report via interview (3 assessment time points, same population at all 3 time points)	*History of COVID-19 (n = 1,192)* *Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91).* *6 months after symptom onset, n (%)*

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
		Joint pain: 126/1,147 **(11.0);** 40/287 **(14.0);** 70/772 **(9.0);** 16/88 **(18.0)** Myalgia: 31/1,147 **(3.0);** 9/287 **(3.0);** 19/772 **(2.0);** 3/88 **(3.0)** Fatigue or muscle weakness: 593/1,151 **(52.0);** 143/286 **(50.0);** 385/776 **(50.0);** 65/89 **(73.0)** *12 months after symptom onset, n (%)* Joint pain: 141/1,188 **(12.0);** 33 **(11.0);** 93/802 **(12.0);** 15 **(16.0)** Myalgia: 50/1,188 **(4.0);** 11 **(4.0);** 34/802 **(4.0);** 5 **(5.0)** Fatigue or muscle weakness: 240/1,188 **(20.0);** 60 **(20.0);** 161/802 **(20.0);** 19 **(21.0)** *2 years after symptom onset, n (%)* Joint pain: 117/1,190 **(10.0);** 30/294 **(10.0);** 79/805 **(10.0);** 8 **(9.0)** Myalgia: 88/1,190 **(7.0);** 22/294 **(7.0);** 59/805 **(7.0);** 7/8 **(8.0)** Fatigue or muscle weakness: 357/1,190 **(30.0);** 89/294 **(30.0);** 235/805 **(29.0);** 33 **(36.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Joint pain: 202 (**18**); 94 (**8**) p < 0.0001 Myalgia: 94 (**8**); 9 (**1**) p < 0.0001 Fatigue or muscle weakness: 351 (**31**); 55 (**5**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Muscle pain, n (%): 65 **(16.0)** Joint pain, n (%): 110 **(27.0)** Back pain, n (%): 41 **(10.0)** *6 months follow-up (n=406)* Muscle pain, n (%): 12 **(3.0)** Joint pain, n (%): 24 **(6.0)** Back pain, n (%): 16 **(4.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* ***6 months follow-up*** *Musculoskeletal, n (%), [95%CI]* Adults (n=1,013): 87/1013 **(8.6)**; 95% CI: 6.91% to 10.37% Children (n=360): 6/360 **(1.7)**; 95% CI: 0.56% to 3.06% ***12 months follow-up*** *Musculoskeletal, n (%), [95%CI]*

Author Country	Long COVID assessment mode	Musculoskeletal symptom cluster prevalence estimates
		Adults (n=1,013): 31 **(3.1)**, [2.1 to 4.2] Children (n=360): 3 **(0.8),** [0.0 to 1.9]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n = 453) vs Non-exposed cohort - hospitalised due to other causes (n = 453)(matched by institution and date of admission)* Muscle or joint pain, n (%); p-value: 42 **(9.3)** vs 48 **(10.6**); 0.505 Muscle weakness, n (%); p=value: 14 **(3.1)** vs 8 **(1.8);** 0.195
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No 58,581 (96) Yes 2,421 (4)* **Symptoms 6-12 months after test, n (%)** Reduced strength legs/arms: 302 **(12.5)** Muscle/joint pain: 201 **(8.3)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Myalgia*: **7%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	*History of COVID-19 (n = 1,038)* *30 days follow-up, n (%)* Muscle aches: 117 (**50.6)**

Key: UK, United Kingdom; US, United States.

Gastrointestinal Symptom Cluster

Twenty studies reported symptoms related to the gastrointestinal symptom for adults only,[24, 27, 28, 30-32, 37, 40, 41, 45, 47, 52, 56, 65, 70, 85, 117-120] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates ranged from 1.4%[65] to 41.4%[30] in those with a history of COVID-19, and from 5%[117] to 58.7%[37] in those identified as having long COVID (see Table 4.18). Diarrhoea and weight loss were the most commonly reported symptoms, with prevalence estimates ranging from 0.8%[65] to 40.7%[37] and 9.0%[118] to 54.9%,[85] respectively. Differences in prevalence estimates for adults were noted by sex and over time.

Two studies reported a decrease in the prevalence of diarrhoea prevalence over time in adults, with one study reporting a decrease from 3% to 2% from the three to six month period to the six to 12 month period,[118] and another reporting a decrease from 4% to 0% from three to six months post-acute COVID-19.[119] Barreto et al.[37] found a higher prevalence of loss of appetite among females compared to males (13.2% versus 17.9%), in those self-reporting with long COVID. Two studies reported a reduction in the prevalence of loss of appetite in adults over time, with one study reporting a decrease from 8% to 3% observed from six month to two-year follow-up,[52] and another study reported a decrease from 6.2% to 1.3% from six months to 12 months post-acute COVID-19.[66] Two studies investigated differences in the prevalence of neurological symptoms in matched cohorts. Huang et al.[52] reported a significantly higher prevalence of decreased appetite and of nausea or vomiting, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izquierdo et al.[22] reported significantly lower prevalence of digestive symptoms, and specifically lower prevalence of diarrhoea and abdominal pain in those previously hospitalised with COVID-19 compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.18. Gastrointestinal symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations at each time point)	*History of COVID-19 (n = 2,685)* *3-6 month follow-up, n (%)* Diarrhoea: 73 **(3.0)** Abdominal pain: 88 **(3.0)** Weight loss: 251 **(9.0)** Weight gain: 147 **(5.0)** *History of COVID-19 (n = 1,996)* *6-12 month follow-up, n (%)* Diarrhoea: 42 **(2.0)** Abdominal pain: 56 **(3.0)** Weight loss: 130 **(7.0)** Weight gain: 101 **(5.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent symptoms ≥1 month post the acute phase of infection, n (%)*** Gustatory dysfunction (n=1,029): 167 **(16.2)** Loss of appetite (n=1,148): 176 **(15.3)** ***Persistent symptoms (≥1 month post the acute phase of infection) separated by sex and disease severity*** **Mild (Male n=89; Female n=262)** *Gustatory dysfunction, n (%)* Male: 9/84 **(10.7);** Female: 73/249 **(29.3)** *Loss of appetite, n (%)* Male: 7 **(7.9);** Female: 53/259 **(20.5)** **Moderate (Male n = 155; Female n = 183)** *Gustatory dysfunction, n (%)* Male: 8/138 **(5.8);** Female: 28/158 **(17.7)** Loss of appetite, n (%) Male: 13/153 **(8.5);** Female: 31/182 **(17.0)**

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
		Severe (Male n=262; Female n=213) Gustatory dysfunction, n (%) Male: 24/221 **(10.9);** Female: 25/179 **(14.0)** Loss of appetite, n (%) Male: 34/258 **(13.2);** Female: 37/207 **(17.9)** ***New symptoms after recovery from acute illness (n=809), n (%)*** Diarrhoea: 329 **(40.7)** Vomiting/Nausea: 293 **(36.2)** Gustatory dysfunction: 475 **(58.7)** **Clinical presentation of long COVID by calendar time according to variant predominance distribution** **Ancestral (n=736), Period August 2020 to January 2021, n (%)** Appetite Loss (n=734): 121 **(16.5)** Gustatory dysfunction (n=622): 124 **(19.9)** **Gama Variant (n=249), Period March 2021 to July 2021, n (%)** Appetite Loss: 33/237 **(13.9%)** Gustatory dysfunction: 17/233 **(7.3%)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Weight loss: 186 **(41.4)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%)* Weight loss: 102 **(23.4)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was hospitalised - 106.8 ±61.5 days.* *Overall reported symptoms – hospitalised (n = 376), n (%)* Loss of appetite or weight loss: 98 **(23.5)**
Comelli et al.[31] Italy	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 456)* *12-month follow-up, n (%)*

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
		Altered gastrointestinal function (altered bowel habits and bloating): 149 **(32.8)** Decreased appetite: 34 **(7.5)** *Severe medical issues after COVID-19, n (%)* GI problems: 1 **(0.2)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of long COVID >4 weeks post-COVID-19, n (%)* Gastrointestinal symptoms: 110 **(29.8)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Constipation: 141/811 **(17.4)** Diarrhoea: 113/804 **(16.5)** Abdominal pain: 119/808 **(14.7)** Stomach pain: 108/802 **(13.5)** Loss of appetite: 97/808 **(12.0)** Nausea/vomiting: 71/809 **(8.8)** Weight loss: 56/809 **(6.9)** *5 month (paired) data* Constipation: 106/600 **(17.7)** Diarrhoea: 99/599 **(16.5)** Abdominal pain: 91/604 **(15.1)** Stomach pain: 81/584 **(13.9)** Loss of appetite: 74/605 **(12.2)** Nausea/vomiting: 62/597 **(10.4)** Weight loss: 59/593 **(9.9)** *1 year (paired) data* Constipation: 104/600 **(17.3)** Diarrhoea: 89/599 **(15.8)** Abdominal pain: 85/604 **(14.4)** Stomach pain: 73/584 **(12.5)** Loss of appetite: 69/605 **(11.4)** Nausea/vomiting: 47/597 **(7.9)** Weight loss: 42/593 **(7.1)**
Fang et al.[65] China	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,233)* *Symptoms at 1-year follow-up, n (%)* Diarrhoea: 9 **(0.7)**

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
		Nausea: 1 **(0.1)** Vomiting: 1 **(0.1)** Anorexia: 13 **(1.1)** *Severe patients, n (%)* Diarrhoea: 3 **(0.7)** Anorexia: 6 **(1.4)** *Non-severe patients, n (%)* Diarrhoea: 6 **(0.8)** Nausea: 1 **(0.1)** Vomiting: 1 **(0.1)** Anorexia: 7 **(0.9)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* ***Symptoms ≥2months following COVID-19, n (%)*** *Total (n=398)* Weight loss (at least 3kg): 132 **(33.5)** *Long COVID (n=124)* Weight loss (at least 3kg): 67 **(54.9)** *Full recovery (n=270)* Weight loss (at least 3kg): 64 **(23.7)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 1,969)* Participants assessed on average 8.4 months after hospital discharge Gastrointestinal Problems, n (%): 133 **(6.8)** Diarrhoea, n (%): 49 **(2.5)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* ***Symptoms ≥2 Years Post-COVID-19, n (%)*** *Hospitalised* Gastrointestinal problems: 8 **(2.2)** Diarrhoea: 0 (**0**)
Fernández-de-las-Peñas et al.[28]	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan Post-COVID-19 Symptoms (mean follow-up 6.5 months), n (%)*

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
Spain		Diarrhoea: 15 **(7.4)** *Alpha Post-COVID-19 Symptoms (mean follow-up 6 months), n (%)* Diarrhoea: 11 **(5.2)** *Delta Post-COVID-19 Symptoms (mean follow-up 6.3 months), n (%)* Diarrhoea: 30 **(15.0)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Additional symptoms,* follow-up was a median of 200 days (IQR 185-235)*n (%)* Abdominal symptoms: 101 **(14.0)** Appetite loss: 91 **(12.0)** Diarrhoea: 44 **(6.0)** Nausea/vomiting: 24 **(3.0)**
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Loss of appetite: 11 **(5.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* **Hospitalised (n=447)** Gastrointestinal, n (%) [95%CI]: 8 **(1.8)** [0.8-3.5] *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%), p value* Anorexia, loss of appetite: 0 (**0**); 0 (**0**) NA Gastrointestinal: 8 (**2.0**); 5 (**1.3**) p = 0.58
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance *Hospitalised (n=547); Emergency Dept (n=212)* Diarrhoea: 20 **(3.7);** 6 **(2.8)** Abdominal pain: 13 **(2.4);** 11 **(5.2)**
Huang et al.[52]	Self-report via interview	*History of COVID-19 (n = 1,192)*

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
China	(3 assessment time points, same population at all 3 time points)	Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91) *6 months after symptom onset, n (%)* Decreased appetite: 92/1,151 **(8.0);** 25/286 **(9.0);** 56/776 **(7.0);** 11/89 **(12.0)** Nausea or vomiting: 17/1,150 **(1.0);** 8/286 **(3.0);** 9/775 **(1.0);** 0/89 **(0.0)** *12 months after symptom onset, n (%)* Decreased appetite: 34/1,188 **(3.0);** 6 **(2.0);** 25/802 **(3.0);** 3 **(3.0)** Nausea or vomiting: 10/1,188 **(1.0);** 4 **(1.0);** 4/802 **(0.0);** 2 **(2.0)** *2 years after symptom onset, n (%)* Decreased appetite: 33/1,190 **(3.0);** 10/294 **(3.0);** 21/805 **(3.0);** 2 **(2.0)** Nausea or vomiting: 27/1,190 **(2.0);** 8/294 **(3.0);** 18/805 **(2.0);** 1 **(1.0)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Decreased appetite: 35 (**3**); 11 (**1**) p = 0.0003 Nausea or vomiting: 29 (**3**); 4 (**<1**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Dyspepsia, n (%): 97 **(24.0)** Diarrhoea, n (%): 16 **(4.0)** *6 months follow-up (n=406)* Dyspepsia, n (%): 24 **(6.0)** Diarrhoea, n (%): 0 **(0.0)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* *6 months follow-up* Gastrointestinal, n (%), [95%CI] Adults (n=1,013): 63 **(6.2),** [4.8 to 7.8] Children (n=360): 14 **(3.9)**, [1.9 to 6.1] *12 months follow-up* Gastrointestinal, n (%), [95%CI] Adults (n=1,013): 13 **(1.3**), [0.6 to 2.0]

Author Country	Long COVID assessment mode	Gastrointestinal symptom cluster prevalence estimates
		Children (n=360): 2 **(0.6)**, [0.0 to 1.4]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19 (n=453) vs Non-exposed cohort - hospitalised due to other causes (n=453) (matched by institution and date of admission)* Digestive symptoms, n (%); p-value: 9 **(2.0)** vs 32 **(7.1);** <0.001 Diarrhoea, n (%); p-value: 4 **(0.9)** vs 16 **(3.5)**; 0.007 Constipation, n (%); p-value: 3 **(0.7)** vs 8 **(1.8);** 0.129 Abdominal pain, n (%); p-value: 4 **(0.9)** vs 16 **(3.5);** 0.007
Sorensen et al.[56] Denmark	Self-report via questionnaire (Single assessment time point)	*Hospitalised due to COVID-19 among positive test cases (n,%) No 58,581 (96) Yes 2,421 (4)* **Symptoms 6-12 months after test, n (%)** Nausea: 69 **(2.9)** Abdominal pain: 71 **(2.9)** Reduced appetite: 90 **(3.7)** Diarrhoea: 57 **(2.4)**
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Gastrointestinal*: **7%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.

Key: UK, United Kingdom; US, United States.

Dermatologic Symptom Cluster

Eighteen studies reported symptoms related to the dermatologic cluster for adults only,[24, 27, 28, 30, 32, 37, 40, 41, 44, 45, 47, 52, 74, 85, 117-120] and one study focused on prevalence estimates for both children and adults.[66] Prevalence estimates ranged from less than 1%[74] to 67.2%[117] in those with a history of COVID-19, and from 2%[117] to 40.8%[117] in those identified as having long COVID (see Table 4.19). Hair loss was the most commonly reported symptom, with prevalence estimates ranging from 2.0%[118] to 67.2%.[37] Differences in prevalence estimates were noted by sex and over time.

Barreto et al.,[37] found a higher prevalence of hair loss among females than males (67.2% versus 18.5%), in those self-reporting with long COVID. Three studies reported reductions in hair loss prevalence over time,[30, 52, 119] from 64.4% to 9.6% at 30 days and 180 days follow-up,[30] from 22% to 11% at six months and 12 months follow-up and reductions of 28% to 1% from three months to six months post-acute COVID-19.[119] However, Huang et al.[52] also reported similar prevalence estimates from 12 months (11%) to two years (12%) for hair loss. One study reported the prevalence of skin rash over time with similar estimates observed (3% at six months, 4% at 12 months and 3% at two years post COVID-19).[52] Two studies investigated differences in the prevalence of dermatologic symptoms in matched cohorts. Huang et al.[52] reported significantly higher prevalence of hair loss and skin rash, at two-year follow-up, in a SARS-CoV-2 test positive cohort hospitalised with COVID-19, compared to an age, sex and comorbidity matched community dwelling cohort who had never tested positive for SARS-CoV-2. Rivera-Izquierdo et al.[22] reported a significantly lower prevalence of dermatologic symptoms in those previously hospitalised with COVID-19, compared to an institution and admission date matched cohort hospitalised for other reasons, at 12 months follow-up.

Table 4.19. Dermatologic symptom cluster prevalence estimates in those with a history of severe COVID-19 illness

Author Country	Long COVID assessment mode	Dermatologic symptom cluster prevalence estimates
Asadi-Pooya et al.[118] Iran	Self-report via questionnaire (Single assessment time point, data split by follow-up time, different populations for each time point)	*History of* COVID-19 (n=4,681) *Additional (not specified to a follow-up time point), n (%)* Hair loss: 102 **(2.0)**
Barreto et al.[37] Brazil	Self-report via in-person assessment (Single assessment time point)	*Long COVID (n = 1,164)* ***Persistent hair loss ≥1 month post the acute phase of infection, n (%)*** Hair loss (n=594): 230 **(38.7)** ***Persistent hair loss (≥1 month post the acute phase of the infection) separated by sex and disease severity, n (%)*** **Mild (Male n=89; Female n=262)** Male (n=37): 2 **(5.4)** Female (n=95): 44 **(46.3)** **Moderate (Male n=155; Female n=183)** Male (n=83): 12 **(14.5);** Female (n=93): 53 **(57.0)** **Severe (Male n=262; Female n=213)** Male (n=151): 28 **(18.5)** Female (n=134): 90 **(67.2)** **Clinical presentation of long COVID by calendar time according to variant predominance distribution** **Ancestral (n=736) Period August 2020 to January 2021, n (%)** Hair Loss (n=181): 65 **(35.9)** **Gama Variant (n = 249) Period March 2021 to July 2021, n (%)** Hair Loss 9n=238): 97 **(40.8)**
Boglione et al.[30] Italy	Self-report via questionnaire (2 assessment time points, same population)	*History of COVID-19 (n = 449)* *30 days post-COVID-19, n (%)* Hair loss: 289 **(64.4)** Psoriasis: 83 **(18.5)** *History of COVID-19 (n = 435)* *180 days post-COVID-19, n (%)*

Author Country	Long COVID assessment mode	Dermatologic symptom cluster prevalence estimates
		Hair loss: 42 **(9.6)** Psoriasis: 18 **(19)**
Buttery et al.[44] UK	Self-report via survey (Single assessment time point)	*All participants self-reported long COVID* *Average length of time between onset of long COVID symptoms and completing survey (days ±SD) was hospitalised - 106.8 ±61.5 days.* *Overall reported symptoms – hospitalised (n = 376), n (%)* Hair loss: 42 **(10.1)**
de Oliveira et al.[40] Brazil	Self-report via questionnaire (Single assessment time point)	*Long COVID (n = 369)* *Symptoms of long COVID >4 weeks post-COVID-19, n (%)* Skin lesion: 51 **(13.8)**
Evans et al.[45] UK	Self-report via questionnaire (2 assessment time points, population could participate in either or both time points)	*History of COVID-19 (at 1 year follow-up n = 924)* *Symptoms at 1-year follow-up, n (%)* Skin rash (n=776): 127 **(16.4)** Lumpy lesions (purple/pink/bluish) on toes (n=776): 35 **(4.5)** *5 month (paired) data* Skin rash: 100/563 **(17.8)** Lumpy lesions (purple/pink/bluish) on toes: 21/544 **(3.9)** *1 year (paired) data* Skin rash: 89/563 **(15.8)** Lumpy lesions (purple/pink/bluish) on toes: 27/544 **(5.0)**
Feldman et al.[85] Canada	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 398)* *Symptoms ≥2 months following COVID-19, n (%)* *Total (n=398)* Hair loss: 22 **(5.5)**
Fernández-de-las-Peñas et al.[24] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,969)* Follow-up was 8.4 months on average after acute phase of the infection. Hair Loss: 470 **(23.9)** Skin Rashes: 236 **(12)**
Fernández-de-las-Peñas et al.[27] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 668)* *Symptoms ≥2 Years Post-COVID-19, n (%)* *Hospitalised:* Hair loss: 27 **(7.5)**

