EVIDENCE SYNTHESIS BRIEFING NOTE

TOPIC: **UNDERSTANDING LONG COVID-19**

Information finalized as of May 7, 2021.[a]

This Briefing Note was completed by the Research, Analysis, and Evaluation Branch (Ministry of Health) based on information provided by a member of the COVID-19 Evidence Synthesis Network. Please refer to the Methods section for further information.

Purpose: This note summarizes the research evidence associated with "long COVID", including definitions, risk factors (i.e., sex/gender, age), symptomatology, prognosis, therapeutics, and other emerging research findings.

Key Findings: Commonly, long COVID is characterized as the persistence of any COVID signs and symptoms that continue or develop between four to 12 weeks after acute COVID-19, including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.

- **Emerging Research Findings**: Sixteen systematic, narrative review, and living reviews, and four studies yielded the following details:
  - Risk factors: The following factors may increase the risk for long COVID: a higher acuity of COVID-19 infection or presence of many acute COVID-19 symptoms, being female, being of older age, having a higher body mass index (e.g., obesity), pre-existing comorbidities, psychiatric disorders, and being a health care worker. In addition:
  - Symptomatology: The most common symptoms reported were: fatigue, dyspnea (e.g., shortness of breath), headache, and pain (e.g., chest, joint, muscle); however, persistent symptoms have also been described for the cognitive, musculoskeletal, respiratory, gastrointestinal, cardiac, and psychological systems.
- **Management of Long COVID Patients**: Research suggests that treating people with long COVID requires a multidisciplinary approach including evaluation, symptomatic treatment, treatment of underlying problems, physiotherapy, occupational therapy and psychological support.

Limitations: The limited evidence base currently precludes a precise definition of long COVID-19 symptoms and prevalence. In addition, no identified studies provided evidence regarding prognosis for individuals with long COVID. There is a clear need for robust, controlled, prospective cohort studies, including different at-risk populations and settings, incorporating appropriate investigations, collected and recorded in a standardised way.

Analysis for Ontario: Since the time frame for assessing the risk factors and symptoms associated with long COVID has just been seven months, there has been scant time to understand the longer-term implications of COVID-19 infection. The knowledge regarding long term effects and treatment options is still evolving.

[a] This briefing note includes current available evidence as of the noted date. It is not intended to be an exhaustive analysis, and other relevant findings may have been reported since completion.

Supporting Evidence

Table 1 below summarizes the emerging research evidence associated with 'long COVID', including definitions, risk factors, symptomatology, prognosis, and emerging trends or findings. In the Appendix, additional details on proposed definitions of 'long COVID' are provided in Table 2, reports from systematic and narrative reviews are provided in Table 3, and the results of single long COVID studies are included in Table 4.

Table 1: Summary of Emerging Research on 'Long COVID'

Scientific Evidence	• **'Long COVID' Defined**: The hashtag '#Long COVID' has been frequently used in social media; however, according to the identified literature, long COVID lacks a commonly accepted case definition.[1] Commonly, long COVID is characterized as the persistence of any COVID signs and symptoms that continue or develop between four to 12 weeks after acute COVID-19, including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.[2,3,4,b] More formal definitions have also been proposed (see Table 2).
	• **Emerging Research Findings**: Sixteen systematic, narrative, and living reviews (Table 3) and four studies (Table 4) yielded the following details:
	  ○ Risk factors: The following factors may increase the risk for long COVID: a higher acuity of COVID-19 infection or presence of many acute COVID-19 symptoms, having a higher body mass index (e.g., obesity), pre-existing comorbidities, psychiatric disorders, and being a health care worker.[5,6,7,8,9,10,11,12,13,14,15,16,17] In addition:
	  ▪ Gender: Research suggests women are more likely to develop long COVID than men.[18,19] One review (2021) suggests women are twice as likely to develop symptoms of long COVID.[20]
	  ▪ Older Age: Research suggests people of older age are more likely to develop long COVID.[21,22] One review (2021) suggests that patients with long COVID are around four years older than those without.[23]
	  ○ Symptomatology: The most common symptoms reported were: fatigue, dyspnea (e.g., shortness of breath), headache, and pain (e.g., chest, joint, muscle); however, persistent symptoms have also been described for the cognitive, musculoskeletal, respiratory, gastrointestinal, cardiac, and psychological systems.[24,25,26,27,28,29,30,31,32,33]
	• **Management of Long COVID Patients**: Research suggests that treating people with long COVID requires a multidisciplinary approach including evaluation, symptomatic treatment, treatment of underlying problems, physiotherapy, occupational therapy and psychological support.
	  ○ Treatment of Minor Symptoms: Cough, pain, myalgia can be treated symptomatically with paracetamol (i.e., acetaminophen), cough suppressants, and oral antibiotics (if secondary bacterial infection is suspected).