Author Country	Long COVID assessment mode	Dermatologic symptom cluster prevalence estimates
		Rashes: 7 **(1.9)**
Fernández-de-las-Peñas et al.[28] Spain	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 614)* *Wuhan Post-COVID-19 Symptoms (mean follow-up 6.5 months), n (%):* Hair loss: 58 **(28.9)** Skin rashes: 26 **(12.9)** Alpha Post-COVID-19 Symptoms *(mean follow-up 6 months),* n (%): Hair loss: 33 **(15.7)** Skin rashes: 12 **(5.7)** Delta Post-COVID-19 Symptoms *(mean follow-up 6.3 months),* n (%): Hair loss: 73 **(36.2)** Skin rashes: 10 **(5.0)**
Ferreira et al.[41] Brazil	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 749)* *Additional symptoms*, n (%)* Skin problems: 113 (**15.0**) *Follow-up was a median of 200 days (IQR 185-235)
Frontera et al.[117] US	Completion of validated scales and self-report via interview (2 assessment time points, population could participate in either or both time points)	*Long COVID (n = 239)* *Symptoms at 12 months, n (%)* Lumpy toes (COVID toes): 4 **(2.0)**
Funk et al.[77] Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Self-report via caregivers (Single assessment time point)	*History of COVID-19 (n = 1,884)* ***Hospitalised (n=447)*** Skin condition or rash, n (%); [95%CI]: 1 **(0.2)**; [0.0 to 1.2] *Reported 90-days post–COVID-19 conditions (hospitalised SARS-CoV-2–positive children; frequency matched hospitalised SARS-CoV-2–negative children), n (%), p value* Skin condition or rash: 1 (**0.3**); 0 (**0**) p >0.994
Heightman et al.[47] UK	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 1,325)* The post-COVID-19 service accepted referrals from: (1) post-hospitalisation with COVID-19 (2) post-emergency department individuals with persistent symptoms at 4–6 weeks after attendance. *Hospitalised (n=547); Emergency Dept (n=212)* Skin rash, n (%):12 **(2.2);** 16 **(7.5)**
Huang et al.[52]	Self-report via interview	*History of COVID-19 (n = 1,192)*

Author Country	Long COVID assessment mode	Dermatologic symptom cluster prevalence estimates
China	(3 assessment time points, same population at all 3 time points)	Total (n=1,192); Scale 3: not requiring supplemental oxygen (n=295); Scale 4: requiring supplemental oxygen (n=806); Scale 5-6: requiring high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation (n=91) *6 months after symptom onset, n (%)* Hair loss: 252/1,151 **(22)**; 61/286 **(21);** 169/776 **(22);** 22/89 **(25)** Skin rash: 36/1,151 **(3);** 11/286 **(4);** 21/776 **(3);** 4/89 **(4)** *12 months after symptom onset, n (%)* Hair loss: 131/1,188 **(11)**; 27 **(9);** 97/802 **(12)**; 7 **(8)** Skin rash: 50/1,188 **(4);** 13 **(4);** 35/802 **(4);** 2 **(2)** *2 years after symptom onset, n (%)* Hair loss: 142/1,190 **(12)**; 41/294 **(14);** 88/805 **(11);** 13 **(14)** Skin rash: 34/1,190 **(3);** 6/294 **(2);** 25/805 **(3);** 3 **(3)** *Symptoms at 2-year follow up (n %) p value (those with a positive SARS-CoV-2 test and hospitalised with COVID-19 (n = 1,127); Those who never had a positive SARS-CoV-2 test and were community dwelling (matched for age, sex and comorbidities) (n = 1,127))* Hair loss: 201 (**18**); 94 (**8**) p < 0.0001 Skin rash: 52 (**5**); 4 (**<1**) p < 0.0001
Özcan et al.[119] Turkey	Self-report via interview and physical examination (2 assessment time points, same population at both time points)	*History of COVID-19 (n = 406)* *3 months follow-up (n=406)* Hair loss, n (%): 114 **(28)** Pruritus, n (%): 12 **(3)** *6 months follow-up (n=406)* Hair loss, n (%): 4 **(1)** Pruritus, n (%): 4 **(1)**
Pazukhina et al.[66] Russia	Self-report via questionnaire (2 assessment time points, same population at both time points)	*History of COVID-19 (adults: n = 1,013; children: n = 360)* *6 months follow-up* *Dermatological, n (%); [95%CI]* Adults (n=1,013): 132 **(13.0);** [11.1 to 15.1] Children (n=360): 17 **(4.7);** [2.8 to 6.9] *12 months follow-up* *Dermatological, n (%); [95%CI]*

Author Country	Long COVID assessment mode	Dermatologic symptom cluster prevalence estimates
		Adults (n=1,013): 36 **(3.6)**; [2.5 to 4.7] Children (n=1,013): 7 **(1.9)**; [0.6 to 3.6]
Rivera-Izquierdo et al.[22] Spain	Self-report via interview (Single assessment time point)	*History of COVID-19 (n = 453)* Post-discharge syndrome was defined as the persistence of symptoms in the most severe cases (i.e., those requiring hospitalisation) of COVID-19 after hospital discharge. Follow-up was 12 months post-hospital discharge. *Exposed cohort - hospitalised due to COVID-19) n=453) vs Non-exposed cohort - hospitalised due to other causes n=453) (matched by institution and date of admission)* Dermatological symptoms, n (%); p-value: 9 **(2.0)** vs 24 **(5.3)**; 0.008
Spinicci et al.[32] Italy	Self-report via questionnaire (Single assessment time point)	*History of COVID-19 (n = 428)* Hair loss*: **10%** Dermatological*: **6%** *The follow-up visit was performed a median 53 days (IQR 40–64) after hospital discharge and 69 days (IQR 55–82) after the first positive result by PCR on nasopharyngeal swab.
Yoo et al.[74] US	Self-report via questionnaire (3 assessment time points, population could participate in any or all time points)	*History of COVID-19 (n = 1,038)* *At least 60 days follow-up* Rash: **<1%**

Key: UK, United Kingdom; US, United States.

5.3.2 New onset conditions

Six studies identified new onset conditions, separate to the symptoms reported in section 5.3.1.[22, 30, 54, 56, 71, 118] Whitaker et al.[54] reported venous thromboembolism (VTE) as a new onset condition following infection with COVID-19, with 33% of those recruited from the general population reporting VTE at 12 weeks follow-up post-acute COVID-19.

Rivera-Izquirdo et al.[22] noted 1.1% of those with a history of severe COVID-19 illness reported thrombotic events. In a study by Boglione et al.[30] 9.1% reported VTE at 30-days follow-up, with 2.7% reporting VTE at 180 days post-acute COVID-19. The study by Boglione et al.[30] also reported diabetes mellitus as a new onset condition following a COVID-19 infection (reporting method was unclear), with 24.3% reporting diabetes mellitus at 30 days post-acute COVID-19, reducing to 8.9% at 180 days post-acute COVID-19. New onset diabetes mellitus (n=18) was also reported in a study by Asadi-Pooya et al.[118] involving a telephone survey of individuals at three to six months (n=2,915) and six to 12 months (n=1,996) following hospitalisation with COVID-19. Asadi-Pooya et al.[118] also noted that one participant reported new onset chronic renal failure and 11 participants reported new-onset hypertension. The timing of these conditions relative to the follow-up period was not specified.

Findings from a nationwide questionnaire study of adults in Denmark by Sorensen et al.[56] included estimates of the risk of new self-reported medical diagnoses in SARS-COV-2 test-positive and test-negative controls. In test-positive respondents, the most frequently reported diagnoses for a follow-up period up to six to 12 months post-test were chronic fatigue syndrome (4.0%), depression (3.5%), and anxiety (3.4%), with post-traumatic stress disorder (PTSD) (1.3%) and fibromyalgia (1.0%) also reported. A number of these new diagnoses were more common among test positive compared with test negative controls, with statistically significant risk differences (RDs) reported for chronic fatigue syndrome (2.53% (95% CI: 2.35–2.71%)), depression (1.00% (95% CI 0.81–1.19%)), anxiety (1.15% (95% CI 0.95–1.34%)) and PTSD (0.16% (95% CI 0.03–0.28%)).[56] Two further studies reported diagnoses of PTSD. Belkacemi et al.[71] identified that 13% of patients on dialysis with long-lasting clinical symptoms reported PTSD, depression or anxiety, while Boglione et al.[30] reported a prevalence of 38.0% and 30.8% at 30 days and 180 days follow-up, in those with a history of severe COVID-19.

5.3.3 Quality of life, return to work and physical activity or functioning

Across the studies included within this review, a wide range of measures were used to assess quality of life, return to work and physical activity or functioning in

individuals with long COVID. As such, it is difficult to compare or present a ranges of outcomes across studies. The following sections, provide a summary of the outcomes measures presented according to the sub-group of interest (general population, age (those aged under 18 years and those aged 65 years or older), medically vulnerable and those with a history of severe COVID-19 illness).

General population

None of the nine primary research studies which recruited 10,000 people or more from a general population specifically investigated quality of life (QoL) associated with long COVID. Two studies investigated participants' ability to work post-acute COVID-19 (see Appendix 6 General population, Table 3).[53, 62] Estimates related to return to work ranged from 6.3% of participants reporting an inability to work[53] to 47.1%[62] of participants reporting their working capacity had not fully recovered to 100%.

Two of the nine primary research studies specifically investigated limitation to daily activities.[43, 53] Ayoubkhani et al.[43] identified that 16.7% of participants reported a limitation in physical activities at least once during an approximately eight-month follow-up post-acute COVID-19 infection, while Bernas et al.[53] found that 4.7% reported impairments in their basic activities of daily living. Data from the UK ONS (collected over the four-week period ending 4 December 2022) showed that long COVID symptoms adversely affected the day-to-day activities of 1.6 million people (76% of those with self-reported long COVID), with 389,000 (18%) reporting that their ability to undertake their day-to-day activities had been "limited a lot".[11] US CDC estimates derived from phase 3.7 of the Household Pulse Survey (4 January to 16 January 2023) noted that among adults who ever had COVID-19, 78.9% were experiencing some activity limitations and 26.6% were experiencing significant activity limitations due to long COVID.[80]

Age (those aged under 18 years, those aged 65 years or older)

Two of the 15 primary research studies which focused on specific age groups reported QoL associated with long COVID (see Appendix 7 Age, Table 3). Both of these looked at those aged under 18 years. Kikkenborg et al.[64] assessed the health-related quality of life (HRQoL) of children aged under 14 years with a previous SARS-CoV-2 positive test result, compared with an age- and sex-matched cohort who had never tested positive for SARS-CoV-2, using the Paediatric Quality of Life Inventory (PedsQL). Statistically significant lower emotional functioning scores (indicating worse HRQoL) were reported in 105 children aged 13 to 24 months with a history of COVID-19 compared to 325 children without (emotional functioning: 73.6 versus 77.0, $p < 0.0001$). Conversely, statistically significantly higher emotional functioning scores ($p < 0.0001$) (indicating better HRQoL) were noted in children

aged four to 14 years with a history of COVID-19 (n=9,548) than their age- and sex-matched comparators (n=29,161). A second primary research study conducted by Kikkenborg et al.[88] compared the HRQoL of 24,315 adolescents aged 15 to 18 years with a history of COVID-19 with that of 97,257 age- and sex-matched controls without a history of COVID-19, using the PedsQL. They reported that adolescents in the case group had better quality of life scores than in the control group for both the emotional functioning (mean score: 77.1 versus 71.7; p <0.0001) and social functioning (mean score:93.1 versus 88.4; p<0.0001) domains.

Four studies investigated physical activity and or physical functioning in children and adolescents aged less than 18 years with a history of COVID-19.[51, 64, 86, 88] Two primary research studies conducted by Kikkenborg et al.[64, 88] and one primary research study conducted by Nugawela et al.[86] used validated scales to assess physical activity (EQ-5D-Y index) and physical functioning (the PedsQL). Kikkenborg et al.[64] reported that children with a previous SARS-CoV-2 positive test result had better physical functioning scores than those who had never tested positive for SARS-CoV-2, but the difference in effect size was noted to not be clinically significant. Another Kikkenborg et al.[88] study reported that adolescents aged between 15 to 18 years with a previous SARS-CoV-2 positive test result reported better physical functioning scores than those who had never tested positive for SARS-CoV-2 (88.7 versus 86.5 mean score on the physical functioning domain of the PedsQL, p <0.0001).

Both Nugawela et al.[86] and Miller et al.[51] identified that long COVID impacted the day-to-day activities of children with a history of COVID-19. Nugawela et al.[86] identified that 16.1% of children reported some and or a lot of problems performing usual activities, compared to 13.3% of their age- and sex-matched SARS-CoV-2 test negative comparators.[86] Miller et al.[51] observed that while 44% of children with a history of COVID-19 reported that symptoms impacted regular activities, a similar proportion of SARS-CoV-2 test negative children also reported experiencing persistent symptoms (46.1%).[51]

Daitch et al.[67] was the only study identified that assessed QoL, return to work or physical activity in older adults. They investigated physical activity associated with post COVID-19 conditions, using physician collected data.[67] Although 16.3% of those aged 65 years and older reported that physical activity levels worsened post COVID-19 infection, 29.2% reported that physical activity levels had improved.

Medically vulnerable (those aged under 65 years who are medically vulnerable (as outlined by the HSE)

None of the studies who recruited those identified as medically vulnerable reported quality of life, return to work and or physical functioning data associated with long COVID.

Those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19)

Fifteen of the 32 studies which recruited individuals hospitalised with COVID-19 reported QoL, return to work, or physical functioning data associated with long COVID (See Appendix 9 Severe COVID-19, Table 3).

Eight studies reported specifically on QoL.[37, 38, 40, 41, 47, 52, 117, 118] Five studies used the EUROQoL (EQ-5D) quality of life index.[37, 38, 40, 47, 52] Three studies reported extreme values in one domain of the EQ-5D index ranging from 0.5% to 8.4% for those with a history of severe COVID-19 illness.[33, 34, 36] Three studies reported on HRQoL.[45, 47, 52] Heightman et al.[47] reported that at a median follow-up time of 69 days the median self-reported proportion with optimal health was 80% (IQR: 65%-95%) while Huang et al.[52] reported a median HRQoL of 80 (70-90) at two year follow-up as assessed using the EuroQoL Visual Analogue scale (range 0 to 100, with 0 representing worst possible health and 100, best imaginable health). At five-month and one year follow-up, in those self-reporting that they were not recovered from COVID-19, Evans et al.[45] reported median (IQR) values of 0.69 (0.52 - 0.80) and 0.66 (0.43 - 0.77) using the EQ5DL utility index (a score of one represents full health while a score of zero represents the worst possible health state). Evans et al.[45] also reported no change in the median values of the EQ-5D-5L VAS, at the same time periods (70 (IQR: 50-80), in this cohort, reflecting sustained substantial decrements in HRQoL. Ferreira et al.[41] at a median of 200 days follow-up reported a QoL VAS median (IQR) score of 80 (60-90). Asadi-Pooya et al.[118] found that 3.6% of participants reported their overall QoL was much worse than before their COVID-19 infection.

Two studies reported data on returning to work in those previously hospitalised with COVID-19.[47, 52] Huang et al.[52] reported approximately 11% of participants had not returned to work at 12 month and at two year follow-up, with 33% (12-month follow-up) and 38% (two-year follow-up) of those not returning to work stating it was due to decreased physical function. Heightman et al.[47] also reported that of those hospitalised due to COVID-19 and employed prior to acute COVID-19 infection, 34.3% were unable to return to employment at a median (range) follow-up of 69 (51 to 111) days post-acute COVID-19 infection.

Thirteen studies assessed physical activity associated with the development of a post COVID condition.[22, 23, 26, 37-41, 45, 52, 117, 119] Eight studies with a follow-up time points ranging from one to 24 months reported on physical activity levels in those

previously hospitalised with COVID-19.[22, 23, 26, 37, 38, 41, 117, 118] The percentage reporting severe limitations ranged from 1.8%[38] to 36%.[22, 23, 26, 37, 38, 41, 117, 118] Two studies assessed physical functioning using walking assessments, with Evans et al.[45] using the Incremental Shuttle Walk Test (ISWT) and Huang et al.[52] assessing distance walked in six minutes. Evans et al.[45] reported a reduction in ISWT scores for participants not recovered from COVID-19 (n=1,079) compared with participants recovered from COVID-19 (n=501) at five months follow-up (385m versus 488m). Huang et al.[52] reported a range of 8% to 14% of those previously hospitalised with COVID-19 displaying walking distances below the lower limit of normal range (as defined by the authors), at six, 12 and 24 months follow-up. Ozcan et al.[119] reported that, at six months follow-up, 8.5% of participants walked slower than individuals of the same age due to breathlessness or needing to stop to catch their breath, when walking at their own pace on a level surface.

In regards to physical functioning, five studies reported some degree of alteration which impacted daily activities, post-acute COVID-19 at follow-up periods ranging from 2.3 months to 12 months post-hospital discharge.[22, 26, 37, 38, 40] The percentage of participants reporting a degree of alteration or being unable to perform their usual activities ranged from 32%[37] to 89%.[37] Fernández-de-las-Peñas et al.[26] and Battistella et al.[38] also identified that 55% and 71% of participants reported at least one functional limitation with daily living activities or limited daily activities.

Two studies also reported on functional dependence, with Rivera-Izquierdo et al.[22] identifying that 15% of those previously hospitalised with COVID-19 were dependent on help during daily living 12 months post-discharge and Battistella et al.[38] reporting that 2% of participants had reduced functional independence (scores of 18 to 60 out of 126, on a functional independence measure) at three to 11 months post discharge.

5.3.4 Factors associated with the development of long COVID

General population

Eight of the nine primary research studies which recruited 10,000 or more people reported factors associated with long COVID (See Appendix 6 General Population, Table 4) in those with a history of COVID-19. Five of these studies specifically investigated factors associated with the development of long COVID[43, 48, 57] or similar, such as the post COVID-19 condition[58] and persistent symptoms (generally).[54] Older age was identified as a factor that increased the odds of developing long COVID (or similar) in four of the five studies,[48, 54, 57, 58] with statistically significant adjusted odds ratios (aOR) ranging from 1.05[48] to 2.10[58] for age (by increasing year, decade or age category). Female sex was identified as a factor that increased the odds of developing long COVID (or similar) in three of the

five studies,[54, 57, 58] with aORs ranging from 1.23[58] to 1.95.[57] The presence of asthma was associated with an increase in the odds of long COVID development in two studies[48, 58] with aORs ranging from 1.28 (95% CI: 1.21 – 1.35)[48] to 1.38 (95% CI: 1.19 – 1.59).[58]

Increased household income and vaccination were identified as protective factors against the development of long COVID in two studies,[43, 54, 57] with household income aORs ranging from 0.76[57] to 0.84 (across multiple increased income ranges),[54] while for complete vaccination prior to acute COVID-19 illness the aOR was 0.72 (95% CI: 0.60 to 0.86)[57] and complete vaccination following acute COVID-19 illness the aOR was 0.91 (95% CI: 0.86 to 0.97).[43] Contrasting results were identified across two studies for urbanicity,[48, 57] with living in a higher population density area associated with both increased (conurbation aOR: 1.46; 95% CI 1.39 – 1.53)[48] and decreased odds (urban aOR: 0.76; 95% CI: 0.65 – 0.88)[57] of long COVID development, compared to rural living.

Data from the ONS showed that the prevalence of long COVID was greatest in people aged 35 to 69 years, in females, in people living in more deprived areas, in those not working in social care, in those aged 16 years and over who were not working and not looking for work, and in those with another activity-limiting condition or disability.[11]

Two of the seven primary research studies investigated factors associated with the development of specific symptoms associated with long COVID, such as fatigue and dyspnoea.[53, 56] Both Bernas et al.[53] and Sorensen et al.[56] investigated long COVID symptoms in adults with a history of COVID-19, compared to controls (either without a history of COVID-19 or test negative). Bernas et al.[53] identified that, in general, younger age and a history of less severe acute COVID-19 were associated with a lower risk of experiencing daily symptoms, than older age and a history of more severe acute COVID-19. Compared to controls, the odds of developing specific daily symptoms in those who reported a positive SARS-CoV-2 test result was highest for anosmia/ageusia (aOR ranging from 25.73 – 94.98 depending on age group and severity of acute COVID-19), followed by chest pain (aOR: 19.88; 95% CI: 5.64 – 70.05) and dyspnoea (aOR: 18.55; 95% CI: 11.59 – 29.68), with both of the latter observed in those aged 40 – 61 years with a history of severe acute COVID-19. This is in contrast to the findings of Sorensen et al.[56] who identified that the largest risk differences (RD) were for dysosmia (distortion of smell) (RD: 10.92%, 95% CI: 10.68 – 11.21%), dysgeusia (distortion of taste) (RD: 8.68%, 95% CI: 8.43 – 8.93%), and fatigue/exhaustion (RD: 8.43%, 95% CI: 8.14 – 8.74%). Peter et al.[62] also investigated factors associated with the development of symptom clusters, identifying that type of care required (outpatient and inpatient versus no medical care) was most strongly associated with symptom cluster development (adjusted

prevalence ratios (aPRs) ranging from 1.23 - 4.06), along with female sex (aPRs ranging from 1.33 to 4.77).

CDC data reported an increased risk for those aged 18 to 64 years with a previous COVID-19 diagnosis, compared to those without, for 22 incident conditions such as cardiovascular disease, asthma and renal failure (risk ratios (RR) ranging from 1.1 (anxiety) to 2.1 (acute pulmonary embolism).[79] No significant differences were observed between those with and without previous COVID-19 infection, for cerebrovascular disease, or mental health conditions, such as mood disorders, other mental conditions, and substance-related disorders.[79]

Age (those aged under 18 years, those aged 65 years or older)

Twelve of the 14 studies that focused on specific age groups reported factors associated with long COVID (see Appendix 7 Age, Table 4). Six of these studies specifically investigated factors associated with the development of post COVID-19 conditions,[66, 69, 77] persistent symptoms (generally),[50] or long COVID[36, 86] in children and adolescents less than 18 years old, with a history of COVID-19. Older age was identified as significantly increasing the odds, prevalence or risk of long COVID (or similar) in five of the six studies.[36, 50, 69, 77, 86] This was reported primarily when grouping children via age, with crude ORs of 1.36 to 1.70 in 14 – 15, and 16 – 17 year olds,[86] adjusted ORs ranging from 2.18[36] in 11 -16 year olds, to 2.67 in 14 – 18 year olds,[77] and an adjusted risk ratio (aRR) of 3.14 (95% CI: 1.71 – 5.48)[69] in 13 – 17 year olds, all relative to younger age groups. Dumont et al.[50] also reported an adjusted prevalence ratio (aPR) of 1.1 (95% CI: 1.0 - 1.3) for increasing age in years, in children aged six months to 17 years. The presence of a comorbidity increased the odds, risk or prevalence of long COVID in three studies,[50, 66, 69] either for any chronic condition (aPR: 3.5; 95% CI: 2.0 – 6.1)',[66]or for the following specified comorbidities: anxiety (RR: 2.53; 95% CI: 1.05 – 6.11), somatoform disorders (RR: 2.11; 95% CI: 1.02 – 4.39),[69] and neurological comorbidities (at six months post hospital discharge: aOR: 4.38; 95% CI: 1.36 – 15.67; at 12 months post hospital discharge: aOR: 8.96; 95% CI: 2.55 – 34.82).[66]

Miller et al.[51] reported increased odds of persistent symptoms with older age and the presence of a long term condition. However, participants were not required to have had a history of COVID-19. An allergic respiratory condition,[66, 69] and the occurrence of[66] or number of symptoms during acute COVID-19,[77] were also associated with long COVID development, in children with a history of COVID-19. No protective factors associated with the development of long COVID in children with a history of COVID-19 were reported. Kildegaard et al.[55] also investigated the risk of long COVID in children and adolescents less than 18 years old. Children with a history of COVID-19 displayed an increased risk of developing long COVID, with risk

ratios (RR) of 18.61 and 18.15, compared to a reference group of children tested for COVID-19 and a control group of children with a negative SARS-CoV-2 test result, respectively.

Five of the 12 primary research studies also investigated factors associated with the development of specific long COVID symptoms or symptom clusters in children and adolescents.[36, 56, 64, 77, 88] Four studies compared COVID-19 positive children and adolescents to control participants.[56, 64, 77, 88] All of the studies identified an increase in the odds or prevalence of long COVID symptoms in those with a history of COVID-19. For example, Kikkenborg et al.[64] identified increased odds of reporting trouble breathing (aORs ranging from 2.61 – 4.40), cough (aORs ranging from 1.83 - 4.65) and fatigue (aORs ranging from 1.39 – 3.50) in children younger than 15 years old across all age ranges (0-3 years, 4-11 years and 12-14 years). A second study by Kikkenborg et al.[88] reported increased odds of reporting trouble breathing (aOR 2.70), cough (aOR 1.63) and sore throat (aOR 1.59) in adolescents aged between 15 and 18, for those with a history of COVID-19. Trapani et al.[36] also reported significantly increased odds for a range of symptoms with older age (relative to 1-5 years) and for those with a history of symptomatic acute infection in children aged 16 years and under. Specifically, significantly increased odds of abnormal fatigue (age 11 – 16 years aOR: 7.05; symptomatic acute infection aOR: 12.22), psychological symptoms (age 11 – 16 years aOR: 3.79; symptomatic acute infection aOR: 3.08) and neurological symptoms (age 6 – 10 and 11 – 16 years aORs: 5.27 and 8.73; symptomatic acute infection aOR: 6.61) were reported.

CDC data reported an increased risk of a number of symptoms and conditions in children and adolescents with previous COVID-19, compared to those without.[78] For those aged 2 – 4 years the highest adjusted hazard ratios (aHRs) were reported for myocarditis and cardiomyopathy (aHR = 2.39; 95% CI: 1.57 – 3.65), acute and unspecified renal failure (aHR: 1.52; 95% CI: 1.07 – 2.14), and coagulation and hemorrhagic disorders (aHR: 1.47; 95% CI: 1.20 – 1.80). For children aged 5–11 years, the highest aHRs were reported for myocarditis and cardiomyopathy (aHR: 2.84; 95% CI: 2.39 – 3.37), venous thromboembolic event (aHR: 2.69; 95% CI: 1.73 – 4.19), and acute and unspecified renal failure (aHR: 1.38; 95% CI: 1.16 - 1.63). For those aged 12–17 years, the highest aHRs were reported for acute pulmonary embolism (aHR: 2.03; 95% CI: 1.61 – 2.56), myocarditis and cardiomyopathy (aHR: 1.66; 95% CI: 1.48 – 1.88), and venous thromboembolic event (aHR: 1.52; 95% CI: 1.22 – 1.91).

Two studies investigated factors associated with long COVID or specific long COVID symptoms in older adults (greater than 59 years[65] or 65 years[67]) with a history of COVID-19. Daitch et al.[67] reported that obesity and female sex increased the odds of developing long COVID fatigue (obesity: aOR: 1.59; 95% CI: 1.12 – 2.26 and

female sex: aOR: 2.07; 95% CI: 1.57 – 2.73) and also of dyspnoea (obesity: aOR: 1.69; 95% CI: 1.20 – 2.38 and female sex: aOR: 1.67; 95% CI: 1.26 – 2.22). However, no association between sex and post- and emerging COVID sequelae were noted in a study by Fang et al.[65] Age (per year) along with disease severity during hospitalisation were identified by Fang et al.[65] as factors that increased the odds of chronic obstructive pulmonary disease (COPD) assessment test (CAT) scores of greater than or equal to 10 (age per year aOR: 1.07, 95% CI: 1.04 – 1.09; severity during hospitalisation aOR: 1.81, 95% CI: 1.23 – 2.67).[65]

CDC data reported increased risk for those aged 65 years and older with a previous COVID-19 diagnosis, compared to those without, in all 26 incident conditions such as cardiac dysrhythmia, asthma and renal failure (risk ratios (RR) ranging from 1.2 (substance-related disorder) to 2.2 (acute pulmonary embolism).[79] No significant differences were observed between those with and without previous COVID-19 infection, for cerebrovascular disease, or mental health conditions, such as mood disorders, other mental conditions, and substance-related disorders.[79]

Medically vulnerable (those aged under 65 years who are medically vulnerable (as outlined by the HSE)

Two studies reported factors associated with long COVID, in those identified as medically vulnerable (See Appendix 8 Medically vulnerable, Table 4). Both Belkacemi et al.[71] and Garjani et al.[46] identified pre-acute COVID-19 variables and comorbidities associated with long COVID. In patients on dialysis, Belkacemi reported that each year on dialysis (OR: 1.03, 95% CI: 1.01 – 1.06), having diabetes, (OR: 1.53, 95% CI: 1.08 - 2.17) and living with overweight (OR: 1.96 (1.10 – 3.52) or obesity (OR: 2.35; 95% CI: 1.30 – 4.26) increased the odds of reporting long-lasting clinical COVID-19 symptoms at six months post-acute COVID-19 onset. Similarly, in those with MS, Garjani et al.[46] found a decreased probability of recovery from COVID-19 in those that reported having anxiety and or depression before COVID-19 onset (aHR: 0.71; 95% CI: 0.53 – 0.94) and in those having a pre–COVID-19 web-based Expanded Disability Status Scale (Web-EDSS) score of ≥7 (aHR: 0.61; 95% CI: 0.38 – 0.99). While Belkacemi et al.[71] identified younger age as a protective factor to developing long-lasting clinical symptoms and long-lasting impaired general condition (extreme fatigue or weight loss) in those on dialysis, Garjani et al.[46] did not identify an association between age and recovery from COVID-19 in those with MS. Belkacemi et al. [71] further identified the odds of long-lasting clinical symptoms increased in those with a history of moderate or severe acute COVID-19 (moderate: OR: 1.64, 95% CI 1.16 – 2.33; severe: OR: 5.03, 95% CI: 2.94 – 8.61), while Garjani et al.[46] identified that females with MS were less were less likely to report recovery from COVID-19 (HR 0.76; 95% CI: 0.61 – 0.94).

Those with a history of severe COVID-19 illness (defined as those hospitalised or admitted to intensive care due to COVID-19)

Twenty-eight of the 32 studies which recruited those hospitalised with COVID-19 (both those under 18 years and 18 years or older) conducted analysis on risk factors related to long COVID (See Appendix 9 Severe COVID-19, Table 4). Fifteen of these studies specifically investigated factors associated with COVID-19 recovery,[45, 47] the development of post COVID-19 conditions or sequelae,[65, 66, 74, 117] persistent symptoms (generally)[31] or long COVID.[24, 30, 32, 40, 48, 52, 85, 118]

Female sex was identified to significantly increase the odds of long COVID development (or similar) in seven of the 15 studies,[24, 31, 32, 52, 66, 85, 118] with aORs ranging from 1.27[118] to 2.54.[24] Heightman et al.[47] also reported that compared to females, males who were hospitalised or who attended the emergency department with COVID-19 were more likely to return to work full-time (hospitalised aOR: 1.88, 95% CI: 1.33 – 2.67; emergency department aOR: 1.79, 95% CI: 1.04 – 3.10) and to report at least 75% functional recovery (hospitalised aOR: 2.58, 95% CI: 1.94 – 3.42; emergency department: aOR: 2.98, 95% CI: 1.78 – 4.98) post-acute COVID-19.

Obesity was also identified as increasing the odds of long COVID development in three studies,[48, 74, 85] with aORs ranging from 1.02[74] to 2.24.[85] Additionally, Evans et al.[45] identified that females and those with obesity were less likely to report recovery at a one-year follow-up post-COVID (female: aOR: 0.68; 95% CI: 0.46 – 0.99; BMI ≥30 kg/m^2: aOR: 0.50; 95% CI: 0.34 – 0.74). The presence of comorbidities was identified to significantly increase the odds of long COVID development in four studies,[31, 48, 66, 74] with diabetes (aORs of 1.48[74] and 1.66[48]), hypertension (aOR: 1.42; 95% CI: 1.04 – 1.94),[66] asthma (aOR: 1.27; 95% CI: 1.10 – 1.47)[48] and chronic kidney disease (aOR: 1.44; 95% CI: 1.08 – 1.9)[48] specifically identified. Those who required specific treatments during their hospitalisation episode for acute COVID-19 were identified as being at an increased odds of developing long COVID in three studies,[32, 65, 117] with requirements for mechanical ventilation (aOR: 6.37; 95% CI: 2.16 – 18.78),[117] immunosuppressant drugs (aOR: 6.6; 95% CI: 1.5 – 28.5),[31] corticosteroid-related therapy (aORs ranging from 2.08 – 4.15, dependent on disease severity and emerging or any post-sequelae),[65] and advanced oxygen support (aOR: 1.9; 95% CI: 1.1 – 3.3)[32] identified. Conversely, Boglione et al.[30] identified that treatment with remdesivir was associated with a reduced odd of developing long COVID (aOR 0.64; 95% CI: 2.08 – 4.15). Factors related to the hospitalisation episode for acute COVID-19, such as disease severity (aORs ranging from 1.03[65] - 1.4[52]), length of hospital stay (increase per one day aOR: 1.03; 95% CI: 1.01 – 1.06)[85] and ICU admission (aORs ranging from 2.55[30] – 2.6[40]) were also associated with the development of long

COVID. Among those previously hospitalised with COVID-19 similar risks of reporting long COVID-19 sequelae were identified in a study by Norgard et al.[75] when comparing those with and without chronic inflammatory disease (adjusted Hazard Ratio (aHR): 1.08; 95% CI: 0.79 – 1.49).

Fifteen of the 28 primary research studies also investigated factors associated with the development of specific long COVID symptoms or symptom clusters,[23-27, 37-39, 41, 52, 65, 73, 85, 117, 119] in those hospitalised with COVID-19. Female sex was significantly associated with long COVID fatigue in four studies[25, 26, 41, 52] (aORs ranging from 1.25[25] to 1.80[26]), anxiety and or depression in four studies[37, 41, 52, 117] (aORs ranging from to 1.61[24] – 1.94[52]), dyspnoea in five studies[24-26, 38, 41] (aORs ranging from 1.41[24] – 1.86[26]) and pain in four studies[23, 24, 37, 38] (aORs ranging from 1.35[23] – 1.66[37]). Male sex was identified as a significant protective factor for development of long COVID anxiety (aOR: 0.21; 95% CI: 0.06 – 0.74).[117] The presence of or number of comorbidities was also significantly associated with development of long COVID fatigue and dyspnoea in three studies,[26, 27, 41] with aORs ranging from 1.21[26] to 1.93[27] for fatigue and 1.21[26] to 1.91[27] for dyspnoea.

The presence of asthma before hospitalisation was also specifically identified to significantly increase the odds of long COVID fatigue (aOR: 5.44; 95% CI: 1.27 – 23.26) and dyspnoea (aOR: 2.57; 95% CI: 1.53 – 4.32).[25] Factors associated with long COVID symptom clusters were also investigated including the development of respiratory,[65] physical,[85] cardiovascular,[65, 119] neurological[65] and psychological symptoms.[85] Older age (aORs of 1.03[119] and 1.03[65]) and severity of acute COVID-19 (aORs of 1.66[65] and 2.58[119]) were significantly associated with ongoing cardiovascular symptoms in two studies,[65, 119] with severity of acute COVID-19 also associated with significantly increased odds of respiratory (aOR: 1.73; 95% CI: 1.18 - 2.53)[65] and neurological symptoms (aOR: 1.31; 95% CI: 1.01 - 1.70).[65] Feldman et al.[85] also identified female sex as significantly increasing the odds of developing physical (aOR: 2.17; 95% CI: 1.27 – 3.71) and psychological symptoms (aOR: 2.06; 95% CI: 1.25 – 3.39).

6 Discussion

As of January 2023, it has been estimated that, based solely on documented COVID-19 cases, at least 65 million people worldwide have long COVID.[121] When considering also the vast number of undocumented COVID-19 cases, it is likely that this figure is in fact much higher.

Characterised by more than 200 symptoms (such as fatigue, dyspnoea and chest pain), and impacting multiple organ systems,[121] long COVID presents a complex

condition in which multidisciplinary assessment and treatment may be required and which may result in a potentially substantial impact on the daily lives of those with long COVID as well as having a significant impact on healthcare systems and national economies as a whole.[122] To meet the demands of the population with long COVID and to ensure an adequate response is in place, healthcare systems worldwide have developed and implemented clinical infrastructures (such as post-COVID clinics and online support tools) and models of care (including clinical guidelines and pathways).[108]

For example, the HSE's interim long COVID model of care proposes a three pillar approach to a national post-COVID service:

1) patient-led rehabilitation and recovery (with an online support and education platform to manage symptoms at home)

2) general assessment, support, and rehabilitation (supported by General Practice and primary care rehabilitation)

3) specialist assessment, support, and rehabilitation (by means of specialist acute hospital clinics supported by primary care health and social care professionals with early discharge back to primary care for ongoing follow-up where appropriate).

However, key to the successful implementation of these infrastructures and models of care is a thorough understanding of the epidemiology of long COVID, particularly given the condition's evolving evidence base. Ascertainment of national long COVID prevalence estimates and symptoms may assist with the allocation of resources within health system infrastructures and models of care, to appropriately meet demands due to long COVID. Furthermore, identification of risk and protective factors associated with the development of long COVID, may support identification of those most at risk of developing long COVID with a view to early implementation of effective interventions, where available.[123]

This systematic review therefore aimed to address two research questions:

(1) what is the epidemiology and clinical burden of long COVID internationally

(2) among those who have had a SARS-CoV-2 infection, what are the associations between risk and or protective factors, and development of long COVID.

The UK ONS estimated that 2.1 million people in the UK (3.3% of the population) were experiencing long COVID symptoms (as of January 2023).[11] In the US, data from the CDC estimated that 5.9% of all US adults, and 11% of adults who ever had

COVID-19 were experiencing symptoms of long COVID as of January 2023.[80] This review (using data from primary research studies and international disease registries) presents estimates from the general population that are broadly consistent with these figures, although the range is wider, with reported estimates ranging from 15.2%[57] to 53.1%[56] in studies based on self-report data, and from 1.8%[48] to 8.3%[58] in studies considering those with a diagnosis of or referral for long COVID. Similarly, in the subgroups identified as being of relevance to this review, marked variation was seen in the reported prevalence estimates between studies. For adults aged 65 and over, prevalence estimates ranged from 18.3%[57] to 80.8%[54] in studies based on self-report data, and 5.6% to 8.6% in a study considering those with a diagnosis of long COVID.[58] In paediatric populations, prevalence estimates ranged from 4%[34] to 65.7%[88] in studies based on self-report data and from 0.1%[55] to 57.9%[69] in studies considering those with a long COVID diagnosis, indicating that self-reported long COVID is more prevalent in older adults compared to children. Two studies were identified for inclusion with respect to those identified as medically vulnerable (as defined by the HSE), with self-reported prevalence estimates of 29.7% and 12.4% (at 4 weeks, and 12 weeks follow-up, respectively)[46] and 17.7% (at six month follow-up)[64] noted. Finally, among those hospitalised with COVID-19 illness, prevalence estimates ranged from 9.8%[88] to 20%[66] in those under 18 years, and from 30.8%[36] to 94.6%[45] in those 18 years and older. These figures are higher than the estimates given for the general population, and are consistent with the hypothesis that long COVID is more prevalent among those with a history of severe COVID-19 illness.[124]

Long COVID is associated with a broad range of symptoms. January 2023 prevalence estimates from the UK ONS indicate that the most commonly reported symptoms in the general population were fatigue (71%), difficulty concentrating (49%), shortness of breath (47%) and muscle ache (46%).[11] These are broadly consistent with the findings from this review which, while again noting marked variation between studies. Among the general population, the symptoms with the highest prevalence estimates were fatigue, with prevalence estimates ranging from 2.9%[54] to 69%,[58] and brain fog, memory loss and or confusion, with prevalence estimates ranging from 0.2%[48] to 45.7%.[57] However, this review found that anosmia and or dysosmia was the next highest prevalence estimate reported, with prevalence estimates ranging from 1.6%[48] to 43.7%.[57] In the ONS bulletin anosmia was the thirteenth most commonly reported symptom (25%) in those with self-reported long COVID. Shortness of breath was another symptom with high prevalence estimates identified in this review, with prevalence estimates ranging from 3.4%[53] to 39.7%;[57] with the range maximum in line with data from the ONS (prevalence of 47%). Finally, 5.7%[56] to 16.8%[63] of general population participants identified in studies in this review reported muscle aches as a symptom of long

COVID, which is a lower prevalence estimate than that reported by the ONS for the general population (46%).

The range of symptoms with the highest prevalence estimates was consistent among the subgroups in this review (general population, those under 18 years old and 65 years or older, those medically vulnerable, and those with a history of severe COVID-19 illness). However, as with the prevalence of long COVID overall, there was marked variation in estimates between studies. In the age sub-group, fatigue was the symptom with the highest prevalence estimates in those under 18 years old (ranging from 1.1%[77] to 22%,[34] and in those aged 65 years or older (ranging from 4.9%[56] to 38.7%[67]). In those medically vulnerable, symptoms with the highest prevalence estimates were new or worse fatigue in those with MS (ranging from 63.2% to 68.3%),[46] and muscle or weight loss greater than 5% in patients on dialysis.[71] In those with a history of severe COVID-19 illness, fatigue was the symptom with the highest prevalence estimates in those under 18 years (ranging from 1.6%[77] to 9.4%[66]), and in those 18 years and older (ranging from 8.2%[22] to 91.1%[85]). Although estimates differed markedly between studies, respiratory symptoms were typically reported with high prevalence estimates in those under 18 years (ranging from 0.7%[77] to 22%[51]), those aged 65 years or older (ranging from 6.0%[56] to 29.9%[67]), patients on dialysis (14.%),[71] those with MS (ranging from 4.8% to 58.3%[46]) and adults with a history of severe COVID-19 illness (ranging from 3.9%[27] to 83.1%[37]). Shortness of breath was also typically reported as a respiratory symptom with a high prevalence estimate for adults aged 65 years or older (ranging from 5%[65] to 29.9%[67]), and in adults (18 years and older) with a history of severe COVID-19 illness (ranging from 3.9%[27] to 83.1%[52]), while cough was reported as a symptom with a high prevalence estimate for those under 18 years old (ranging from 0.6%[88] to 6.4%[88]). Considering symptoms within the ear, nose and throat cluster, high prevalence estimates were reported in those under 18 years (ranging from 0.5%[77] to 21.1%,[51] and in those with MS (22.1% to 29.5%).[46] Specifically, high prevalence estimates for anosmia (ranging from 4%[24] to 64.4%[30]) and ageusia (ranging from 2.7%[24] to 49.8%[30]) were also reported in adults with a history of severe COVID-19 illness.