[b] Acute COVID-19: Signs and symptoms of COVID-19 for up to four weeks; Ongoing symptomatic COVID-19: Signs and symptoms of COVID-19 from four to 12 weeks; Post-COVID-19 syndrome: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis (NICE, 2020).

	○ Etiology: Etiology behind the symptoms, if any, like pulmonary embolism, cerebrovascular accident, coronary artery disease, has to be treated as per the standard protocol; chest physiotherapy and neuro rehabilitation is important in patients with pulmonary and neuromuscular sequelae. ○ Follow-up: The ideal frequency and duration of follow up is not clearly defined. In people with COVID-19 interstitial pneumonia, in the first 12 months, seven interactions with health care professionals (four face-to-face) are recommended, alongside four high-resolution CT scans, four six-minute walk tests (6MWT); four blood tests (including blood count and metabolic panel); and two SARS-CoV-2-IgG tests (i.e., antibody tests). ○ Social and Economic Impact: As the disease continues to spread, more people may need health care support in the future, which could put more demand on the health care system. Clear guidelines regarding management of long COVID may help clear confusion among health care providers.[34] • **Limitations**: The limited evidence base currently precludes a precise definition of COVID-19 symptoms and prevalence. In addition, no identified studies provided evidence regarding prognosis for individuals with long COVID. There is a clear need for robust, controlled, prospective cohort studies, including different at-risk populations and settings, incorporating appropriate investigations, collected and recorded in a standardized way.[35]

Methods

Individual peer-reviewed articles and review articles were identified through PubMed, and Google Scholar. The search was limited to English sources and therefore may not capture the full extent of initiatives in non-English speaking countries. Full-text results extracted were limited to those available through Open Access or studies made available to the Ministry by our partners.

The COVID-19 Evidence Synthesis Network is comprised of groups specializing in evidence synthesis and knowledge translation. The group has committed to provide their expertise to provide high-quality, relevant, and timely synthesized research evidence about COVID-19 to inform decision makers as the pandemic continues. The following members of the Network provided evidence synthesis products that were used to develop this Evidence Synthesis Briefing Note:

- Evidence Synthesis Unit, Research Analysis and Evaluation Branch, Ontario Ministry of Health; and
- COVID-19 Evidence Network to support Decision-making (COVID-END).

For more information, please contact the Research, Analysis and Evaluation Branch (Ministry of Health).

APPENDIX

Table 2: Proposed Definitions of Long COVID-19

National Institute for Health Care Excellence (NICE)	De Sire et al., 2020 & Ceravolo, et al., 2020	Fernández-de-las-Peñas, et al., 2021	Becker, R.C. (2021)
• NICE's COVID-19 rapid guideline on managing the long-term effects of COVID-19 provides the following definitions: ○ Ongoing symptomatic COVID-19: Signs and symptoms of COVID-19 from 4 to 12 weeks. ○ Post-COVID-19 syndrome: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. ○ Long COVID: Signs and symptoms that continue or develop after acute COVID-19, including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome.[36]	• Post-acute: Continuing from the acute phase of COVID-19 and its treatment. • Late-onset: Appeared as a consequence of COVID-19 but after the end of the acute phase. • Chronic: Definition not reported.[37,38]	• Based on relapsing/remitting nature of post-COVID symptoms, researchers proposed this classification: ○ Potentially infection-related symptoms: Up to 4–5 weeks; ○ Acute post-COVID-19 symptoms: From week 5 to week 12; ○ Long post-COVID-19 symptoms: From week 12 to week 24; and ○ Persistent post-COVID-19 symptoms: Lasting more than 24 weeks.[39]	• Type 1: Cases with varying lengths of recovery and rehabilitation that directly correlated with the severity of infection, target organ damage and pre-existing medical conditions at the time of infection. • Type 2: Cases with mild initial symptoms, lasting >6 weeks from the onset. • Type 3: Cases with mild initial symptoms with a period of quiescence or near recovery, followed by a return of symptoms that persist for ≥3 months or ≥6 months. • Type 4: Cases that are initially asymptomatic or minimally symptomatic, then develop symptoms 1–3 months or ≥3 months after confirmed COVID-19 positivity, that lasts for varying periods of time. • Type 5: Cases that are initially asymptomatic or minimally symptomatic, who experience sudden death within 12 months.[40]