In the medically vulnerable subgroup, high prevalence estimates were also reported for gastrointestinal symptoms and joint or muscle pain in those with MS, while impairment of memory or concentration was notable in those aged 65 years or older. In both of these populations (those with MS and those aged 65 years or older) headache was a symptom for which high prevalence estimates were reported. Additionally, in those with MS, symptom prevalence estimates generally increased or remained stable overtime (at four and 12 weeks post COVID-19). High prevalence estimates for gastrointestinal symptoms, joint or muscle pain, memory or concentration impairment, and headache were not generally observed among those

under 18 years old (in both those with and without a history of severe COVID-19 illness).

A number of paediatric studies investigated the association between a history of symptomatic or any SARS-CoV-2 infection with development of long COVID and also the persistence of symptoms over time. In paediatric populations, there was some evidence that those with a history of symptomatic or any SARS-CoV-2 infection were more likely to develop long COVID symptoms than those who had asymptomatic COVID-19 or no history of COVID-19, with a significantly higher prevalence of some symptom clusters noted in those with a history of SARS-COV-2 infection (however this did vary by symptom and age group).

Across the two studies that investigated the persistence of symptoms over time in paediatric populations, one study reported decreasing prevalence of all investigated symptom clusters when comparing six month and 12 month follow-data,[66] while another study reported inconsistent trends in symptom prevalence across and within symptom clusters when comparing follow-up data at one to five months, six to nine months, and 12 months or more.[34] However, in this latter study, there was significant attrition (> 50%) in the number of children participating which may have contributed to the inconsistencies observed.[34]

Among those with a history of severe COVID-19 (defined as those hospitalised or admitted to intensive care due to COVID-19), the most common symptoms reported were fatigue, memory and or concentration impairment, headache, anosmia, ageusia, palpitations or tachycardia, sleep disturbances, and anxiety. Prevalence estimates for this cohort differed by sex and over time. Specifically, higher reporting of each of these symptoms was identified in females compared to males, with the exception of shortness of breath.[37, 57] Across studies that investigated the persistence of symptoms over time, the prevalence of all symptoms was noted to reduce over time in those under 18 years, with mixed trends observed over time (dependent on the symptom and time point) in those 18 years and older. Follow-up time periods ranged from 30 days to two years post-acute COVID-19.

Six new onset conditions were identified in this review, venous thromboembolism (VTE), diabetes mellitus, chronic renal failure, chronic fatigue syndrome, fibromyalgia and post-traumatic stress disorder (PTSD). Increased risk of new onset diabetes among individuals experiencing long COVID was noted within one study in this review.[30] The finding is consistent with the broader literature in relation to post-acute sequelae of COVID-19, with one systematic review of over four million COVID-19 patients and 43 million controls noting that COVID-19 is associated with a significantly higher risk of incident diabetes among survivors (risk ratio: 1.66; 95% CI 1.38-2.00).[125] A number of studies reported in relation to VTE, with some

evidence that the elevated risk decreases over time. While limited to studies reporting prevalence of long COVID, these findings are consistent with the broader literature in which an association between COVID-19 and VTE has been documented.[126, 127] One study in this review[30] identified a report of new onset chronic renal failure. The literature however suggests that approximately 28% of those hospitalised with COVID-19 are diagnosed with an acute kidney injury.[128] It is plausible that this injury may endure over time resulting in chronic renal impairment or failure.

Across studies reporting new onset of PTSD, prevalence estimates varied depending on the population cohort. In the general population, the prevalence estimate of new diagnosis of PTSD was 1.3% at six to 12 months post-acute COVID-19.[56] Higher prevalence estimates of PTSD were reported in those hospitalised with acute COVID-19 with some decrease noted over time from 38% at 30 days post-COVID-19 to 30.8% at 180 days post-COVID-19; these estimates included individuals admitted to intensive care due to COVID-19.[30] While there is a potential association between COVID-19 and PTSD, elevated risk of PTSD symptoms is well documented in adult critical care survivors, potentially impacting 20% of those discharged and with prevalence estimates of 20% up to 12 months post discharge.[129] In addition to the evidence of direct PTSD and neuropsychiatric consequences due to COVID-19, there is systematic review evidence of an increase in psychiatric symptoms or morbidities among both health care workers and the general public attributable to indirect effects of the COVID-19 pandemic on mental health.[130] In those classified as medically vulnerable, one study reported prevalence estimates of 13% for PTSD, depression or anxiety at six months following SARS-CoV-2 infection.[71]

Within this review, there is potential under-reporting of new onset conditions that may be attributable to COVID-19. This may be due to the majority of studies included reported long COVID and or long COVID symptom prevalence using patient-reported outcome measures, such as questionnaires and surveys. Additionally, as the studies limited reporting to new-onset conditions, this will underestimate the burden associated with exacerbation of pre-existing conditions due to COVID-19. While not specific to long COVID, with many long COVID definitions outlining that symptoms cannot be attributable to alternative diagnosis, published literature has reported exacerbation of pre-existing conditions due to COVID-19. This includes systematic reviews reporting neurological sequelae in individuals with chronic neurological disease,[131, 132] and a short report of dermatological flare-ups in individuals with chronic autoimmune diseases (including dermatological conditions).[133]

Overall, there was limited evidence related to quality of life (QoL) across three of the four subgroups assessed (general population, those under 18 years old and 65 years

or older, and those medically vulnerable). For those with a history of severe COVID-19 illness and or who were hospitalised due to COVID-19, 15 identified studies reported evidence on QoL associated with long COVID. Generally, it was reported that those hospitalised with COVID-19 who subsequently developed long COVID had worse QoL, or displayed decreased scores in QoL assessments. Evidence of significant reductions in QoL have been reported in other systematic reviews of post-COVID-19 patients who were hospitalised due to COVID-19. There is also evidence of substantial reductions in QoL in critical illness survivors (including ICU survivors), thus the findings may be related to survivors of critical illness more generally rather than specifically attributable to long COVID.[134, 135]

There was also limited evidence relating to returning to work, across three of the four subgroups assessed (general population, those under 18 years old and 65 years or older, and those medically vulnerable). For those with a history of severe COVID-19 illness and or hospitalised due to COVID-19, two studies were identified that reported prevalence estimates for return to work with 34%[52] unable to return to work at 69 days follow-up and 11%[52] unable to return at two years follow-up. Lack of physical function was stated as the main reason for being unable to return to work. It should be noted however that reduced employment is well documented in ICU survivors with systematic review evidence of suggesting up to one-third of previously employed ICU survivors being jobless at 60 months post-hospital discharge.[136]

Physical activity and or physical functioning was reported in 22 of the primary research studies included, and in the US CDC disease registry documentation. Generally, there was a reduction in physical activity levels reported in those with a history of COVID-19 infection, when compared to those without. Physical activity levels varied in the hospitalised subgroup, with results ranging from 8.5% of participants walking slower than individuals their same age due to breathlessness,[119] to 14% of participants walking distances below the lower limit of the normal range.[52] This is further supported by Wright et al.[137] who, when investigating physical activity patterns and physical activity advice received in those with long COVID, found that long COVID was associated with a reduction in physical activity and a loss of independence in the majority of their 477 participants.

Regarding physical functioning, this was generally reduced in participants with long COVID, with the UK ONS identifying that 18% of 1.6 million people reported being limited in day-to-day activities post-acute COVID-19 infection.[11] The US CDC also reported that as of January 2023, 26.6% of adults were experiencing significant activity limitations due to long COVID.[80] Within the primary research studies there was a lack of evidence in the reporting of physical functioning, with only two studies identified from those with a history of severe COVID-19 illness subgroup reporting

on functional dependence. One study identified that 15% of participants were dependent on help with daily living,[22] while another reported that the majority of participants displayed a high level of independence (86.5%) using the functional independence measure.[38] Again, COVID-19 aside, substantial impairment in physical functioning that improves over time is well documented in ICU survivors.[138]

When investigating factors associated with the development of long COVID and or long COVID symptoms, female sex was identified as a risk factor by multiple primary research studies and in UK ONS data in three of the four sub-groups (general population, age, specifically those aged 65 year or older, and those with severe COVID-19 or hospitalised with COVID-19). This is widely supported throughout the literature with numerous, large, multicentre studies[139, 140] identifying female sex as a risk factor for the development of long COVID.[14, 121] However, in the current review, female sex did not appear to be as widely associated with development of long COVID in children and adolescents under 18 years of age. Currently, the literature presents contrasting results as to whether female sex increases the risk of developing long COVID or not in children, with a systematic review by Pellegrino et al.[141] indicating it was more frequently associated with persistent symptoms. However, the literature also indicates that a lack of sufficient epidemiological research around long COVID in children and adolescents, and that our understanding of the condition in this population is lacking.[142] Older age was also identified as a risk factor for long COVID in the general population with this finding widely supported throughout the literature for the general population.[14] When considering those aged 18 years and under, prevalence of long COVID was also noted to be higher for older relative to younger children. In children and adolescents, while recent studies also identify older age as a risk factor for long COVID,[141, 143] it is also likely that younger children do not consistently report symptoms of long COVID, leading to an underestimate of prevalence estimates.[141]

The presence of asthma or an allergic respiratory condition prior to COVID-19 infection was identified as a risk factor for the development of long COVID in the general population, in children and adolescents under 18 years old and in those with a history of severe COVID-19 (that is hospitalised or admitted to ICU due to COVID-19). This is in contrast to the findings in a large US retrospective cohort study[144] which reported similar prevalence estimates for persistent symptoms three months post-acute COVID-19, in asthmatic and non-asthmatic cohorts. However, a February 2023 study,[145] investigating long COVID outcomes in an adult cohort with asthma suggested that asthma type may be a discerning factor, with the risk of long COVID increased in those with a history of severe asthma, but eosinophilic and T2-asthma possibly acting as protective mechanisms. In those with severe COVID-19 illness and or who were hospitalised with COVID-19, factors related to hospitalisation, such as the type of treatment required, acute disease severity, length of hospital stay and

ICU admission, were identified as risk factors for long COVID development. This is supported throughout the literature with Nalbandian et al.[146] suggesting that those at high risk of long COVID, such as those with severe acute illness and those admitted to ICU, should be prioritised for follow-up care post hospital discharge.

A 2023 systematic review and meta-analysis by Tsampasian et al.[147] reported similar findings to this report. The study evaluated the demographic characteristics and comorbidities that have been found to be associated with an increased risk of developing post-COVID condition (long COVID) in adults aged 18 years or older. Female sex, older age, higher body mass index, smoking were associated with an increased risk of long COVID, with higher risks again observed in those with pre-existing comorbidities and in those who experienced severe COVID-19 (hospitalisation or ICU admission due to acute COVID-19).[147]

Limited evidence was identified in regards to factors which protect against the development of long COVID. Within the general population, increased household income[54, 57] and vaccination[43, 57] were identified as protective factors in two studies each. The role of vaccination is partially supported by a 2022 systematic review which found that vaccination prior to COVID-19 infection reduced the risk of long COVID development, although the low level of evidence (grade III, case-controls, cohort studies) was noted as a significant caveat.[148] Similarly, the 2023 systematic review and meta-analysis by Tsampasian et al.[147] found that the risk of long COVID was significantly lower in those vaccinated against COVID-19 (two doses) compared with those who were not vaccinated.[147]

The epidemiology of long COVID in those who have experienced recurrent episodes of COVID-19 is uncertain with this issue not explicitly considered within the studies included within this review. ONS data published in February 2023 reported that after adjusting for multiple factors related to the risk of both COVID-19 reinfection and self-reported long COVID (such as sociodemographic characteristics and vaccination status), the odds of new-onset, self-reported long COVID among adults were 28% lower after a second COVID-19 infection, compared with a first infection.[149] However, evidence from a large US study suggests that beyond the acute phase, reinfection with SARS-CoV-2 contributes to a significant increased risk of all-cause mortality, hospitalisation and post-acute sequelae (in both pulmonary and extra-pulmonary organs)[150, 151] with risks and clinical burden noted to increase according to the number of infections. Despite the mixed evidence available surrounding SARS-CoV-2 re-infection and long COVID development, prevention of reinfection is likely to still protect from additional health risks.

6.1 Strengths and limitations

This systematic review presents a comprehensive analysis of the epidemiology of long COVID internationally, with over 60 primary research studies and registry data included within the final report. There are a number of notable strengths to this review.

Firstly, the majority of the primary research studies identified within this analysis were deemed to be of good or fair quality (79%), with only studies of sufficient quality included within the final analysis. Additionally, while long COVID definitions can vary in terms of their minimum time point for long COVID onset, the NICE definition used within this study included all signs and symptoms of COVID-19 from four weeks post-acute infection.[108] This ensured that studies which used an alternative long COVID definition (such as the WHO definition[152]) and or investigated long COVID in a differing time period post-acute infection (such as long post-COVID symptoms from week 12 to week 24, and persistent post-COVID symptoms lasting more than 24 weeks)[153] were eligible for inclusion. Within Ireland the HSE currently defines long COVID within the interim model of care as symptoms not attributable to alternative diagnosis, lasting greater than 12 weeks from acute COVID-19.

This review was also strengthened by the use of multiple sub-groups: general population; children and adolescents and older adults; those with severe COVID-19 or hospitalised due to COVID-19 (further split into those less than 18 years and those 18 years or older); and those identified as medically vulnerable. Previously large systematic reviews on long COVID have often focused on one sub-group only,[154] such as hospitalised populations[155] or children and adolescents.[156] While this allows for a thorough investigation of a specific population of interest, the application of sub-groups within this narrative analysis has allowed for comparison of long COVID prevalence estimates and risk factors across specific populations of interest. This is particularly relevant when considering the application of these learnings to healthcare resource allocation across the publicly funded healthcare system in Ireland.

While no Irish primary research study or national registry document was identified for inclusion within the current review, the evidence which was obtained from a broad range of European countries was considered broadly applicable to the Irish population given some of the similarities in demography and the trajectory of the COVID-19 pandemic.

However, this review is subject to a number of important limitations. Firstly, systematically assessing the prevalence of long COVID and its associated symptoms remains difficult, primarily due to the evolving definition of long COVID, heterogeneous study designs and outcome measures, lack of appropriate

comparison groups and varying data quality.[154] Heterogeneous study designs are regularly cited within the literature as a difficulty when analysing long COVID epidemiology.[155] This includes, but is not limited to, variation in the number of follow-up time points and or assessments; the time period(s) at which follow-up is conducted, the measurement methods used and the range of symptoms assessed.

Additionally, symptom prevalence estimates presented within this review have been reported, where data were available, both for those with a history of COVID-19 (based on a clinical diagnosis, positive SARS-COV-2 test, or as defined by the study author) and in those identified as having long COVID. This is due to the multiple definitions available for long COVID, and to ensure we did not restrict inclusion to only those studies with an author-defined long COVID subgroup. The inclusion of symptom prevalence estimates derived from populations which included those with a history of COVID-19 (with and without persistent symptoms), along with prevalence estimates derived from those specified as long COVID may have contributed to the wide range of prevalence estimates observed across studies.

Furthermore, while a wide range of symptoms and their associated prevalence's were identified within this review, it is likely further symptoms are experienced by those living with long COVID. For example, limited information regarding post-exertional malaise (PEM) was identified. It is possible that PEM reporting may have been masked within studies which reported on more generally fatigue and or malaise, as well as the reporting of symptoms "following activity". Additionally, a 2023 long COVID review stated PEM may not be widely known, and therefore is often not included in study's investigating long COVID.[121] It should also be noted that symptoms reported within this review are not specific to long COVID and have been associated with a substantial burden in other conditions. For example, cognitive impairments experienced by those with long COVID is often subjectively described as "brain fog", and characterised by a range of symptoms such as poor concentration, feeling confused, thinking more slowly than usual, short-term memory loss and mental fatigue.[157] Similar symptoms have been reported with lupus, multiple sclerosis, myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), fibromyalgia and post-concussion syndrome. While associated with a substantial burden, the underlying neurobiology of these symptoms is uncertain. Neuropsychological deficits are inconsistent and there is an absence of structural lesions on conventional neuroimaging.[158] Improved understanding of the shared cognitive symptoms of long COVID and ME/CFS may support faster development of effective evidence-based treatments.

Within this review, the majority of studies included reported the prevalence of long COVID and or the prevalence of long COVID symptoms using patient-reported outcome measures, such as questionnaires and surveys. This aided in the

identification of symptoms assumed to be associated with the acute COVID-19 infection, and which were not attributed to an alternative diagnosis or underlying condition. However, it may also have resulted in the omission of new-onset conditions diagnosed by a physician which were attributable to COVID-19. Studies which primarily used electronic health databases (such as the US Veterans Health Administration) and ICD-10 codes to identify post-acute sequelae of COVID-19, were largely excluded,[150] as these could not exclusively be attributed to previous COVID-19 infection.

Additionally, only eight studies were included within the final dataset which investigated the prevalence of long COVID and or long COVID symptoms in matched cohorts.[22, 52, 55, 56, 64, 77, 86, 88] This may limit our understanding of the baseline estimation of symptoms within our sub-groups. Furthermore, while those with previous (confirmed or suspected) COVID-19 generally comprised the case cohort, matched control cohorts varied across studies and included those with a negative SARS-CoV-2 test result,[56] those who never tested positive for SARS-CoV-2 infection,[64, 88] or those hospitalised for reasons other than COVID-19.[22] It is therefore possible participants within matched control cohorts had previous undocumented SARS-CoV-2 infection. Reasons for this may have included that they were unable to access PCR testing during periods of significant demand, or that they did not present for testing as they were asymptomatic. Furthermore, the timing of the PCR test may have influenced the results: testing very early or late in the disease course when the virus is undetectable may result in a negative test result; for example, a 2022 systematic review suggested that 58% of COVID-19 patients may have initial false-negative PCR results.[159] It is possible therefore that participants within negative SARS-CoV-2 test result cohorts may also have had COVID-19. It is also important to note that participants within both case and control groups may have also have had other acute viral infections such as Respiratory Syncytial Virus (RSV) and influenza and this may have led to some of the burden associated to these conditions being misattributed long COVID. However, the contrary is also possible, with those who were asymptomatic and or never tested for SARS-CoV-2 infection, attributing long COVID symptoms, to a subsequent acute viral infection such as RSV. Factors for which case and control cohorts were matched also varied across studies and included time of SARS-CoV-2 test,[56] age,[52, 64, 88] sex,[52, 64, 88] the presence of comorbidities,[52] and or hospital admission date and institution.[22]

Lastly, limited evidence was identified in relation to the association between vaccination status and development of long COVID or between COVID-19 variant type and development of long COVID. Worldwide COVID-19 vaccination distribution (outside of clinical trial) began in late 2020, with the majority of studies included within this review relating to participants who were infected with COVID-19 prior to

or during vaccination distribution. Similarly, only a limited number of studies identified the predominant variant or variants in their study region during participant COVID-19 infection periods, using genome sequencing data available (Global Initiative in Sharing All Influenza Data,[55, 57] COG UK Mutation Explorer.[160] These factors limit the ability to draw conclusions regarding the association between vaccination status and variant type and the development of long COVID.

As the studies included within this review were conducted internationally, and at various time points, vaccination status and variant type may have impacted the prevalence estimates outlined. No Irish primary research study or national registry document was included within the current review and therefore an understanding of the Irish national prevalence estimate of long COVID, and its associated symptoms, is required. On 14 March 2023, the HSE launched an online survey: Follow-up After Disease Acquisition (FADA).[161] The survey was aimed at understanding more about how people are recovering from COVID-19 and or living with long COVID in Ireland. This survey will be used to estimate the prevalence rate of long COVID in the Irish community, and may further inform the allocation of healthcare resources within the interim long COVID model of care in Ireland.

7 Conclusion

Long COVID is a heterogeneous, complex condition impacting multiple organ systems. It can manifest in the form of over 200 different symptoms and can significantly impact the lives of those affected. This systematic review presents the international epidemiology of long COVID up to January 2023. It includes fifty-one primary research studies and four international registry documents in the final dataset.

From the evidence included, a wide range of prevalence estimates were identified for long COVID (as a broad condition), within and across our specified sub-groups (general population, age (those aged under 18 years and those 65 years or older), those classified by the HSE as medically vulnerable, and those with a history of severe COVID-19 illness). Focusing more specifically on long COVID symptoms, findings across the primary research studies and international registry documents were broadly consistent for the general population, with fatigue and neurological symptoms frequently reported. Fatigue was also frequently identified as a long COVID symptom within the remaining sub-groups (age (those aged under 18 years and those 65 years or older), medically vulnerable and those with a history of severe COVID-19 illness).

Further symptoms of long COVID which are frequently reported included respiratory symptoms such as dyspnoea in those aged 65 years or older and in adults with

severe COVID-19 illness, and cough in paediatric populations. Limited evidence was identified in relation to the quality of life and the ability to return to work in those with long COVID. However, it was generally reported that physical activity levels were decreased in those with a history of COVID-19 infection with more substantial impairments noted in those with a history of severe COVID-19. Female sex and older age were the most commonly reported risk factors for the development of long COVID or long COVID symptoms across the sub-groups. However, in paediatric populations, female sex did not appear to be as widely associated with the development of long COVID or long COVID symptoms. In those with a history of severe COVID-19 illness, factors related to the hospitalisation episode (such as length of stay and ICU admission) were most commonly identified as risk factors for the development of long COVID or long COVID symptoms. While prevalence estimates differed substantially between studies, reductions in the prevalence of long COVID were typically noted in studies reporting prevalence over time.

While the evidence presented outlines an up-to-date analysis of the epidemiology of long COVID internationally, heterogeneity of study designs, long COVID definitions within studies, outcome assessment methods and follow-up time points are likely to have contributed to the wide range of prevalence estimates observed throughout the included evidence. While only studies deemed to be of fair and good quality were included in the final analysis, the majority of studies were based on self-reported long COVID and long COVID symptoms and therefore bias may be inherent throughout.

Long COVID is a complex condition potentially involving a wide range of symptoms and which may result in sustained, significant reductions in quality of life and functioning in some individuals and a substantial burden on healthcare systems as well as having a broader economic impact. In planning healthcare delivery for this population, a focus on multi-disciplinary holistic care will likely be necessary.

References

1. World Health Organization (WHO). WHO coronavirus dashboard 2023. Available from:https://covid19.who.int
2. World Health Organization (WHO). Clinical management of COVID-19: living guideline, 13 January 2023. Geneva: World Health Organization, 2023.
3. van Kessel SAM, Olde Hartman TC, Lucassen P, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. Fam Pract. 2022;39(1):159-67.
4. Kluge HHP, Muscat NA, Mishra S, Nielsen S, Tille F, Pfeifer D, et al. Call for action: Health services in the European region must adopt integrated care models to manage Post-Covid-19 Condition. The Lancet Regional Health – Europe. 2022;18.
5. World Health Organization (WHO). Post COVID-19 condition (Long COVID) 2022. Available from:https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition
6. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2023.
7. Castanares-Zapatero D, Chalon P, Kohn L, Dauvrin M, Detollenaere J, Maertens de Noordhout C, et al. Pathophysiology and mechanism of long COVID: a comprehensive review. Annals of Medicine. 2022;54(1):1473-87.
8. Wainwright TW, Low M. Why the biopsychosocial model needs to be the underpinning philosophy in rehabilitation pathways for patients recovering from COVID-19. Integrated Healthcare Journal. 2020;2(1).
9. Garg M, Maralakunte M, Garg S, Dhooria S, Sehgal I, Bhalla AS, et al. The conundrum of 'long-covid-19: A narrative review. International Journal of General Medicine. 2021;14:2491-506.
10. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. Jama. 2022;328(16):1604-15.
11. Office for National Statistics (ONS). Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 5 January 2023 2023 updated 5 January 2023. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/5january2023
12. de Oliveira Almeida K, Nogueira Alves IG, de Queiroz RS, de Castro MR, Gomes VA, Santos Fontoura FC, et al. A systematic review on physical function, activities of daily living and health-related quality of life in COVID-19 survivors. Chronic illness. 2023;19(2):279-303.
13. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid - Mechanisms, risk factors, and management. The BMJ. 2021;374:n1648.
14. Tene L, Bergroth T, Eisenberg A, David SSB, Chodick G. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID. International Journal of Infectious Diseases. 2023;128:3-10.

15. Health and Information Quality Authority (HIQA). COVID-19 Evidence Synthesis: Protocol for an international review of the epidemiology of long COVID 2023. Available from:https://www.hiqa.ie/sites/default/files/2023-01/Protocol_for_an_international_review_of_the_epidemiology_of_long_COVID_0.pdf
16. Health Service Executive (HSE). People at higher risk from COVID-19 2022 updated12 September 2022. Available from:https://www2.hse.ie/conditions/covid19/people-at-higher-risk/overview/
17. Health Information and Quality Authority (HIQA). International review of clinical guidelines and models of care for long COVID. 2022 16 December 2022. Report No.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.
19. Black N, Barker M, Payne M. Cross sectional survey of multicentre clinical databases in the United Kingdom. Bmj. 2004;328(7454):1478.
20. Bergia M, Sanchez-Marcos E, Gonzalez-Haba B, Hernaiz AI, de Ceano-Vivas M, Garcia Lopez-Hortelano M, et al. Comparative study shows that 1 in 7 Spanish children with COVID-19 symptoms were still experiencing issues after 12 weeks. Acta Paediatrica, International Journal of Paediatrics. 2022;111(8):1573-82.
21. Martin-Loeches I, Motos A, Menéndez R, Gabarrús A, González J, Fernández-Barat L, et al. ICU-Acquired Pneumonia Is Associated with Poor Health Post-COVID-19 Syndrome. Journal of clinical medicine. 2021;11(1).
22. Rivera-Izquierdo M, Láinez-Ramos-Bossini AJ, de Alba IG-F, Ortiz-González-Serna R, Serrano-Ortiz Á, Fernández-Martínez NF, et al. Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes-a multicentre cohort study. BMC medicine. 2022;20(1):92.
23. Fernandez-de-Las-Penas C, de-la-Llave-Rincon AI, Ortega-Santiago R, Ambite-Quesada S, Gomez-Mayordomo V, Cuadrado ML, et al. Prevalence and risk factors of musculoskeletal pain symptoms as long-term post-COVID sequelae in hospitalized COVID-19 survivors: a multicenter study. Pain. 2022;163(9):e989-e96.
24. Fernandez-De-las-penas C, Martin-Guerrero JD, Pellicer-Valero OJ, Navarro-Pardo E, Gomez-Mayordomo V, Cuadrado ML, et al. Female Sex Is a Risk Factor Associated with Long-Term Post-COVID Related-Symptoms but Not with COVID-19 Symptoms: The LONG-COVID-EXP-CM Multicenter Study. Journal of Clinical Medicine. 2022;11(2):413.
25. Fernandez-De-Las-Penas C, Ryan-Murua P, Rodriguez-Jimenez J, Palacios-Cena M, Arendt-Nielsen L, Torres-Macho J. Serological Biomarkers at Hospital Admission Are Not Related to Long-Term Post-COVID Fatigue and Dyspnea in COVID-19 Survivors. Respiration. 2022;101(7):658-65.
26. Fernandez-De-las-Penas C, Palacios-Cena D, Gomez-Mayordomo V, Palacios-Cena M, Rodriguez-Jimenez J, de-La-Llave-Rincon AI, et al. Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously

Hospitalized Patients: Related Functional Limitations and Disability. Respiration. 2022;101(2):132-41.
27. Fernández-de-las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, Guerrero-Peral A, Martín-Guerrero JD, García-Azorín D, et al. Post–COVID-19 Symptoms 2 Years After SARS-CoV-2 Infection Among Hospitalized vs Nonhospitalized Patients. JAMA Network Open. 2022;5(11):e2242106-e.
28. Fernandez-De-las-penas C, Cancela-Cilleruelo I, Rodriguez-Jimenez J, Gomez-Mayordomo V, Pellicer-Valero OJ, Martin-Guerrero JD, et al. Associated-Onset Symptoms and Post-COVID-19 Symptoms in Hospitalized COVID-19 Survivors Infected with Wuhan, Alpha or Delta SARS-CoV-2 Variant. Pathogens. 2022;11(7):725.
29. Bai F, Tomasoni D, Falcinella C, Barbanotti D, Castoldi R, Mule G, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. Clinical Microbiology and Infection. 2022;28(4):611.e9-.e16.
30. Boglione L, Meli G, Poletti F, Rostagno R, Moglia R, Cantone M, et al. Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect? QJM : monthly journal of the Association of Physicians. 2022;114(12):865-71.
31. Comelli A, Viero G, Bettini G, Nobili A, Tettamanti M, Galbussera AA, et al. Patient-Reported Symptoms and Sequelae 12 Months After COVID-19 in Hospitalized Adults: A Multicenter Long-Term Follow-Up Study. Frontiers in Medicine. 2022;9:834354.
32. Spinicci M, Graziani L, Tilli M, Nkurunziza J, Vellere I, Borchi B, et al. Infection with SARS-CoV-2 Variants Is Associated with Different Long COVID Phenotypes. Viruses. 2022;14(11).
33. Buonsenso D, Martino L, Morello R, De Rose C, Valentini P. Chronic Olfactory Dysfunction in Children with Long COVID: A Retrospective Study. Children (Basel, Switzerland). 2022;9(8).
34. Buonsenso D, Pazukhina E, Gentili C, Vetrugno L, Morello R, Zona M, et al. The Prevalence, Characteristics and Risk Factors of Persistent Symptoms in Non-Hospitalized and Hospitalized Children with SARS-CoV-2 Infection Followed-Up for up to 12 Months: A Prospective, Cohort Study in Rome, Italy. Journal of Clinical Medicine. 2022;11(22):6772.
35. Damanti S, Cilla M, Cilona M, Fici A, Merolla A, Pacioni G, et al. Prevalence of Long COVID-19 Symptoms After Hospital Discharge in Frail and Robust Patients. Frontiers in Medicine. 2022;9:834887.
36. Trapani G, Verlato G, Bertino E, Maiocco G, Vesentini R, Spadavecchia A, et al. Long COVID-19 in children: an Italian cohort study. Italian journal of pediatrics. 2022;48(1):83.
37. Barreto APA, Barreto Filho MA, Duarte LC, Cerqueira-Silva T, Camelier A, Tavares NM, et al. Metabolic disorders and post-acute hospitalization in black/mixed-race patients with long COVID in Brazil: A cross-sectional analysis. PloS one. 2022;17(10):e0276771.
38. Battistella LR, Imamura M, De Pretto LR, Van Cauwenbergh SKHAA, Delgado Ramos V, Saemy Tome Uchiyama S, et al. Long-term functioning status of COVID-19 survivors: a prospective observational evaluation of a cohort of patients surviving hospitalisation. BMJ open. 2022;12(7):e057246.

39. Damiano RF, Neto DB, Oliveira JVR, Magalhães Santos J, Alves JVR, Guedes BF, et al. Association between chemosensory impairment with neuropsychiatric morbidity in post-acute COVID-19 syndrome: results from a multidisciplinary cohort study. European archives of psychiatry and clinical neuroscience. 2022.
40. de Oliveira JF, de Avila RE, de Oliveira NR, da Cunha Severino Sampaio N, Botelho M, Goncalves FA, et al. Persistent symptoms, quality of life, and risk factors in long COVID: a cross-sectional study of hospitalized patients in Brazil. International Journal of Infectious Diseases. 2022;122:1044-51.
41. Ferreira JC, Moreira TCL, de Araujo AL, Imamura M, Damiano RF, Garcia ML, et al. Clinical, sociodemographic and environmental factors impact post-COVID-19 syndrome. Journal of global health. 2022;12:05029.
42. Nakayama LF, Urias MG, Goncalves AS, Ribeiro RA, Macruz TDA, Pardo RB. Post-discharge follow-up of patients with COVID-19: A Brazilian experience. SAGE Open Medicine. 2022;10.
43. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. The BMJ. 2022:e069676.
44. Buttery S, Philip KEJ, Williams P, Fallas A, West B, Cumella A, et al. Patient symptoms and experience following COVID-19: Results from a UK-wide survey. BMJ Open Respiratory Research. 2021;8(1):e001075.
45. Evans RA, Leavy OC, Richardson M, Elneima O, McAuley HJC, Shikotra A, et al. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. The Lancet Respiratory Medicine. 2022;10(8):761-75.
46. Garjani A, Middleton RM, Nicholas R, Evangelou N. Recovery From COVID-19 in Multiple Sclerosis: A Prospective and Longitudinal Cohort Study of the United Kingdom Multiple Sclerosis Register. Neurology(R) neuroimmunology & neuroinflammation. 2022;9(1).
47. Heightman M, Prashar J, Hillman TE, Marks M, Livingston R, Ridsdale HA, et al. Post-COVID-19 assessment in a specialist clinical service: A 12-month, single-centre, prospective study in 1325 individuals. BMJ Open Respiratory Research. 2021;8(1):e001041.
48. Meza-Torres B, Delanerolle G, Okusi C, Mayor N, Anand S, Macartney J, et al. Differences in Clinical Presentation With Long COVID After Community and Hospital Infection and Associations With All-Cause Mortality: English Sentinel Network Database Study. JMIR public health and surveillance. 2022;8(8):e37668.
49. Hudson JI, Pope HG, Jr., Glynn RJ. The cross-sectional cohort study: an underutilized design. Epidemiology (Cambridge, Mass). 2005;16(3):355-9.
50. Dumont R, Richard V, Lorthe E, Loizeau A, Pennacchio F, Zaballa M-E, et al. A population-based serological study of post-COVID syndrome prevalence and risk factors in children and adolescents. Nature Communications. 2022;13(1).
51. Miller F, Nguyen DV, Navaratnam AM, Shrotri M, Kovar J, Hayward AC, et al. Prevalence and Characteristics of Persistent Symptoms in Children During the

COVID-19 Pandemic: Evidence From a Household Cohort Study in England and Wales. The Pediatric infectious disease journal. 2022;41(12):979-84.
52. Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. The Lancet Respiratory medicine. 2022.
53. Bernas SN, Baldauf H, Real R, Sauter J, Markert J, Trost S, et al. Post-COVID-19 condition in the German working population: A cross-sectional study of 200k registered stem cell donors. J Intern Med. 2022.
54. Whitaker M, Elliott J, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, et al. Persistent COVID-19 symptoms in a community study of 606,434 people in England. Nature communications. 2022;13(1):1957.
55. Kildegaard H, Lund LC, Hojlund M, Stensballe LG, Pottegard A. Risk of adverse events after covid-19 in Danish children and adolescents and effectiveness of BNT162b2 in adolescents: Cohort study. The BMJ. 2022:e068898.
56. Sørensen AIV, Spiliopoulos L, Bager P, Nielsen NM, Hansen JV, Koch A, et al. A nationwide questionnaire study of post-acute symptoms and health problems after SARS-CoV-2 infection in Denmark. Nature communications. 2022;13(1):4213.
57. Perlis RH, Santillana M, Ognyanova K, Safarpour A, Lunz Trujillo K, Simonson MD, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. JAMA network open. 2022;5(10):e2238804.
58. Kostev K, Smith L, Koyanagi A, Jacob L. Prevalence of and Factors Associated With Post-Coronavirus Disease 2019 (COVID-19) Condition in the 12 Months After the Diagnosis of COVID-19 in Adults Followed in General Practices in Germany. Open Forum Infectious Diseases. 2022;9(7):ofac333.
59. Borch L, Holm M, Knudsen M, Ellermann-Eriksen S, Hagstroem S. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. European Journal of Pediatrics. 2022;181(4):1597-607.
60. Donnachie E, Hapfelmeier A, Linde K, Tauscher M, Gerlach R, Greissel A, et al. Incidence of Post-Covid Syndrome and Associated Symptoms in Outpatient Care in Bavaria, Germany. medRxiv. 2022.
61. Hastie CE, Lowe DJ, McAuley A, Winter AJ, Mills NL, Black C, et al. Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. Nat Commun. 2022;13(1):5663.
62. Peter RS, Nieters A, Krausslich HG, Brockmann SO, Gopel S, Kindle G, et al. Prevalence, determinants, and impact on general health and working capacity of post-acute sequelae of COVID-19 six to 12 months after infection: a population-based retrospective cohort study from southern Germany. medRxiv. 2022.
63. Peter RS, Nieters A, Kräusslich H-G, Brockmann SO, Göpel S, Kindle G, et al. Post-acute sequelae of covid-19 six to 12 months after infection: population based study. BMJ (Clinical research ed). 2022;379:e071050.
64. Kikkenborg Berg S, Palm P, Nygaard U, Bundgaard H, Petersen MNS, Rosenkilde S, et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0-14 years and matched controls in Denmark (LongCOVIDKidsDK): a

national, cross-sectional study. The Lancet Child and Adolescent Health. 2022;6(9):614-23.
65. Fang X, Ming C, Cen Y, Lin H, Zhan K, Yang S, et al. Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study. Journal of Infection. 2022;84(2):179-86.
66. Pazukhina E, Andreeva M, Spiridonova E, Bobkova P, Shikhaleva A, El-Taravi Y, et al. Prevalence and risk factors of post-COVID-19 condition in adults and children at 6 and 12 months after hospital discharge: a prospective, cohort study in Moscow (StopCOVID). BMC medicine. 2022;20(1):244.
67. Daitch V, Yelin D, Awwad M, Guaraldi G, Milić J, Mussini C, et al. Characteristics of long COVID among older adults: a cross-sectional study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2022.
68. Funk AL, Florin TA, Kuppermann N, Tancredi DJ, Xie J, Kim K, et al. Outcomes of SARS-CoV-2-Positive Youths Tested in Emergency Departments: The Global PERN-COVID-19 Study. JAMA network open. 2022;5(1):e2142322.
69. Kostev K, Smith L, Koyanagi A, Konrad M, Jacob L. Post-COVID-19 conditions in children and adolescents diagnosed with COVID-19. Pediatric Research. 2022.
70. Bahat G, Medetalibeyoglu A, Senkal N, Cebeci T, Oren MM, Basaran S, et al. Symptomatology and imaging findings in early post-Covid period: A comparative study in older vs younger patients. Experimental Gerontology. 2022;167:111907.
71. Belkacemi M, Baouche H, Gomis S, Lassalle M, Couchoud C. Long-lasting clinical symptoms 6 months after COVID-19 infection in the French national cohort of patients on dialysis. Journal of Nephrology. 2022;35(3):787-93.
72. Oto OA, Ozturk S, Arici M, Velioğlu A, Dursun B, Guller N, et al. Middle-term outcomes in renal transplant recipients with COVID-19: a national, multicenter, controlled study. Clinical kidney journal. 2022;15(5):999-1006.
73. Gonzalez-Islas D, Sanchez-Moreno C, Orea-Tejeda A, Hernandez-Lopez S, Salgado-Fernandez F, Keirns-Davis C, et al. Body composition and risk factors associated with sarcopenia in post-COVID patients after moderate or severe COVID-19 infections. BMC Pulmonary Medicine. 2022;22(1):223.
74. Yoo SM, Liu TC, Motwani Y, Sim MS, Viswanathan N, Samras N, et al. Factors Associated with Post-Acute Sequelae of SARS-CoV-2 (PASC) After Diagnosis of Symptomatic COVID-19 in the Inpatient and Outpatient Setting in a Diverse Cohort. Journal of general internal medicine. 2022;37(8):1988-95.
75. Norgard BM, Zegers FD, Nielsen J, Kjeldsen J. Post COVID-19 hospitalizations in patients with chronic inflammatory diseases - A nationwide cohort study. Journal of Autoimmunity. 2021;125:102739.
76. Lorusso R, De Piero ME, Mariani S, Di Mauro M, Folliguet T, Taccone FS, et al. In-hospital and 6-month outcomes in patients with COVID-19 supported with extracorporeal membrane oxygenation (EuroECMO-COVID): a multicentre, prospective observational study. The Lancet Respiratory Medicine.
77. Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Kim K, et al. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. JAMA Network Open. 2022;5(7):E2223253.