Table 3: Systematic and Narrative Reviews of Long COVID-19[c]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International • N=12 • Pragmatic review	• Objective: To understand the prevalence of and the risk factors for developing long COVID-19. • Population: COVID-19 cases in the UK or US (minimum of 250 cases included per study). • Follow-up time: ≥3 weeks after onset of acute COVID-19.	• In the first 12 weeks after the onset of COVID-19, between 5–36% of cases report still having symptoms, with those who were previously hospitalized reporting higher rates. • Between 2-15% of cases report having symptoms 12 weeks or more after the onset of COVID-19. • Most commonly reported long-term symptoms: ○ Fatigue: 8 studies, 17-98%; ○ Dyspnea: 7 studies, 17-93%; and ○ Headache: 4 studies, 38-91%.	• Cases with long COVID are more likely to be older, suffer from pre-existing comorbidities, obesity, or psychiatric disorders and have blood type A. • A higher number of symptoms in the acute phase and specific acute symptoms like fatigue, headache, dyspnea, pain with deep breath, sensitive skin, hoarse voice, and myalgia may also be risk factors for developing long COVID-19.	• In N=210 cases, the need for care assistance significantly increased (52.4%) after COVID-19 infection compared to before (7.7%), with 41.1% of cases who were not dependent previously, at least partially dependent on others in the performance of daily activities subsequently.[41]
• International • N=24 post-acute; 18 acute; 10 chronic • Living rapid systematic review	• Objective: To understand the prevalence and characteristics of emerging disability after COVID-19. • Population: COVID-19 cases. • Follow up time: Not reported.	• At median 54 days post-discharge in N=384, 69% fatigue, 53% breathlessness, 34% cough, 15% depression, and 38% chest radiographs remain abnormal. • At 6 weeks post-discharge in N=200, 19.5% fatigue, 18.5% dyspnea, 18% weakness, and 14.5% activity intolerance. • In N=180 COVID-19 cases (N=8 hospitalized) with a mean follow up of 125 days after onset, 53.1% reported at	• None reported.	• In N=1,409 COVID-19 patients discharged from hospital receiving home care, 10% were readmitted within 32 days, with the risk of readmittance being higher in male patients (hazard ratio [HR]: 1.45) and patients presenting with a comorbidity (heart failure HR 2.12; diabetes HR 1.71.)[42,43]

[c] Some articles are preprints and have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behaviour and should not be reported in news media as established information.

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		least 1 symptom, 33.3% reported up to 2 symptoms, and 19.4% reported 3 more, with the most persistent symptoms being fatigue, loss of smell and taste, and arthralgias. • In N=128 COVID-19 cases (55.5% hospitalized), a median follow-up of 10 weeks after discharge or after the last day of acute COVID-19 symptoms, 52.3% persistent fatigue with no association with acute COVID-19 severity. • In N=145 COVID-19 cases 100 days after onset, 36% dyspnea, 24% night-sweats, 22% sleep disorder, 19% hyposmia/anosmia. • In N=18 young mild or moderate cases, 20–100 days after recovery, 78% mild cognitive deficits.		
• International (preprint) • N=15 • Systematic review	• Objective: To identify long-term COVID-19 effects and estimate their prevalence. • Population: COVID-19 cases (minimum of 100 cases included per study). • Follow -up time: ≥2 weeks after initial symptoms.	• 80% of cases continue to have at least one COVID-19 effect beyond two weeks after the acute infection (follow up ranged from 14 to 110 days). • Most common manifestations of long COVID: ○ Fatigue: 58%; ○ Headache: 44%; ○ Attention disorder: 27%; ○ Hair loss: 25%; and ○ Dyspnea: 24%.	• Fatigue, post-activity polypnea, and alopecia was more commonly reported in females.	• None reported.[44]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• International (preprint) • N=28 • Living rapid systematic review	• Objective: Examine the frequency, profile, and duration of persistent symptoms among people with confirmed or suspected COVID-19, including previously hospitalized and never hospitalized people. • Population: The analysis included 9,442 adult COVID-19 cases (aged 37.7 to 73.9 years old) from 13 countries. • Follow-up time: 21 days post-onset or anytime post-hospital discharge; longest mean follow-up period was 111 days post-hospital discharge.	• Most commonly reported persisting symptoms, overall: ○ Breathlessness: 13 studies; ○ Smell and taste disturbance: 12 studies; and ○ Fatigue: 11 studies. • Most commonly reported persisting psychological symptoms: ○ Anxiety: seven studies; ○ Depression: five studies; ○ Sleep disorders: four studies; and ○ PTSD: three studies. • Most commonly reported persisting musculoskeletal symptoms: ○ Myalgia: seven studies.	• Risk factors could not be identified due to the limitations of the existing data.	• In N=115 patients discharged from hospital receiving rehabilitation, increased dependency in activities of daily living (ADLs; personal care and social activities) was reported on 47.5% of cases.[45]
• International • N=24 • Systematic review	• Objective: To understand the prevalence of long-term COVID-19 symptoms. • Population: COVID-19 cases. • Follow up time: 4 to 12 weeks, or after 12 weeks, from the onset of acute COVID-19.	• Most common symptoms at four to 12 weeks for previously hospitalized cases (prevalence range): ○ Shortness of breath: 32–74%; ○ Fatigue: 28–68%; ○ Cough: 7–43%; ○ Sleep disturbance: 18–57%; ○ Cognitive impairment: 18–22%; ○ Sore throat: 3–9%; ○ Loss of smell: 12–15%; and ○ Loss of taste: 9–10%. ○ In N=402 hospitalized cases, 55.7% scored in the clinical range in at least one psychopathological	• Consistent pattern of people who were predominantly female, most likely middle aged, and of white ethnicity. • Persisting symptoms were significantly associated with: ○ Hospital admission at symptom onset; ○ Initial clinical presentation; ○ Dyspnea; ○ Abnormal auscultation; ○ Age >40 years old; and ○ Being a health care worker.	• One study concluded that clinical abnormalities requiring action are infrequent.[46]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		dimension, one month after hospital discharge. • Most common symptoms continuing past 12 weeks for previously hospitalized cases (prevalence range): ○ Shortness of breath: 6.7–94.6%; and ○ Pain: 10.5–45.9%. • Most common symptoms at four to 12 weeks for non-hospitalized cases (prevalence range): ○ Loss of smell: 7–51%; ○ Lost of taste: 5–51%; ○ Shortness of breath: 8–71%; ○ Chest pain: 6.9–44%; ○ Joint pain: 2–31%; ○ Headache: 5–38%; ○ Fatigue: 27–87%; ○ Palpitations: 10–32%; ○ Fever: 2–11%; and ○ Cognitive impairment: 2–29%. • Most common symptoms continuing past 12 weeks for non-hospitalized cases (prevalence range): ○ Shortness of breath: 9–87%; ○ Fatigue: 21–98%; and ○ Myalgia: 7–88%. • In one study, a diagnosis of COVID-19 led to significantly more first diagnoses of		