78. Centers for Disease Prevention and Control (CDC). Post–COVID-19 Symptoms and Conditions Among Children and Adolescents — United States, March 1, 2020–January 31, 2022 CDC2022. Available from:https://www.cdc.gov/mmwr/volumes/71/wr/mm7131a3.htm?s_cid=mm7131a3_w
79. Centers for Disease Prevention and Control (CDC). Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021 2022. Available from:https://www.cdc.gov/mmwr/volumes/71/wr/mm7121e1.htm#:~:text=Among%20those%20aged%20%E2%89%A565,attributable%20to%20previous%20COVID%2D19
80. Centers for Disease Prevention and Control (CDC). Household Pulse Survey 2022. Available from:https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm.
81. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 September 2022. 2022.
82. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 3 November 2022 [Internet]. 2022;cited2022 Nov 14]. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/3november2022
83. Bek LM, Berentschot JC, Heijenbrok-Kal MH, Huijts S, Van Genderen ME, Vlake JH, et al. Symptoms persisting after hospitalisation for COVID-19: 12 months interim results of the CO-FLOW study. ERJ Open Research. 2022;8(4):00355-2022.
84. Dryden M, Mudara C, Vika C, Blumberg L, Mayet N, Cohen C, et al. Post-COVID-19 condition 3 months after hospitalisation with SARS-CoV-2 in South Africa: a prospective cohort study. The Lancet Global Health. 2022;10(9):e1247-e56.
85. Feldman DE, Boudrias MH, Mazer B. Long COVID symptoms in a population-based sample of persons discharged home from hospital. Canadian journal of public health = Revue canadienne de sante publique. 2022:1-10.
86. Nugawela MD, Stephenson T, Shafran R, De Stavola BL, Ladhani SN, Simmons R, et al. Predictive model for long COVID in children 3 months after a SARS-CoV-2 PCR test. BMC medicine. 2022;20(1):465.
87. Ozonoff A, Schaenman J, Jayavelu ND, Milliren CE, Calfee CS, Cairns CB, et al. Phenotypes of disease severity in a cohort of hospitalized COVID-19 patients: Results from the IMPACC study. eBioMedicine. 2022;83:104208.
88. Kikkenborg Berg S, Dam Nielsen S, Nygaard U, Bundgaard H, Palm P, Rotvig C, et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKidsDK): a national, cross-sectional study. The Lancet Child and Adolescent Health. 2022;6(4):240-8.
89. Damanti S, Ramirez GA, Bozzolo EP, Rovere-Querini P, De Lorenzo R, Magnaghi C, et al. Six-month respiratory outcomes and exercise capacity of COVID-19 acute respiratory failure patients treated with continuous positive airway pressure. Internal Medicine Journal. 2021;51(11):1810-5.

90. Agency for Clinical Innovation NSW. Clinical practice guide for assessment and management of adults with post-acute sequelae of COVID-19: Guidance for NSW health clinicians. . 2022 1 August 2022. Report No.
91. Alberta Health Services. Provincial post-covid rehabilitation taskforce. 2020.
92. American Academy of Pediatrics. Post-COVID-19 Conditions in Children and Adolescents 2022 updated2 September 2022. Available from:https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/post-covid-19-conditions-in-children-and-adolescents
93. Australian National COVID-19 Clinical Evidence Taskforce Caring for people with COVID-19 2022 updatedSeptember 2022. Available from:https://clinicalevidence.net.au/covid-19/
94. British Columbia Ministry of Health. Approach to assessment and management of long-term COVID-19 symptoms in primary care. 2021.
95. Esposito S, Principi N, Azzari C, Cardinale F, Di Mauro G, Galli L, et al. Italian intersociety consensus on management of long covid in children. Italian Journal of Pediatrics. 2022;48(1):42.
96. Fine JS, Ambrose AF, Didehbani N, Fleming TK, Glashan L, Longo M, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). Pm r. 2022;14(1):96-111.
97. Franke C, Berlit P, Prüss H. Neurological manifestations of post-COVID-19 syndrome S1-guideline of the German society of neurology. Neurological research and practice. 2022;4(1):28.
98. Funke-Chambour M, Bridevaux PO, Clarenbach CF, Soccal PM, Nicod LP, von Garnier C. Swiss Recommendations for the Follow-Up and Treatment of Pulmonary Long COVID. Respiration. 2021;100(8):826-41.
99. Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, Ammirati E, et al. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play. Journal of the American College of Cardiology. 2022;79(17):1717-56.
100. Herrera JE, Niehaus WN, Whiteson J, Azola A, Baratta JM, Fleming TK, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. Pm r. 2021;13(9):1027-43.
101. Maley JH, Alba GA, Barry JT, Bartels MN, Fleming TK, Oleson CV, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of breathing discomfort and respiratory sequelae in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). Pm r. 2022;14(1):77-95.
102. Ontario Health. Assessment and management of the Post-COVID-19 condition. 2022.
103. Paterson I, Ramanathan K, Aurora R, Bewick D, Chow CM, Clarke B, et al. Long COVID-19: A Primer for Cardiovascular Health Professionals, on Behalf of the CCS Rapid Response Team. The Canadian journal of cardiology. 2021;37(8):1260-2.

104. Sisó-Almirall A, Brito-Zerón P, Conangla Ferrín L, Kostov B, Moragas Moreno A, Mestres J, et al. Long Covid-19: Proposed Primary Care Clinical Guidelines for Diagnosis and Disease Management. Int J Environ Res Public Health. 2021;18(8).
105. van Haastregt JCM, Everink IHJ, Schols J, Grund S, Gordon AL, Poot EP, et al. Management of post-acute COVID-19 patients in geriatric rehabilitation: EuGMS guidance. European geriatric medicine. 2022;13(1):291-304.
106. Whiteson JH, Azola A, Barry JT, Bartels MN, Blitshteyn S, Fleming TK, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cardiovascular complications in patients with post-acute sequelae of SARS-CoV-2 infection (PASC). Pm r. 2022;14(7):855-78.
107. Yelin D, Moschopoulos CD, Margalit I, Gkrania-Klotsas E, Landi F, Stahl J-P, et al. ESCMID rapid guidelines for assessment and management of long COVID. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2022;28(7):955-72.
108. National Institute for Health and Care Excellence (NICE) SIGNS, and Royal College of General Practitioners (RCGP) COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2022.
109. Nurek M, Rayner C, Freyer A, Taylor S, Järte L, MacDermott N, et al. Recommendations for the recognition, diagnosis, and management of long COVID: a Delphi study. Br J Gen Pract. 2021;71(712):e815-e25.
110. Singapore Ministry of Health. Interim COVID-19 clinical management guidelines. 2021.
111. Centers for Disease Prevention and Control (CDC). Post-COVID Conditions: Information for Healthcare Providers 2022. Available from:https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-care%2Fpost-covid-index.html.
112. Istituto Superiore di Sanità. Interim Guidance on Long-COVID Management Principles. 2021.
113. Royal Australian College of General Practitioners. Caring for patients with post–COVID-19 conditions 2022. Available from:https://www.racgp.org.au/clinical-resources/covid-19-resources/clinical-care/caring-for-patients-with-post-covid-19-conditions/introduction.
114. Gil-Manso S, Miguens Blanco I, López-Esteban R, Carbonell D, López-Fernández LA, West L, et al. Comprehensive Flow Cytometry Profiling of the Immune System in COVID-19 Convalescent Individuals. Frontiers in immunology. 2022;12:793142.
115. Instituto de Saude Publica da Universidade do P, Centro Hospitalar De São João EPE, Porto IIDPEIMDUD. COVID-19: A Scope Research on Epidemiology and Clinical Course. 2023.
116. McGrath LJ, Scott AM, Surinach A, Chambers R, Benigno M, Malhotra D. Use of the Postacute Sequelae of COVID-19 Diagnosis Code in Routine Clinical Practice in the US. JAMA Network Open. 2022;5(10):e2235089-e.

117. Frontera JA, Sabadia S, Yang D, de Havenon A, Yaghi S, Lewis A, et al. Life stressors significantly impact long-term outcomes and post-acute symptoms 12-months after COVID-19 hospitalization. Journal of the Neurological Sciences. 2022:120487.
118. Asadi-Pooya AA, Akbari A, Emami A, Lotfi M, Rostamihosseinkhani M, Nemati H, et al. Risk factors associated with long covid syndrome: A retrospective study. Iranian Journal of Medical Sciences. 2021;46(6):428-36.
119. Ozcan S, Ince O, Guner A, Katkat F, Donmez E, Tugrul S, et al. Long-Term Clinical Consequences of Patients Hospitalized for COVID-19 Infection. Anatolian Journal of Cardiology. 2022;26(4):305-15.
120. Rivera J, Rodriguez T, Pallares M, Castrejon I, Gonzalez T, Vallejo-Slocker L, et al. Prevalence of post-COVID-19 in patients with fibromyalgia: a comparative study with other inflammatory and autoimmune rheumatic diseases. BMC Musculoskeletal Disorders. 2022;23(1):471.
121. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology. 2023;21(3):133-46.
122. Parkin A, Davison J, Tarrant R, Ross D, Halpin S, Simms A, et al. A multidisciplinary NHS COVID-19 service to manage post-COVID-19 syndrome in the community. Journal of primary care & community health. 2021;12:21501327211010994.
123. Mizrahi B, Sudry T, Flaks-Manov N, Yehezkelli Y, Kalkstein N, Akiva P, et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ. 2023;380:e072529.
124. Bovil T, Wester CT, Scheel-Hincke LL, Andersen-Ranberg K. Risk factors of post-COVID-19 conditions attributed to COVID-19 disease in people aged ≥50 years in Europe and Israel. Public Health. 2023;214:69-72.
125. Ssentongo P, Zhang Y, Witmer L, Chinchilli VM, Ba DM. Association of COVID-19 with diabetes: a systematic review and meta-analysis. Scientific reports. 2022;12(1):20191.
126. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Jerndal H, Lundevaller EH, Sund M, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. BMJ. 2022:e069590.
127. Zuin M, Barco S, Giannakoulas G, Engelen MM, Hobohm L, Valerio L, et al. Risk of venous thromboembolic events after COVID-19 infection: a systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis. 2023:1-9.
128. Yende S, Parikh CR. Long COVID and kidney disease. Nature Reviews Nephrology. 2021;17(12):792-3.
129. Righy C, Rosa RG, da Silva RTA, Kochhann R, Migliavaca CB, Robinson CC, et al. Prevalence of post-traumatic stress disorder symptoms in adult critical care survivors: a systematic review and meta-analysis. Critical Care. 2019;23(1):213.
130. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain Behav Immun. 2020;89:531-42.

131. Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: A systematic review. Clinical neurology and neurosurgery. 2021;200:106349.
132. Sakibuzzaman M, Hassan A, Hayee S, Haque FA, Bushra SS, Maliha M, et al. Exacerbation of Pre-existing Neurological Symptoms With COVID-19 in Patients With Chronic Neurological Diseases: An Updated Systematic Review. Cureus. 2022;14(9):e29297.
133. Aram K, Patil A, Goldust M, Rajabi F. COVID-19 and exacerbation of dermatological diseases: A review of the available literature. Dermatol Ther. 2021;34(6):e15113.
134. Gerth AMJ, Hatch RA, Young JD, Watkinson PJ. Changes in health-related quality of life after discharge from an intensive care unit: a systematic review. Anaesthesia. 2019;74(1):100-8.
135. Nandasena H, Pathirathna ML, Atapattu A, Prasanga PTS. Quality of life of COVID 19 patients after discharge: Systematic review. PLoS One. 2022;17(2):e0263941.
136. Kamdar BB, Suri R, Suchyta MR, Digrande KF, Sherwood KD, Colantuoni E, et al. Return to work after critical illness: a systematic review and meta-analysis. Thorax. 2020;75(1):17.
137. Wright J, Astill SL, Sivan M. The Relationship between Physical Activity and Long COVID: A Cross-Sectional Study. International Journal of Environmental Research and Public Health. 2022;19(9):5093.
138. Parry SM, Nalamalapu SR, Nunna K, Rabiee A, Friedman LA, Colantuoni E, et al. Six-Minute Walk Distance After Critical Illness: A Systematic Review and Meta-Analysis. J Intensive Care Med. 2021;36(3):343-51.
139. Wong MC, Huang J, Wong NY, Wong GL, Yip TC, Chan RN, et al. Epidemiology, symptomatology, and risk factors for long COVID symptoms: Multi-centre study. JMIR Public Health Surveill. 2023.
140. Schlemmer F, Valentin S, Boyer L, Guillaumot A, Chabot F, Dupin C, et al. Respiratory recovery trajectories after severe-to-critical COVID-19: a 1-year prospective multicentre study. Eur Respir J. 2023.
141. Pellegrino R, Chiappini E, Licari A, Galli L, Marseglia GL. Prevalence and clinical presentation of long COVID in children: a systematic review. European Journal of Pediatrics. 2022.
142. Mathew JL, Singhal KK. Chapter 8 - Long COVID in children. In: Leung C, editor. Clinical Management of Pediatric COVID-19: Academic Press; 2023. p. 175-84.
143. Morello R, Martino L, Buonsenso D. Diagnosis and management of post-COVID (Long COVID) in children: a moving target. Current Opinion in Pediatrics. 2023;35(2):184-92.
144. Eggert LE, He Z, Collins W, Lee AS, Dhondalay G, Jiang SY, et al. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. Allergy. 2022;77(1):173-85.
145. Laorden D, Domínguez-Ortega J, Carpio C, Barranco P, Villamañán E, Romero D, et al. Long COVID outcomes in an asthmatic cohort and its implications for asthma control. Respir Med. 2023;207:107092.

146. Nalbandian A, Desai AD, Wan EY. Post-COVID-19 Condition. Annual review of medicine. 2022.
147. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors Associated With Post– COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Internal Medicine. 2023.
148. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. eClinicalMedicine. 2022;53:101624.
149. (ONS) OfNS. New-onset, self-reported long COVID after coronavirus (COVID-19) reinfection in the UK: 23 February 2023 2023 updated23 February 2023. Available from:https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/newonsetselfreportedlongcovidaftercoronaviruscovid19reinfectionintheuk/23february2023#main-points#
150. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med. 2022.
151. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nature medicine. 2022:1-8.
152. World Health Organization (WHO). Post COVID-19 condition (Long COVID) 2022. Available from:https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition#:~:text=It%20is%20defined%20as%20the,months%20with%20no%20other%20explanation.
153. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. Int J Environ Res Public Health. 2021;18(5).
154. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine. 2023;55:101762.
155. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: A living systematic review. BMJ Global Health. 2021;6(9):e005427.
156. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. Scientific reports. 2022;12(1):9950.
157. Laura M, Heather S, Ingrid H, Anna C, Jon S, Alan JC. What is brain fog? Journal of Neurology, Neurosurgery & Psychiatry. 2023;94(4):321.
158. Tiago T, Mark JE, Jeremy DI. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(12):1308.
159. Pecoraro V, Negro A, Pirotti T, Trenti T. Estimate false-negative RT-PCR rates for SARS-CoV-2. A systematic review and meta-analysis. European journal of clinical investigation. 2022;52(2):e13706.

160. Explorer CUM. COG UK Mutation Explorer 2022. Available from:https://sars2.cvr.gla.ac.uk/cog-uk/
161. Did you have COVID-19 during the pandemic? HSE Public Health wants to know 'how you are now' as part of FADA survey [press release]. 2023.
162. Cui D, Wang Y, Huang L, Gu X, Huang Z, Mu S, et al. Rheumatic Symptoms Following Coronavirus Disease 2019 (COVID-19): A Chronic Post-COVID-19 Condition. Open Forum Infectious Diseases. 2022;9(6):ofac170.

Appendix 1: Adapted Newcastle-Ottawa Assessment tool for cross-sectional study assessment

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES (Adapted for cross-sectional studies)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection category. A maximum of two stars can be given for Comparability and a maximum of three stars can be given for the Outcome category.

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community*
b) somewhat representative of the average _____ in the community*
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort

2) Sample size
a) Justified and satisfactory*
b) Not justified

3) No-response rate
a) the response rate is satisfactory*
b) the response rate is unsatisfactory, or no description

4) Ascertainment of the screening/surveillance tool
a) Validated screening/surveillance tool*
b) Non-validated screening/surveillance tool, but the tool is available or described
c) No description of the measurement tool

Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for key confounders (age, sex and comorbidities)*
b) study controls for any additional factor*

Outcome
2) Assessment of outcome
a) independent blind assessment**
b) record linkage**
c) self report*
d) no description

2*) Statistical test*
a) the statistical test used to analyse the data is clearly described and appropriate*
b) the statistical test is not appropriate, not described or incomplete

TOTAL SCORE (ACROSS ALL DOMAINS):

INFO: We rated the quality of the studies (good, fair and poor) by awarding stars in each domain following the guidelines of the Newcastle–Ottawa Scale.

"Good" quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
"Fair" quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
"Poor" quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Appendix 2: Primary research study characteristics

Author	Country (ies)	Study Design	Population included*	Sample size (n) and characteristics	Ascertainment of COVID-19 diagnosis	Outcome(s) of interest†	Follow-up assessment time	Follow-up assessment mode
Asadi-Pooya et al.[118]	Iran	Cohort study (R)	COVID-19 hospitalised patients (post discharge)	n = 4,681 Sex: 47.1% female Mean (SD) age: 52.0 (15.0) years	RT-PCR	Presence of LC symptoms, severity of symptoms and risk factors associated with LC development	3 to 6 months and 6 to 12 months after acute COVID-19 illness	Questionnaire (telephone)
Ayoubkhani et al.[43]	UK	Cohort study (P)	Adults who received at least one dose of vaccine after testing positive for COVID-19 in the community (general population)	n = 28,356 Sex: 55.6% female Mean (SD) age: 46.0 (14.0) years	RT-PCR or COVID-19 antibody (serology) test (either within the current study or self-reported outside of the study)	Presence of LC symptoms and impact of LC on day-to-day activities	Follow-up visits every week for the first month following recruitment and then monthly for 12 months or longer	Questionnaire (in- person)
Bahat et al.[70]	Turkey	Cohort study (R)	COVID-19 hospitalised patients (post discharge) Population further split into older adults (> 65 years) and younger adults (< 65 years).	n = 665 Sex: 48.0% female Median age: 46.0 years	RT-PCR	Presence of LC symptoms, clinical and radiological findings in older > 65 years and younger adults (< 65 years)	Median follow-up time was 47 days after acute COVID-19 illness.	Multi-branched medical and social assessment (in-person)
Bai et al.[29]	Italy	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 377 patients Sex: 36.3% female Median (IQR) age: 57.0 (49.0 to 68.0) years	RT-PCR	Presence of LC symptoms and risk factors associated with LC development	Median (IQR) follow-up time was 56 (47 - 74) days after virological clearance	Interview (in-person) and blood samples

Barreto et al.[37]	Brazil	Cross-sectional study	LC cases at a public health outpatient clinic Population further split into outpatient, hospitalised non ICU and hospitalised ICU	n = 1,164 Sex: 56.6% female Mean (SD) age: 52.1 (13.4) years	RT-PCR, COVID-19 antibody (serology) test or radiological findings	Presence of LC symptoms	Median (IQR) follow-up time was 2.3 (1.6 to 3.7) months from COVID-19 symptom onset	Evaluation (in-person) via a multidisciplinary team using a standardised form
Battistella et al.[38]	Brazil	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 801 Sex: 47.4% female Mean (SD) age: 55.4 (14.6) years	RT-PCR or antibody (serology) test.	Long-term functional status of hospitalised COVID-19 survivors	Mean (SD) follow-up time was 6.6 (1.6) months after hospital discharge	Questionnaire (telephone) followed by in-person clinical and functional assessments
Bek et al.[83]	the Netherlands	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 492 Sex: 31.9% female Mean (SD) age: 60.2 (10.7) years	RT-PCR, clinical findings or antibody (serology) test	Presence of LC symptoms, and symptom clusters	Mean (SD) follow-up time was 95 (23) days, 185 (28) days, and 368 (17) days after hospital discharge, for the 3-, 6- and 12 month visits	Interview (in-person)
Belkacemi et al.[71]	France	Cohort study (P)	Patients on dialysis who contracted COVID-19 and were alive and still on dialysis 6 months after acute COVID-19 illness	n = 1,217 Sex: 38.7% female Age range group (n/N %): 00-44 years: 140/1217 (11.5%) 45-64 years: 344/1217 (28.3%) 65-74 years: n=337/1,217 (27.7%)	RT-PCR, clinical findings or radiological findings	Presence of LC symptoms and risk factors associated with LC development	6 months after acute COVID-19 illness	National registry data