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		psychiatric illness (HR: 1.58 to 2.24, P<0.0001).		
• International • N=40 research studies • Narrative review	• Objective: To understand the impact of long COVID on health status. • Population: COVID-19 cases. • Follow-up time: Not reported.	• Long COVID consists of dyspnea, headache, fatigue, and anosmia, and can impact the respiratory, cardiovascular, neurological, and other systems and has implications for mental health. • The most commonly reported symptoms are fatigue and dyspnea.	• Long COVID is more likely to be associated with: ○ Increasing age; ○ Increasing BMI; and ○ Female sex.	• None reported.[47]
• International • N=43 research studies • Living review	• Objective: To understand the impact of ongoing effects of COVID-19; health and social care services responses; future research questions. • Population: COVID-19 cases. • Follow-up time: Not reported.	• Case characteristics include:[d] ○ Post-viral fatigue; ○ Viral persistence (i.e., lasting longer than two months from onset); ○ Cardiac, respiratory, other organ impairments; ○ Thromboembolism; ○ Neurological symptoms (e.g., Guillain Barré Syndrome, encephalitis) ○ Psychological aspects (e.g., depression, anxiety); ○ Cognitive difficulties (e.g., 'brain fog').	• The continuing uncertainty about the etiology of long COVID-19 means that it is difficult to predict who will experience severe consequences from it. • Estimates of long COVID vary but it seems that at least 10% of all people who contract COVID-19 have some symptoms for at least 12 weeks. • Long COVID is seen in all age groups. • COVID-19 has a disproportionate effect on certain parts of the population, including care home residents. Black and Asian communities have seen high death rates and there are concerns about other minority groups and the socially disadvantaged. These people are	• None reported.[48]

[d] Much of the evidence is speculative, based on the symptoms people with Long COVID display or generalising from conditions with similar symptoms. It is unclear whether the same pathology seen in the acute phase of COVID-19 also leads to Long COVID (National Institute for Health Research, March 16, 2021).

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
			already seldom heard in research as well as travellers, the homeless, those in prisons, people with mental health problems or learning difficulties; each having particular and distinct needs in relation to ongoing COVID-19 that need to be understood.	
• International • N=31 studies • Systematic review	• Purpose: Identify intermediate and long-term COVID-19 sequelae affecting formerly healthy adults between 18 and 50 years of age. • Population: Adult participants with confirmed SARS-CoV-2 infection. • Follow-up time: 14 days to 90 days.	• Sequelae persistence since infection spanned 14 days to three months. • Sequelae included: ○ Persistent fatigue (39–73% of assessed persons); ○ Breathlessness (39–74%); ○ Decrease in quality of life (44–69%); ○ Impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%); ○ Evidence of peri-/perimyo-/myocarditis (3–26%); ○ Changes in microstructural and functional brain integrity with persistent neurological symptoms (55%); ○ Increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls); and ○ Incomplete recovery of olfactory and gustatory dysfunction (33–36% of evaluated persons).	• None reported.	• None reported.[49]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization

• International
• The review identified 19 studies; however, none reported information of long COVID in children.
  ○ The author provides a case report of five Swedish children
• Systematic review and case report of five children
	• Purpose: Examine symptoms of long COVID in children.
	• Population: In the case reports, five Swedish children (4 girls) with COVID-19, with median age of 12 years (range: 9-15).
	• Follow-up time: Follow-up period was 35 days to two months (systematic review); follow-up period among case reports was six months.
		• Children in case reports:
		  ○ Fatigue, dyspnea, heart palpitations or chest pain, headaches, difficulties concentrating, muscle weakness, dizziness, and sore throats.
			• In the case reports, the children's symptoms were similar to those reported by studies of adults with long COVID.
			• The case reports suggest that females may be more prone to developing long COVID, as seen in adult studies.
			• Some children had improved after 6–8 months, but they all suffered from fatigue and none had fully returned to school.
				• None reported.[50]

• International
• N=120 studies (preprint)
• Systematic scoping review
	• Purpose: To synthesize what is known from literature about persistent COVID-19, its signs and symptoms, its pathophysiology, and the current management recommendations.
	• Population: Not reported.
	• Follow-up time: Not reported.
		• Predominant symptoms among individuals with long COVID were:
		  ○ Fatigue;
		  ○ Breathlessness;
		  ○ Arthralgia;
		  ○ Sleep difficulties; and
		  ○ Chest pain.
		• Reports also point to the risk of long-term sequelae with cutaneous, respiratory, cardiovascular, musculoskeletal, mental health, neurologic, and renal involvement in those who survive the acute phase of the illness.
			• Individuals with five symptoms in the first week are more likely to develop long COVID:
			  ○ Fatigue; headache; shortness of breath; hoarse voice; and myalgia. Illness was more prevalent among women, older people, and those with obesity.
			• Some prolonged COVID-19 symptoms are associated with:
			  ○ Age 40 to 60 years;
			  ○ Hospital admission at symptom initiation;
			  ○ Severe COVID-19; and
			  ○ Dyspnea or abnormal chest auscultation.
			• Mental health risk factors:
			  ○ Loss of a loved one;
			  ○ Hospitalization;
			  ○ Containment measures such as isolation and quarantine;
			  ○ Being in low-income regions;
			  ○ Financial stressors;
			  ○ Having disabilities;
			  ○ Female gender; and
				• None reported.[51]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
			○ Older age.	
• International • N=11 • Rapid review	• Purpose: Aimed at synthesizing evidence on the long-term effects of the SARS-CoV-2 infection among survivors. • Population: Patients who had all been symptomatic during the active infection, ranging from mild to severe and hospitalized cases; the hospitalized patients also included those who were admitted to the intensive care units (ICUs). Participants were: ○ Adults between 18 and above 60 years (ten studies); ○ Children whose average age was 12 years (one study). • Follow-up time: From seven days to 12 weeks after discharge.	• The majority of symptoms reported were: ○ Fatigue; ○ Shortness of breath; ○ Cough; ○ Sleep disorders; and • Other symptoms reported were: ○ Loss of memory; ○ Muscle pain; ○ Weakness; ○ Heart palpitations; ○ Headaches; ○ Difficulties concentrating; ○ Dizziness; ○ Sore throat; ○ Loss of smell; ○ Loss of taste; ○ Skin rashes; ○ Hair loss; ○ Diarrhoea; ○ Vomiting; and ○ Mental conditions (e.g., depression, anxiety).	• Patients were all symptomatic during the active infection, ranging from mild to severe and hospitalized cases. Hospitalized patients also included those who were admitted to the ICUs.	• None reported.[52]
• International • N=35 (preprint) • Systematic review and meta-analysis	• Purpose: To determine long-term symptoms in COVID-19 survivors after infection. • Population: 18,711 patients. • Follow-up time: None reported.	• Eight pain-related symptoms and 26 other symptoms were identified. • The highest pooled incidence among pain-related symptoms was: ○ Chest pain (17%, 95% CI, 12%-25%); ○ Headache (16%, 95% CI, 9%-27%); ○ Arthralgia (13%, 95% CI, 7%-24%);	• Eligible studies were those reporting patients with a confirmed diagnosis of SARS-CoV-2 and who showed any symptoms persisting beyond the acute phase. • The current meta-analysis may provide a complete picture of incidence in post-acute sequelae of SARS-CoV-(PASC). It remains unclear, however, whether post-COVID symptoms progress or	• None reported.[53]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Neuralgia (12%, 95% CI, 3%-38%); and ○ Abdominal pain (11%, 95% CI, 7%-16%). • The highest pooled incidence among other symptoms was: ○ Fatigue (45%, 95% CI, 32%-59%); ○ Insomnia (26%, 95% CI, 9%-57%); ○ Dyspnea (25%, 95% CI, 15%-38%); ○ Weakness (25%, 95% CI, 8%-56%); and ○ Anosmia (19%, 95% CI, 13%-27%).	regress over time or to what extent PASC are associated with age or sex.	
• International • N=65 • Systematic review	• Purpose: Aim is to investigate the available evidence for long-term complications of COVID-19. • Population: Hospitalized COVID-19 patients; COVID-19 patients admitted to ICU. • Follow-up time: None reported.	• Ten potential late complications of COVID-19 were identified, including ○ Neurological injuries; ○ Lung, liver, kidney, and heart injuries; ○ Thromboembolism; ○ Cardiac/brain stroke; ○ Encephalopathy; and ○ Psychological distress. • Furthermore, some studies have pointed out other complications such as: ○ Hypoproteinemia; ○ Septic shock; and ○ Multiple organ dysfunction syndromes. • The most frequent late complications of COVID-19 included: ○ Lung injuries (N=31);	• None reported.	• None reported.[54]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Venous/arterial thrombosis (N=28); ○ Heart injuries (N=26); ○ Cardiac/brain stroke (N=23); and ○ Neurological injuries (N=20).		
• International • N=Not reported • Narrative review	• Purpose: To summarize the most common neurological complications and reported neurological case studies associated with COVID-19, and neurological side effects associated with COVID-19 treatments. • Population: COVID-19 patients. • Follow-up time: None reported.	• Non-specific neurological complications: ○ Headache; ○ Altered mental status; ○ Dizziness; ○ Depressed level of consciousness; ○ Ageusia (loss of taste); ○ Anosmia (loss of smell); ○ Myalgia; and ○ Fatigue. • Specific neurological complications: ○ Cerebrovascular complications; ○ Subarachnoid Hemorrhage; ○ Massive Cerebral Hemorrhage; ○ Encephalopathy; ○ Acute Hemorrhagic Necrotizing Encephalopathy; ○ Encephalitis; ○ Anti-N-Methyl-D-Aspartate Receptor Encephalitis; ○ Meningitis/Encephalitis; and ○ Acute Myelitis. • Demyelinating Disorders: ○ Guillain–Barré Syndrome; ○ Miller Fisher Syndrome;	• None reported.	• None reported.[55]