				75-84 years: n=266/1,217 (21.8%) 85+ years: n=130/1,217 (10.7%)				
Bergia et al.[20]	Spain	Cohort study (R) (with external control group)	Cohort group: Children < 18 years old with a previous COVID-19 diagnosis Control group: Children < 18 years old without a previous COVID-19 diagnosis	Cohort group: n = 451 Sex: 45% female Mean (SD) age: 5.9 (5.3) years Case group: n = 98 Sex: 43% female Mean (SD) age: 7.8 (4.2) years	Not specified	Presence of LC symptoms and risk factors associated with LC development	Median (IQR) follow-up time was 351 (330–471) days after acute COVID-19 illness	Questionnaire (telephone)
Bernas et al.[53]	Germany	Cross-sectional study	Potential stem cell donors registered with DKMS Germany who had consented to participate in an initial COVID-19 survey Case group: those with a previous COVID-19 diagnosis Control group: those without a previous COVID-19 diagnosis	Cohort group: n = 12,609 Sex: N/A Mean (SD) age: N/A Control group: n = 186,768 Sex: N/A Mean (SD) age: N/A	RT-PCR	Presence of LC symptoms	3 to 15 months after acute COVID-19 illness	Questionnaire (online)
Boglione et al.[30]	Italy	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 449 Sex: 22.0% female Median (IQR) age: 65.0 (56.0 - 75.5) years	Not specified	Prevalence of LC and risk factors associated with LC development	Median (IQR) follow-up time was 33 (30–39) days and 179 (166–212) days after acute COVID-19	Multidisciplinary assessment including biochemical analysis, clinical evaluation and patient

							illness, for visits 1 and 2	interview (in-person)
Borch et al.[59]	Denmark	Cohort study (R) (with external control group)	Cohort group: Children < 18 years old with a previous COVID-19 diagnosis Control group: Children < 18 years old without a previous COVID-19 diagnosis	Cohort group: n = 15,041 Sex: N/A Mean (SD) age: N/A Control group: n = 15,080 Sex: N/A Mean (SD) age: N/A	RT-PCR	Presence and duration of LC symptoms	Follow-up time was > 4 weeks after acute COVID-19 illness	Questionnaire (online), completed by parents for children < 15 years old, completed by adolescents 15 to 17 years old (with parental support advised)
Buonsenso et al.[33]	Italy	Cohort study (R)	Children < 18 years old presenting to a paediatric post-COVID-19 outpatient clinic.	n = 784 Sex: 45.0% female Median (IQR) age: 8.0 (4.6 – 10.8) years	RT- PCR	Prevalence and severity of anosmia and its impact on QoL	Median follow-up time was 107 days after COVID-19 diagnosis	Assessment at post COVID outpatient clinic (presumably clinician led)
Buonsenso et al.[34]	Italy	Cohort study (P)	Children < 18 years with a previous COVID-19 diagnosis	n = 679 Sex: 51.0% female Median (IQR) age: 10.0 (6.0 – 13.0) years	RT-PCR or RADT or antibody (serology) test.	Characterise clusters of LC symptoms	Follow-up assessments were 1–5 months, 6–9 months and 12 months after COVID-19 diagnosis	Interview with parents/caregivers (telephone, survey or in-person)
Buttery et al.[44]	UK	Cohort study (P)	UK wide survey distributed via an online Post-COVID hub (https://wwwpost-covidorguk/) (Adults and children)	n = 3001/3290 completed the survey ≥ 4 weeks after COVID-19 symptom onset Sex (n = 2565): 78.0% female Mean (SD) age: N/A	Not specified	Presence of LC symptoms	Mean (SD) follow-up time was 106 (53) days from LC onset (n = 3023)	Questionnaire (online)

			Population further split into hospitalised and non hospitalised					
Comelli et al.[31]	Italy	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 456 Sex: 36.8% female Mean (SD) age: 59.0 (14.0) years	RT-PCR	Presence of medical problems, patients' perception of general health and presence of LC symptoms	Follow-up time was 12-months after hospital discharge	Interview (telephone)
Cui et al.[162]	China	Cohort study (P) (with matched external control group)	Cohort group: COVID-19 hospitalised patients (post discharge) Control group: those without a previous COVID-19 diagnosis	Cohort group: n = 1,296 Sex: 47.0% female Median (IQR) age: 57.0 (48.0 – 65.0) years Control group: n = 1,181 Sex: N/A Mean (SD) age: N/A Matched cohort group: n/N = 1,181/1,296 Sex: N/A Mean (SD) age: N/A	RT-PCR, antibody (serology) test or viral gene sequencing	Prevalence, characteristics and risk of developing rheumatic symptoms Following COVID-19	Median (IQR) follow-up time was 349 (337–361) days from COVID-19 symptom onset	Interview (in-person)
Daitch et al.[67]	Israel, Switzerland, Spain and Italy	Cohort study (P)	Adults with a previous COVID-19 diagnosis Population further split into those aged 18 to 65 years and those > 65 years	n = 2,333 Sex: 49.2% female Mean (SD) age: 51.3 (16.4)	RT-PCR	Prevalence of LC symptoms among older adults, and risk factors for development of LC fatigue and dyspnoea	Mean (SD) follow-up time was 146 (87) from COVID-19 diagnosis (n = 1601)	Physician collected data (in person or telephone)

Damanti et al.[35]	Italy	Cohort study (P)	Patients with COVID-19 hospitalised for pneumonia (post discharge)	n = 351 - 1 month follow-up n = 216 - 3 month follow-up n = 176 - 6 month follow-up Age and sex characteristics are only available for baseline and disaggregated by frail and robust patients	RT-PCR, clinical findings or radiological findings	Prevalence of LC symptoms in frail and robust patients	Follow-up assessments were 1-, 3- and 6-months after hospital discharge	Multidisciplinary evaluation (in-person) team using a standardised form. LC symptoms were provided during the evaluation or via email to the attending physicians of the follow-up clinic
Damiano et al.[39]	Brazil	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 701 Sex: 47.6% female Mean (SD) age: 55.3 (14.6) years	RT-PCR or clinical and radiological findings.	The association between olfactory and gustatory dysfunctions post COVID-19	6-11 months after hospitalisation	Interviews (in-person)
de Oliveira et al.[40]	Brazil	Cross-sectional study	COVID-19 hospitalised patients (post discharge)	n = 439 Sex: 49.7% female Median (IQR) age: 58.0 (47.0 - 67.0) years	RT-PCR	Prevalence of LC symptoms, QoL and risk factors associated with LC development	Median (IQR) follow-up time was 138 (90-201) days from COVID-19 symptom onset	Questionnaire (online or telephone). All patients >61 years old were assessed via telephone
Donnachie et al.[60]	Germany	Cohort study (R) (with two external control groups)	Cohort group: Patients with a physician consultation related to COVID-19 Control group 1: patients with other upper respiratory infection	Cohort group: n = 391,990 Sex: 54.1% female Mean (SD) age: 42.3 (21.0) years Control group 1: n = 62,659	RT-PCR	Incidence of LC	Up to two years after the index quarter Cohort and case group 1 index quarter: the first quarter with	All data extracted from the Bavarian COVID-19 Cohort (BCC) database

			Control group 2: Patients without a physician consultation related to COVID-19	Sex: 54.1% female Mean (SD) age: 42.0 (20.8) years Control group 2: n = 659, 579 Sex: 54.1% female Mean (SD) age: 42.3 (20.9) years			confirmed COVID-19 diagnosis Case group 2 index quarter: the first quarter with exclusion of COVID-19 diagnosis Control group: Random index quarter	
Dryden et al.[84]	South Africa	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 1,873 Sex: 51.3% female Median (IQR) age: 52.0 (41.0 – 62.0) years	RT-PCR or RADT	Risk factors associated with LC development	1, 3, 6 and 12 months post discharge, with only 1 and 3 month results in the current paper. Three month follow-up: Median (IQR) follow-up time was 95 days (84–126) after hospital discharge	Standardised ISARIC Case Report Form (CRF) (in-person)
Dumont et al.[50]	Switzerland	Data was drawn from the SEROCoV-KIDS cohort study (P)	Children and adolescents 6 months to 17 years old (COVID-19 diagnosis not required)	n = 1,034 (570 tested positive for COVID-19) Sex: 51% female Mean (SD) age: 10.2 (4.2) years	RT-PCR or RADT (parent reported)	Prevalence of paediatric LC and risk factors associated with paediatric LC development	N/A	Questionnaire (online) completed by parent/guardian
Evans et al.[45]	UK	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	5-month follow-up: n = 2,320 Sex: 39% female	RT-PCR or clinical.	Patient-perceived recovery after acute COVID-19 illness	Median (!QR) follow-up time, after hospital discharge,	Multiple questionnaires and physical functioning

				Mean (SD) age: 58 (12.6) years 1-year follow-up: n = 924 Sex: 35.8% female Mean (SD) age: 58.9 (12.5) years Both 5-month and 1-year follow-up: n = 807 Sex: 35.6% female Mean (SD) age: 58.7 (12.5) years			for those attending: the 5 month follow-up was 5 (4-6) months The 1-year follow-up was 13 (12-13) months Both the 5-month and 1-year follow-up was: 5-month follow-up: 178 days (156-197) 1-year follow-up: 384 days (359-409)	assessments (in-person)
Fang et al.[65]	China	Cohort study (P)	COVID-19 hospitalised patients ≥ 60 years (post discharge)	n = 1233 Sex: 52.1% female Median (IQR) age: 68 (64 – 73) years	RT-PCR	Presence of LC symptoms and risk factors associated with LC development	Median (IQR) follow-up was 363 (357–371) days after hospital discharge	Questionnaire (telephone)
Feldman et al.[85]	Canada	Cross-sectional survey study	COVID-19 hospitalised patients (post discharge)	n = 398 Sex: 45.0% female Mean (SD) age: 61.1 (16.5) years	"Confirmed" diagnosis of COVID-19 (no further information)	Prevalence of LC and risk factors associated with LC development	Mean (SD) follow-up time was 281 (140) days after COVID-19 diagnosis.	Interview (telephone)
Fernández-de-las-Peñas et al.[28]	Spain	Cohort study (R)	COVID-19 hospitalised patients (post discharge)	n = 614 Wuhan variant: n = 201 Sex: 54.2% female	RT-PCR and clinical and radiological findings.	Presence of LC in those hospitalised with the Wuhan, Alpha or Delta SARS-CoV-2 variant	Mean (SD) follow-up time was 6.5 (1.0) months, 6.0 (1.2) months and 6.3 () months for Wuhan, Alpha and Delta variants	Interview (telephone)

				Mean (SD) age: 60.5 (15.5) years Alpha variant: n = 211 Sex: 51.2% female Mean (SD) age: 70.5 (15.5) years Delta variant: n = 202 Sex: 54.5% female Mean (SD) age: 56.5 (21.0) years				
Fernández-de-las-Peñas et al.[26]	Spain	Cross-sectional cohort study	COVID-19 hospitalised patients (post discharge)	n = 1,142 Sex: 47.5% female Mean (SD) age: 61.0 (17.0) years	RT-PCR and clinical and radiological findings.	Presence of fatigue and dyspnoea, impact on daily activities, and risk factors associated with fatigue or dyspnoea	Mean (SD) follow-up was 7 (0.6) months after hospital discharge	Interview (telephone)
Fernández-de-las-Peñas et al.[24]	Spain	Cross-sectional cohort study	COVID-19 hospitalised patients (post discharge)	n = 1,969 Sex: 46.4% female Mean (SD) age: 61.0 (16.0) years	RT-PCR and radiological findings	Prevalence and characteristics of LC, and LC differences between males and females	Mean (SD) follow-up time was 8.4 (1.5) months after hospital discharge	Interview (telephone)
Fernández-de-las-Peñas et al.[27]	Spain	Cross-sectional study	Those with a previous COVID-19 diagnosis (hospitalised and non-hospitalised)	n = 360 hospitalised Sex: 45.0% female	RT-PCR	Prevalence of LC symptoms	Mean (SD) follow-up time was 23.8 (0.6) months for hospitalised patients and 23.4 (0.7)	Questionnaire (telephone)

				Mean (SD) age: 60.7 (16.1) years n = 308 non-hospitalised Sex: 59.4% female Mean (SD) age: 56.7 (14.7) years			months for non-hospitalised patients.	
Fernández-de-las-Peñas et al.[23]	Spain	Cohort study (R)	COVID-19 hospitalised patients (post discharge)	n = 1969 Sex: 46.0% female Mean (SD) age: 61.0 (16.0) years	RT-PCR and clinical and radiological findings.	Prevalence of long-term post COVID-19 musculoskeletal (MSK) pain and risk factors associated with post COVID-19 MSK pain	Mean (SD) follow-up time was 8.4 (1.5) months after hospital discharge	Interview (telephone)
Fernández-de-las-Peñas et al.[25]	Spain	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 412 Sex: 47.5% female Mean (SD) age: 62.0 (15.0) years	RT-PCR and clinical and radiological findings	Association between serological biomarkers and the development of LC fatigue and dyspnoea	Mean (range) follow-up time was 6.8 (6–8) months and 13.2 (12–14) months after hospital discharge	Interview (telephone)
Ferreira et al.[41]	Brazil	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 749 Sex: 47.0% female Mean (SD) age: 55.0 (14.0) years	RT-PCR or antibody (serology) test and clinical and radiological findings	Presence of LC symptoms and clinical, sociodemographic, and environmental risk factors associated with LC development	Median (IQR) follow-up time was 200 (185-235) days after hospital discharge	Questionnaire (in-person), physical examination, selected diagnostic tests, and blood samples
Frontera et al.[117]	US	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	6 month follow-up: n = 382 Sex: 35.0% female	RT-PCR	Functional status and disability, activities of daily living, cognition and	Mean (SD) follow-up time was 6.0 (1.0) months and 12.0 (2.0) months from	Interview (telephone)

				Median (IQR) age: 69.0 (57.0-78.0) years 12-month follow-up: 242 Sex: 36.0% female Median (IQR) age: 65.0 (53.0-73.0) years Both 6 month and 12-month follow-up: n = 174 Sex: N/A Median (IQR) age: N/A		Quality of Life (QoL)	COVID-19 symptom onset	
Funk et al.[77]	Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain and the US	Cohort study (P) (with external control group)	Cohort group: Children < 18 years with a previous COVID-19 diagnosis Control group: children < 18 years without a previous COVID-19 diagnosis Population is further split into hospitalised and non-hospitalised	Cohort group: n = 1884 Sex: 47.2% female Median (IQR) age: 3.0 (0.0 – 10.0) years Hospitalised = Cohort group: n = 391; Sex: 46.3% female; Median (IQR) age: N/A Control group: n = 380; Sex: 48.2% female; Median age (IQR): N/A Non-hospitalised = Cohort group: n = 1,295; Sex: 48.5% female; Median age (IQR): N/A Control group: n = 1,321; Sex:	RT-PCR	Prevalence of LC symptoms, stratified by hospitalisation status	Between 90 and 120 days after SARS-CoV-2 test	Caregivers were contacted (mode not specified)

				52.9% female; Median age (IQR): N/A				
Garjani et al.[46]	UK	Cohort study (P)	Those with multiple sclerosis (MS) and a previous diagnosis of COVID-19	n = 571 Sex: 77.2% female Mean (SD) age: 49.0 (11.0) years	Self-report of symptoms suggestive of COVID-19 or clinician confirmed or SARS-CoV-2 test confirmed	Prevalence of LC symptoms, physical and mental status	Follow-up was every 2 weeks after acute COVID-19 illness until reporting full recovery from COVID-19 symptoms. Median (IQR) total follow-up time was 87 (41–185) days	Questionnaire (online)
Gonzalez-Islas et al.[73]	Mexico	Cross-sectional study	Moderate to severe COVID-19 hospitalised patients (post discharge)	n = 530 Sex: 39.1% female Mean (SD) age: 53.8 (12.9) years	RT-PCR	Impact of Invasive mechanical ventilation on body composition, pulmonary function and risk factors associated with the development of sarcopenia	3 months after acute COVID-19 illness	Multidisciplinary assessment (in-person)
Hastie et al.[61]	Scotland	Cohort study (P and R) (with external control group)	Cohort group: Adults > 16 years with a previous COVID-19 infection Further split into those asymptomatic and symptomatic Control group: Adults > 16 years without a previous COVID-19 infection	Cohort group: n = 33,281; asymptomatic: 1,795; symptomatic: 31,486 Sex: 63.6% female; asymptomatic: 53.3%; symptomatic: 64.2% Median (IQR) age: asymptomatic: 43.0 (28.0 – 57.0) years; symptomatic: 44.0 (30.0-56.0) Control group: n = 62,957	RT-PCR	Presence of LC symptoms and impact on daily living	Follow-ups were completed 6-, 12- and 18-months after COVID-19 diagnosis Median (IQR) follow-up time was 7.0 (6.0 – 8.0) months after COVID-19 diagnosis	Questionnaire (online)

				Sex: 59.4% female Median (IQR) age: 45.0 (31.0 – 56.0) years				
Heightman et al.[47]	UK	Cohort study (P)	Those with a previous COVID-19 infection assessed at a post-COVID clinic Population is further split into non-hospitalised, hospitalised and post emergency department (ED)	Total sample: n = 1,325; non-hospitalised: n = 566; hospitalised: n = 547; post ED: n = 212 Sex: Total sample: 56.5% female; non-hospitalised: 68.2% female; hospitalised: 43.0% female; post ED: 59.9% female Median (IQR) age: Total sample: 49.9 (40.1-60.1) years; non-hospitalised: 44.6 (35.6-52.8) years; hospitalised: 58.3 (47.0-67.7) years; post ED: 48.5 (39.4 -55.7) years	RT-PCR or antibody (serology) test or clinical findings	The primary outcomes were long COVID symptoms, health related QoL, and mental health	Median (IQR) follow-up time was 108 (61-97) days, 194 (118-298) days, 69 (51-111) days and 76 (55-128) days from COVID-19 symptom onset, for the total sample, non-hospitalised, hospitalised and those post ED	Multidisciplinary assessment (in-person or virtual)
Huang et al.[52]	China	Cohort study (P and R) (with external matched control group)	Cohort group: COVID-19 hospitalised patients (post discharge) Control group: community dwelling adults without a previous COVID-19 infection Matched cohort group: sub-group of COVID-19 hospitalised patients (post discharge)	Cohort group: n = 1,192 patients completed all three 6-, 12- and 24-month follow-ups Sex: 46.0% female Median (IQR) age: 57.0 (48.0 – 65.0) years Control group: n = 1,127 Sex: 46.0% female Median (IQR) age: 59.0 (50.0 – 67.0) years	Laboratory confirmed COVID-19	The primary outcomes were presence of LC symptoms, health related QoL, mental health, exercise capacity and return to work	Median (IQR) follow-up time was 185 (175-197) days, 349 (337-360) days and 685 (675-698) days from COVID-19 symptom onset for the 6-, 12- and 24 month assessments	Interview (in-person or telephone)

				Matched cohort group: n = 1,127 Sex: 46.0% female Median (IQR) age: 59.0 (60.0 – 67.0) years				
Kikkenborg Berg et al.[64]	Denmark	Cross-sectional study (with external matched control group)	Cohort group: Children < 14 years with a previous COVID-19 diagnosis Control group: age and sex matched children without a previous COVID-19 diagnosis (1:4 ratio)	Cohort group: n = 10,997 Sex: 48.2% female Median (IQR) age: 10.2 (6.6 – 12.8) years Control group: n = 33,016 Sex: 48.3% female Median (IQR) age: 10.6 (6.9 – 12.9) years	RT-PCR	Presence of LC symptoms, overall health and wellbeing, health-related QoL, and sick leave/absence from day-care or school	Aggregate follow-up time was not reported	Questionnaire (online)
Kikkenborg Berg et al.[88]	Denmark	Cross-sectional study (with external matched control group)	Cohort group: Children aged 15 – 18 years with a previous COVID-19 diagnosis Control group: age and sex matched children without a previous COVID-19 diagnosis (1:4 ratio)	Cohort group: n = 6,630 Sex: 58.4% female Median (IQR) age: 17.6 (16.5 – 18.6) years Control group: n = 21,640 Sex: 57.3% female Median (IQR) age: 17.5 (16.4 – 18.5) years	RT-PCR	Presence of LC symptoms, overall health and wellbeing, health-related QoL, and sick leave/absence from day-care or school	Aggregate follow-up time was not reported	Questionnaire (online)