Jurisdiction, Number of Relevant Studies, and Review Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
		○ Central Nervous System Demyelination; ○ Seizures; ○ Symmetrical polyneuropathy; and ○ Rhabdomyolysis.		
• International. • N=Not reported • Narrative review	• Purpose: To analyze various aspects of long COVID. • Population: Patients with long COVID. • Follow-up time: None reported.	• Symptoms reported in long COVID: ○ Fatigue; ○ Cough; ○ Chest tightness; ○ Breathlessness; ○ Palpitations; ○ Myalgia; and ○ Difficulty to focus. • Symptoms could be related to: ○ Organ damage; ○ Post viral syndrome; ○ Post-critical care syndrome; and ○ Others.	• Gender: The risk of long COVID is twice as common in women compared to men.[56] • Age: Increasing age is also a risk factor: ○ Patients with long COVID are around four years older than those without. ○ Presence of more than five symptoms in the acute stage of illness is associated with increased risk of developing long COVID.[57] • Co-morbidities: Presence of co-morbidities also increases the risk of developing post-COVID syndrome. Even those with mild symptoms at initial presentation were noted to develop long COVID.	• None reported.[58]

Table 4: Summary of Long COVID-19 Studies

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
• United States • N=4,182 • Prospective observational cohort study	• Purpose: To examine long COVID-19 symptoms prevalence, risk factors, and possibility of predicting a protracted course early in the disease. • Population: 4,182 COVID-19 incident cases self-reported in COVID Symptom Study app.[e] • Follow-up time: None reported.	• Symptom duration: Participants reported symptoms lasting: ○ ≥28 days (558, 13.3%); ○ ≥8 weeks (189, 4.5%); and ○ ≥12 weeks (95, 2.3%). • Reported symptoms: Long COVID was characterized by symptoms of: ○ Fatigue; ○ Headache; ○ Dyspnea; and ○ Anosmia.	• Symptoms of long COVID-19 were more likely with increasing: ○ Age; ○ Body mass index; and ○ Female sex. • Experiencing more than five symptoms during the first week of illness was associated with long COVID (odds ratio = 3.53 (2.76–4.50)).	• None reported.[59]
• United Kingdom • N=201 participants • Observational study	• Purpose: To assess medium-term organ impairment in symptomatic individuals following recovery from acute SARS-CoV-2 infection. • Population: Community-based individuals from two UK centres between April 1 and September 14, 2020; individuals ≥18 years with persistent symptoms following recovery from acute SARS-CoV-2 infection and age-matched healthy controls. ○ 201 individuals (mean age 45, range 21-71 years, 71% female, 88% white, 32% health care workers). • Follow-up time: An average of	• Most frequently reported symptoms included: ○ Fatigue (98%); ○ Muscle aches (87%); ○ Breathlessness (88%); and ○ Headaches (83%). • Mild organ impairment was present in the: ○ Heart (26%); ○ Lungs (11%); ○ Kidneys (4%); ○ Liver (28%); ○ Pancreas (40%); and ○ Spleen (4%) • Organ repairment: ○ 70% single-organ impairment; and ○ 29% multiorgan impairment.	• Study population was at low risk of COVID-19 mortality (obesity 20%, hypertension 7%, type 2 diabetes 2%, heart disease 5%), with only 19% hospitalized with COVID-19. • 42% of individuals had 10 or more symptoms and 60% had severe post-COVID-19 syndrome. • Severe post-COVID-19 syndrome was associated with radiological evidence of cardiac damage (myocarditis).	• Hospitalization was associated with: ○ Older age (p=0.001); ○ Non-white ethnicity (p=0.016); ○ Increased liver volume (p<0.0001); ○ Pancreatic inflammation (p<0.01); and ○ Fat accumulation in the liver (p<0.05) and pancreas (p<0.01).[60]

[e] The COVID Symptom Study smartphone-based app (previously known as COVID Symptom Tracker) was developed by Zoe Global, in collaboration with King's College London and Massachusetts General Hospital, and was launched in the United Kingdom on March 24, 2020 and in the United States on March 29, 2020 (Menni, C., et al., 2020).

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	141 days following SARS-CoV-2 infection, participants completed the baseline assessment.			
• Spain • N=277 • Prospective cohort study	• Objectives: To analyze the incidence of post-acute COVID-19 syndrome (PCS)[f] and its components, and to evaluate the acute infection phase associated risk factors. • Population: Adult patients who had recovered from COVID-19 (February 27 - April 29, 2020). • Follow-up time: 277 patients who recovered from mild (34.3%) or severe (65.7%) forms of SARS-CoV-2 infection were evaluated 77 days (interquartile range [IQR] 72-85) after disease onset.	• PCS was detected in 141 patients (50.9%; 95%CI 45.0-56.7%). Symptoms were mostly mild. • Alterations in spirometry were noted in 25/269 patients (9.3%), while in radiographs in 51/277 (18.9%).[g]	• No baseline clinical features behaved as independent predictors of PCS development.	• None reported.[61]
• China • N=1,733 • Cohort study	• Purpose: To describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity. • Population: Discharged patients with COVID-19; ○ Patients had a median age	• Six months after acute infection, COVID-19 survivors were mainly troubled with: ○ Fatigue or muscle weakness (63%, 1,038 of 1,655); ○ Sleep difficulties (26%, 437 of 1,655); and • Anxiety or depression (23%; 367 of 1,617) of patients.	• Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations and are the main target population for intervention of long-term recovery.	• None reported.[62]

[f] Post-acute COVID-19 syndrome was defined as the persistence of at least one clinically relevant symptom, or abnormalities in spirometry or chest radiology three weeks after symptom onset (Oscar Moreno-Pérez, et al., 2021).
[g] Spirometry is a common office test used to assess how well a patient's lungs work by measuring how much air they inhale and exhale, and how quickly they exhale. Spirometry is used to diagnose asthma, chronic obstructive pulmonary disease (COPD), and other conditions that affect breathing (Mayo Clinic, n.d.).

Jurisdiction, Number of Participants, and Study Type	Objective, Population, Follow-up time Inclusion	Findings		
		Long-term Symptom(s) and Prevalence	Case Characteristics	Health Care Utilization
	of 57.0 (IQR 47.0 – 65.0) years; and ○ 897 (52%) were men. • Follow-up time: Median follow-up time was 186.0 days after symptom onset.			

REFERENCES

[1] Akbarialiabad, H., Taghrir, M.H., et al. (March, 2021). Long COVID: A comprehensive systematic scoping review. *Preprints*. 2021030490.

[2] National Institute for Health and Care Excellence (December, 2020). *COVID 19 rapid guidelines: Managing the long-term effects of COVID-19 - evidence reviews 2 and 3: Prevalence*. London: NICE; 2020. Report No.: NG188.

[3] National Institute for Health and Care Excellence. (December 18, 2020). *NICE, RCGP and SIGN publish guideline on managing the long-term effects of COVID-19*. National Institute for Health and Care Excellence.

[4] Mendelson, M., et al. (November, 2020). Long-COVID: An evolving problem with an extensive impact. *South Africa Medical Journal, 111* (1), 10-12.

[5] Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P.A., Cuapio, A., et al. (January 30, 2021). More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *medR$_x$iv (preprint)*.

[6] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[7] Canstanares Zapatero, D., Hanquet, G., & Van Den Heede, K. (January, 2021). *Epidemiology of long COVID: A pragmatic review of the literature*. Brussels: Belgian Health Care Knowledge Centre.

[8] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[9] National Institute for Health and Care Excellence (December, 2020). *COVID 19 rapid guidelines: Managing the long-term effects of COVID-19 - evidence reviews 2 and 3: Prevalence.* London: NICE; 2020. Report No.: NG188.

[10] Akbarialiabad, H., Taghrir, M.H., et al. (March, 2021). Long COVID: A comprehensive systematic scoping review. *Preprints*. 2021030490.