Kildegaard et al.[55]	Denmark	Cohort study (R) (with a reference group and external matched control group)	Cohort group: Children < 18 years with a COVID-19 diagnosis or BNT162b2 vaccination Population is further split into hospitalised and non-hospitalised Reference group: random sample of children < 18 years tested for COVID-19 Control group: year of birth, sex and time matched children < 18 years with a negative SARS-CoV-2 test result (ratio 10:1)	Cohort group: n = 74,611; hospitalised: n= 391; non-hospitalised: n = 74,220) Sex: 49% female; hospitalised: 48.8% female; non-hospitalised: 48.9% female Median (IQR) age: 11.0 (7.0-15.0) years; hospitalised: 8.0 (1.0-14.0) years; non-hospitalised: 11.0 (7.0-15.0) years Reference group: n = 991,862 Sex: 48.8% female Median (IQR) age: 10.0 (5.0-14.0) years Control group: n = 745,540 Sex: 51.0% female Median (IQR) age: 11.0 (7.0-15.0) years	RT-PCR	Risk of adverse outcomes in the acute and post-acute COVID-19s of COVID-19 illness and the effectiveness of BNT162b2	The post-acute COVID-19 follow-up occurred in days 30 to 179 (Only the post-acute COVID-19 data can be considered in this analysis)	Data extracted from electronic health records and prescription, health insurance, and vaccination registers
Kostev et al.[69]	Germany	Cohort study (R)	Children < 18 years who attended a general practitioner (GP) or paediatric practice with a COVID-19 diagnosis, and	n = 6,568 Sex: 49.2% female Mean (SD) age: 10.1 (4.9) years	ICD codes were required for inclusion - (ICD-10: U07.1 [COVID-19, virus identified] or U08.9 [personal	Prevalence of LC and risk factors associated with the development of LC	Mean (SD) follow-up time was 106 (87) days in those with LC, and 103 (85) days in those without LC	ICD-10 codes as entered via the GP practice

			had a 12-month follow-up		history of COVID-19, unspecified])			
Kostev et al.[58]	Germany	Cohort study (R)	Those who attended a general practitioner (GP) with a COVID-19 diagnosis	n = 51,630 Sex: 54.3% female Mean (SD) age: 47.1 (19.8) years	ICD codes were required for inclusion (ICD-10: U07.1 [COVID-19, virus identified] or U08.9 [personal history of COVID-19, unspecified])	Prevalence of LC and risk factors associated with the development of LC	Mean (SD) follow-up time was 188 (120) days from GP visit of first COVID-19 diagnosis	ICD-10 codes as entered via the GP practice
Lorusso et al.[76]	UK, Germany, Netherlands, Belgium, Ireland, France, Estonia, Switzerland, Portugal, Spain, Belarus, Turkey, Lithuania, Greece, Denmark, Austria, Israel, Czech Republic, Poland, the Russian	Cohort study (P)	COVID-19 hospitalised patients ≥ 16 years old who received Extracorporeal Membrane Oxygenation (ECMO) during hospitalisation (post discharge)	n = 1,215 Sex (available for n = 1,209): 22.0% female Median (IQR) age: 53.0 (46.0-60.0) years	RT-PCR	In-hospital outcomes, survival and health status (respiratory, cardiac, and neurocognitive symptoms) 6 months after ECMO initiation during acute COVID-19	Follow-up was 6 months after ECMO initiation during acute COVID-19	Direct patient contact (mode not specified) or institutional chart review

	Federation, Norway, Slovenia, Sweden and Italy							
Martin-Loeches et al.[21]	Spain	Cohort study (P)	COVID-19 ICU patients (post hospital discharge)	n = 991 Sex: 32.9% female Mean (SD) age: 58.5 (11.9) years	RT-PCR	Risk factors associated with LC development and poor recovery. Lung function and radiologic abnormalities in critically ill patients after hospital discharge	Median (IQR) follow-up time was 77 (57 - 99) days after hospital discharge	Follow-up assessment (mode not specified) in which information was entered into an electronic case report form by hospital staff
Meza-Torres et al.[48]	UK	Cohort study (R)	Those with a previous COVID-19 infection identified from the primary care sentinel cohort (PCSC) of the Oxford–Royal College of General Practitioners Research and Surveillance Centre Population further split into those with a COVID-19 infection only; those who developed LC, were referred to a LC service or had a symptom score suggestive of LC; and those who were hospitalised/not	n = 416,505 Sex: N/A Mean (SD) ag: N/A	International Classification of Disease and Systematized Nomenclature of Medicine Clinical Terms (SNODMED CT) indicating positive SARS-CoV-2 test	Symptoms, sociodemographic profile, and outcomes of those with LC	Between 1 and 6 months after acute COVID-19 illness.	Data extracted from the primary care sentinel cohort (PCSC) of the Oxford–Royal College of General Practitioners Research and Surveillance Centre

			hospitalised with acute COVID-19					
Miller et al.[51]	England and Wales	Cohort study (P)	Children aged ≤17 years participating in VirusWatch (a household cohort study). Participants were not required to have had a previous COVID-19 infection, but must have answered a question about persistent symptoms or completed surveys which allowed enough follow-up time persistent symptoms to develop	n = 5,032 children (1,062 evidence of past or present COVID-19 infection) Sex: N/A Mean (SD) age: N/A	Self-report or RT-PCR or antibody (serology) test or or linkage to NHS digital data results of SARS-CoV-2 tests	Prevalence and characteristics of LC symptoms, risks associated with LC development	Not specified	Survey (online)
Nakayama et al.[42]	Brazil	Cohort study (R)	Severe and critical COVID-19 hospitalised patients (post discharge)	n = 565 Sex: 43.7% female Mean (range) age: 61.1 (19.0–103.0) years	RT-PCR or radiological findings	Presence of LC symptoms	Median (SD) follow-up was 318.0 (54.3) after hospital discharge	Questionnaire (telephone)
Norgard et al.[75]	Denmark	Cohort study (R)	COVID-19 hospitalised patients (post discharge) Population is further split into those with chronic inflammatory disease and those without	n = 9,665 Sex: N/A Mean (SD) age: N/A Those with chronic inflammatory disease: n = 417 Sex: 55.4% female Median (25th – 75th percentile) age: 71 (59-78) years	Primary diagnosis of COVID-19 without localisation [ICD-10 B342A] or COVID-19 with severe respiratory	Hospitalisation after COVID-19 discharge and cause of hospitalisation, presence of LC symptoms and death after hospital discharge	Median (25^{th}-75^{th} percentile) length of follow-up time was 6.5 (4.4–8.1) months, and 6.6 (4.2–8.5) months for those with chronic inflammatory disease and those without chronic inflammatory disease. Observation	Data extracted from Danish health registries: the National Patient Registry, the Nationwide Prescription Registry, and the Civil Registration System

				Those without chronic inflammatory disease: n =9,248 Sex: 43.7% female Median (25th – 75th percentile) age: 65 (52-77) years	syndrome [ICD-10 B972A]		periods for which outcomes could occur began 1-day, 14-days or 28-days after COVID-19 hospital discharge depending on the analysis	
Nugawela et al.[86]	England	Cohort study (P) (with external matched control group)	Cohort group: Children aged 11 -17 years with a previous COVID-19 diagnosis Control group: month of PCR test, age, sex and geographical area matched children with negative SARS-CoV-2 diagnosis	Cohort group: n = 3,246 Sex: 63.0% female Mean (SD) age: N/A Control group: n = 3,893 Sex: % female Mean (SD) age: N/A	RT-PCR	To update a risk prediction equation identifying those most at risk of LC, 3 months after a RT-PCR test	Median (25^{th} – 50^{th} percentile) follow-up time was 14.9 (13.1 - 18.9) weeks after RT-PCR test	Questionnaire (online)
Oto et al.[72]	Turkey	Cohort study (R) (with external control group)	Cohort group: Kidney transplant recipients with a previous COVID-19 diagnosis Control group: Kidney transplant recipients without a previous COVID-19 diagnosis	Cohort group: n = 523 Sex: 42.1% female Mean (SD) age: 45 (12) years Control group: n = 421 Sex: 45.6% female Mean (SD) age: 46 (12) years	RT-PCR	Ongoing respiratory symptoms	84 days (3 months)	N/A
Özcan et al.[119]	Turkey	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 406 Sex: N/A	RT-PCR	Persistent cardiovascular symptoms	Follow-up assessments were 3 and 6 months after hospital discharge	3-month follow-up: anamnesis and physical examination (in-person)

				Mean (SD) age: N/A				6 month follow-up: anamnesis and physical examination (in-person) and interview (telephone) over the 3-6 month period.
Ozonoff et al.[87]	US	Cohort study (P)	COVID-19 hospitalised patients (post discharge)	n = 589 Sex: 50.9% female Mean (SD) age: 56.1 (14.4) years	RT-PCR	Presence of LC symptoms and risks associated with the development of LC	3, 6, 9 and 12 months after hospital discharge	Survey (in-person, via and app, or telephone)
Pazukhina et al.[66]	Russian Federation	Cohort study (P)	COVID-19 hospitalised patients (post discharge) Population further split into adults ≥ 18 years old and children < 18 years old	n = 1,013 adults ≥ 18 years old Sex: 51.0% female Median (IQR) age: 52.8 (47.0-65.8) years n = 360 children < 18 years old Sex: 52.0% female Mean (SD) age: 9.5 (2.4-14.8) years	RT-PCR	Prevalence and characteristics of LC	**Adults** Median (IQR) follow-up time was 215 (196–235) days and 383 (376–390) days after hospital discharge for 6 – and 12-month follow-ups **Children** Median (IQR) follow-up time was 255 (223–270) days and 367 (351–379) days after hospital discharge for 6 – and 12-month follow-ups	Interview (telephone)

Perlis et al.[57]	USA	Cross-sectional study	Adults > 18 years old with a previous COVID-19 diagnosis	n = 16,091 (tested positive at least 2 months prior to follow-up survey) Sex: 62.6% female Mean (SD) age: 40.5 (15.2) years	RT-PCR or RADT	Prevalence of LC symptoms	N/A	Survey (online)
Peter et al.[63]	Germany	Cross-sectional study	Adults aged 18 – 65 years with a previous COVID-19 diagnosis	n = 11,710 Sex: 58.8% female Mean (SD) age: 44.1 (13.7) years	RT-PCR	To describe LC symptoms and symptom clusters and risk factors associated with LC development	Mean (SD) follow-up time was 8.5 (1.6) months after COVID-19 diagnosis (out of n = 11,512)	Questionnaire (post)
Rivera-Izquierdo et al.[22]	Spain	Cohort study (P) (with external matched control group)	Cohort group: COVID-19 hospitalised patients (post discharge) Control group: Patients hospitalised for other reasons (non-COVID-19)	Cohort group: n = 453 Sex: 42.6% female Mean (SD) age: 61.2 (14.3) years Control group: n = 453 Sex: 53.2% female Mean (SD) age: 55.9 (17.8) years	RT-PCR	Prevalence of LC symptoms	Follow-up was 12-months after hospital discharge	Interview (telephone) and medical record data extraction
Sørensen et al.[56]	Denmark	Cohort study (R) (with external time-matched control group)	Cohort group: adolescents and adults ≥ 15 years old with a previous COVID-19 diagnosis Control group: time-matched adolescents and adults ≥ 15 years old	Cohort group: n = 61,002 Sex: 58.7% female Median (IQR) age: 49 (34-60) years Control group: n = 91,878	RT-PCR	Acute symptoms, presence of LC symptoms, new diagnoses and general health problems	Follow-up was 6-12 months after a positive or negative SARS-CoV-2 test result	Questionnaire (online)

			with a negative SARS-CoV-2 test result Population is further split into adolescents ≤19 years old and age ranges from 20 to 70+ years old	Sex: 62.8% female Median (IQR) age: 53 (40-62)				
Spinicci et al.[32]	Italy	Cohort study (P)	Those attending a LC outpatient clinic (patients are post-hospital discharge)	n = 428 Sex: 41.0% female Median (IQR) age: 64.0 (54.0-76.0) years	RT-PCR	Presence of LC symptoms, risk factors associated with the development of LC and comparison of symptom type and frequency based on variant type	Median (IQR) follow-up time was 69 (55–82) days after the first positive COVID-19 diagnosis and 53 (40–64) days after hospital discharge	Physical examination and questionnaire (in-person)
Trapani et al.[36]	Italy	Cross-sectional study	Children aged 0 – 16 years old with a previous COVID-19 diagnosis	n = 689 Sex: 49.8% female Median (range) age: 8.0 (4.0-11.0) years	RT-PCR	Prevalence of LC	Follow-up time was 2-9 months after acute COVID-19 recovery	Paediatrician completed online questionnaire with information provided by parents (telephone or in-person)
Whitaker et al.[54]	England	Cohort study (R)	Rounds 3-5 and 6 of the React2 programme evaluating community prevalence of SARS-CoV-2 anti-spike protein antibody positivity in adults	Rounds 3-5: n = 508,707 (92,116 with suspected or confirmed COVID-19) Sex: 56.0% female Mean (SD) age: N/A	RT-PCR or suspected COVID-19 with the presence of one or more symptom (from prespecified list of 29 symptoms)	Prevalence of LC symptoms and risk factors associated with development of LC	Follow-up time was ≥ 12 weeks after confirmed or suspected acute COVID-19 illness	Questionnaire (online)

				Round 6: n = 97,727 (14,562 with suspected or confirmed COVID-19) Sex: 58.0% female Mean (SD) age: N/A				
Yoo et al.[74]	US	Cohort study (P)	COVID-19 hospitalised patients (post discharge) and those with a previous COVID-19 diagnosis referred by primary care providers Population is further split into hospitalised (non-ICU), hospitalised (ICU) and outpatient	n = 1,038 Sex: 49.6% female Mean (range) age: 60.0 (37.0-83.0) years Hospitalised (non-ICU): n = 648/1038 Sex: 47.7% female Mean (range) age: 60.0 (38.0-83.0) years Hospitalised (ICU): n = 152/1038 Sex: 38.8% female Mean (range) age: 60.0 (41.0-79.0) years Outpatient: n = 238/1038 Sex: 61.8% female Mean (range) age: 60.0 (36.0-84.0) years	Laboratory confirmed SARS-CoV-2 infection	To evaluate the association of demographic and clinical characteristics with the development of LC	Follow-up time was 30, 60 and 90 days after hospital discharge or outpatient diagnosis	Questionnaire (telephone)

***Identified sub-groups of interest (those aged <18 years, those aged ≥ 65 years, those aged < 65 years who are medically vulnerable and those with a history of severe COVID-19 illness) are also outlined (where applicable). †Outcomes of interest to the current analysis.**

Appendix 3: Quality appraisal table for cohort primary research studies.

	Selection				Comparability		Outcome			Quality
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for key confounders e.g. age/sex/ comorbidities	Study controls for other factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Asadi-Pooya et al.[118]	★	★	★	★	★	★		★	★	Good
Ayoubkhani et al.[43]	★	★	★		★	★		★	★	Good
Bahat et al.[70]	★	★	★	★	★	★	★	★	★	Good
Bai et al.[29]	★	★	★		★	★		★		Poor
Bek et al.[83]	★	★	★	★	★	★		★		Poor
Belkacemi et al.[71]	★	★	★		★	★		★	★	Good
Bergia et al.[20]	★	★	★		★			★		Poor
Boglione et al.[30]	★	★	★	★	★	★		★	★	Good

	Selection				Comparability		Outcome			Quality
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for key confounders e.g. age/sex/ comorbidities	Study controls for other factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Borch et al.[59]	★	★						★		Poor
Buonsenso et al.[33]	★	★	★	★				★	★	Poor
Buonsenso et al.[34]	★	★	★	★	★	★	★	★		Good
Buttery et al.[44]	★	★		★	★	★		★	★	Good
Comellie et al.[31]	★	★	★	★	★	★		★	★	Good
Cui et al.[162]	★	★	★	★	★	★		★		Poor
Daitch et al.[67]	★	★			★	★	★	★	★	Fair
Damanti et al.[89]	★	★	★		★			★		Poor
Damiano et al.[39]	★	★	★		★	★	★	★	★	Good

	Selection				Comparability		Outcome			Quality
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for key confounders e.g. age/sex/ comorbidities	Study controls for other factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Donnachie et al.[60]	★	★	★	★	*		★	★	★	Good
Dryden et al.[84]	★	★	★	★	★	★		★		Poor
Dumont et al.[50]	★	★	★	★	★			★	★	Good
Evans et al.[45]	★	★	★	★	★	★		★	★	Good
Fang et al.[65]	★	★	★	★	★	★		★	★	Good
Fernandez-De-Las-Penas et al.[28]	★	★	★	★		★		★	★	Good
Fernandez-De-Las-Penas et al.[23]	★	★	★	★	★	★	★	★	★	Good
Fernandez-De-Las-Penas et al.[25]	★	★	★	★	★	★		★	★	Good
Ferreira et al.[41]	★	★	★	★	★	★		★	★	Good

	Selection				Comparability		Outcome			Quality
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for key confounders e.g. age/sex/ comorbidities	Study controls for other factors	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Frontera et al.[117]	★	★	★	★	★	★		★	★	Good
Funk et al.[77]	★	★	★	★	★	★		★	★	Good
Garjani et al.[46]	★	★		★	★	★		★	★	Good
Hastie et al.[61]	★	★		★	★	★		★		Poor
Heightman et al.[47]			★	★	★	★		★	★	Fair
Huang et al.[52]	★	★	★	★	★	★		★	★	Good
Kildegaard et al.[55]	★	★	★	★	★	★	★	★		Good
Kostev et al.[69]	★	★	★	★	★	★	★	★	★	Good
Kostev et al.[58]	★	★	★	★	★	★	★	★	★	Good

	Selection				Comparability		Outcome			Quality
Study	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Study controls for key confounders e.g. age/sex/ comorbidities**	**Study controls for other factors**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	
Lorusso et al.[76]			★		★	★	★	★		Poor
Martin Loeches et al.[21]	★	★	★		★	★		★		Poor
Meza-Torres et al.[48]	★	★	★	★	★	★	★	★	★	Good
Miller et al.[51]	★	★	★		★	★		★	★	Good
Nakayama et al.[42]*	★	★			★	★		★	★	Poor
Norgard et al.[75]	★	★	★		★		★	★	★	Good
Nugawela et al.[86]	★	★	★		★	★		★	★	Good
Oto et al.[72]	★	★	★				★	★	★	Poor
Ozcan et al.[119]	★	★	★		★	★	★	★	★	Good

	Selection				Comparability		Outcome			Quality
Study	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Study controls for key confounders e.g. age/sex/ comorbidities**	**Study controls for other factors**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	
Ozonoff et al.[87]	★	★	★		★			★		Poor
Pazukhina et al.[66]	★	★	★		★			★	★	Good
Rivera-Izquierdo et al.[22]	★	★	★	★	★	★	★	★	★	Good
Sørensen et al.[56]	★	★			★			★	★	Fair
Spinicci et al.[32]	★	★	★		★	★		★	★	Good
Whitaker et al.[54]	★	★			★	★		★	★	Fair
Yoo et al.[74]	★	★	★		★	★		★	★	Good

* Nakayama et al. downgraded based on data inconsistencies identified within the article

Appendix 4: Quality appraisal table for cross-sectional and cross-sectional cohort primary research studies.

	Selection			Comparability		Outcome			Quality
Study	**Representativeness of the exposed cohort**	**Sample size**	**No-Response rate**	**Ascertainment of the screening/surveillance tool**	**Study controls for key confounders e.g. age/sex/comorbidities**	**Study controls for other factors**	**Assessment of the outcome**	**Statistical Test**	
Barreto et al.[37]	★		★	★	★	★	★★	★	Good
Battistella et al.[38]		★	★	★	★		★	★	Good
Bernas, et al.[53]	★	★		★	★		★	★	Good
de Oliveira et al.[40]	★		★		★	★	★	★	Fair
Feldman et al.[85]	★			★	★	★	★	*	Fair
Fernandez-de-las-Penas et al.[26]	★	★	★	★	★	★	★	★	Good
Fernandez-de-las-Penas et al.[24]	★	★	★	★	★	★	★	★	Good

	Selection			Comparability		Outcome			Quality
Study	**Representativeness of the exposed cohort**	**Sample size**	**No-Response rate**	**Ascertainment of the screening/surveillance tool**	**Study controls for key confounders e.g. age/sex/comorbidities**	**Study controls for other factors**	**Assessment of the outcome**	**Statistical Test**	
Fernandez-de-las-Penas et al.[27]	★	★		★	★		★	★	Good
Gonzalez-Islas et al.[73]	★	★		★	★	★	★★	★	Good
Kikkenborg Berg et al.[64]	★	★	★	★	★	★	★	★	Good
Kikkenborg Berg et al.[88]	★	★	★	★	★	★	★	★	Good
Perlis et al.[57]	★	★		★	★	★	★	★	Good
Peter et al.[63]	★			★	★	★	★	★	Fair
Trapani et al.[36]	★	★	★	★	★	★	★	★	Good

Appendix 5: Quality appraisal table for international registry documents.

Study		Office for National Statistics (UK)[11]	Centers for Disease Prevention and Control (US) MMWR – Children and Adolescents[78]	Centers for Disease Prevention and Control (US) MMWR – Adults[79]	Centers for Disease Prevention and Control (US) Household Pulse Survey[80]
Completeness of recruitment	Few (<80%) or unknown	★	★	★	★
	Some (80-89%)				
	Most (90-97%)				
	All or almost all (>97%)				
Completeness of data	Few (<80%) or unknown	★			★
	Some (80-89%)				
	Most (90-97%)				
	All or almost all (>97%)		★	★	
Use of explicit definitions of variables	Few (<80%) or unknown				
	Some (80-89%)				
	Most (90-97%)				
	All or almost all (>97%)	★	★	★	★
Independence of observations of primary outcome	Outcome not included				
	Outcome neither independent nor blinded	★			★
	Independent observer not blinded				
	Independent observer blinded or outcome is objective		★	★	
Extent of data validation	No validation				
	Range or consistency checks				
	Range and consistency checks	★	★	★	★
	Range and consistency checks plus external check				

Published by the Health Information and Quality Authority (HIQA).

For further information please contact:

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

info@hiqa.ie

www.hiqa.ie