[11] Sudre, C. H., et al. (2021). Attributes and predictors of Long-COVID: Analysis of COVID cases and their symptoms collected by the COVID Symptoms StudyApp. *Nature Medicine, 27*, 626–631.

[12] Ortona, E., et al. (April 13, 2021). Long COVID: An estrogen-associated autoimmune disease? *Cell Death Discovery, 7* (77).

[13] Sudre, C., et al. (March 10, 2021). Attributes and predictors of long COVID. *Nature Medicine, 27*, 626–631.

[14] British Medical Journal. (September, 2020). Long COVID: How to define it and how to manage it (webinar). *British Medical Journal, 370*, m3489.

[15] British Medical Journal. (September, 2020). Long COVID: How to define it and how to manage it (webinar). *British Medical Journal, 370*, m3489.

[16] Sudre, C., et al. (March 10, 2021). Attributes and predictors of long COVID. *Nature Medicine, 27*, 626–631.

[17] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[18] Sudre, C., et al. (March 10, 2021). Attributes and predictors of long COVID. *Nature Medicine, 27*, 626–631.

[19] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[20] Raveendran, A.V., et al. (2021). Long COVID: An overview. *Diabetes & Metabolic Syndrome: Clinical Research & Review, 15*, 869-875.

[21] Sudre, C., et al. (March 10, 2021). Attributes and predictors of long COVID. *Nature Medicine, 27*, 626–631.

[22] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[23] Raveendran, A.V., et al. (2021). Long COVID: An overview. *Diabetes & Metabolic Syndrome: Clinical Research & Review, 15*, 869-875.

[24] Canstanares Zapatero, D., Hanquet, G., & Van Den Heede, K. (January, 2021). *Epidemiology of long COVID: A pragmatic review of the literature*. Brussels: Belgian Health Care Knowledge Centre.

[25] De Sire, A., Andrenelli, E., Negrini, F., Patrini, M., Lazzarini, S.G., Ceravolo, M.G., et al. (February, 2021). Rehabilitation and COVID-19: A rapid living systematic review by Cochrane rehabilitation field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020. *European Journal of Physical and Rehabilitation Medicine*.

[26] Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P.A., Cuapio, A., et al. (January, 2021). More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *medRxiv (preprint).*

[27] Michelen, M., Manoharan, L., Elkheir, N., Cheng, V., Dagens, D., Hastie, C., et al. (December 9, 2020). Characterising long-term COVID-19: A rapid living systematic review. *medRxiv (preprint).*

[28] National Institute for Health and Care Excellence (December, 2020). *COVID 19 rapid guidelines: Managing the long-term effects of COVID-19 - evidence reviews 2 and 3: Prevalence.* London: NICE; 2020. Report No.: NG188.

[29] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[30] National Institute for Health Research. (March 16, 2021). Living with COVID-19. A dynamic review of the evidence around ongoing COVID-19 - Second Review. *National Institute for Health Research.*

[31] Willi, S., Ruthhold, R., et al. (March/April, 2021). COVID-19 sequelae in adults aged less than 50 years: A systematic review. *Travel Medicine and Infectious Disease, 40*.

[32] Ludvigsson, J. (March, 2021). Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatricia, 110* (3).

[33] Akbarialiabad, H., Taghrir, M.H., et al. (March, 2021). Long COVID: A comprehensive systematic scoping review. *Preprints*. 2021030490.

[34] Raveendran, A.V., et al. (2021). Long COVID: An overview. *Diabetes & Metabolic Syndrome: Clinical Research & Review, 15*, 869-875.

[35] Michelin, M., et al. (December 9, 2020). Characterising long-term COVID-19: A rapid living systematic review. *medRxiv (preprint).*

[36] National Institute for Health and Care Excellence (NICE). *COVID-19 rapid guidelines: Managing the long-term effects of COVID-19 - Evidence reviews 2 and 3: Prevalence.* London: NICE; 2020. Report No.: NG188.

[37] De Sire, A., Andrenelli, E., Negrini, F., Patrini, M., Lazzarini, S.G., Ceravolo, M.G., et al. (February, 2021). Rehabilitation and COVID-19: A rapid living systematic review by Cochrane rehabilitation field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020. *European Journal of Physical and Rehabilitation Medicine*.

[38] Ceravolo, M.G., Arienti, C., de Sire, A., Andrenelli, E., Negrini, F., Lazzarini, S.G., et al. (October, 2020). Rehabilitation and COVID-19: The Cochrane rehabilitation 2020 rapid living systematic review. *European Journal of Physical and Rehabilitation Medicine,* 56 (5), 642-651.

[39] Fernández-de-las-Peñas, et al. (March, 2021). Defining post-COVID symptoms (post-acute COVID, long COVID, persistent post-COVID): An integrative classification. *Environmental Research and Public Health, 18* (5), 2621.

[40] Becker, R.C. (January, 2021). COVID-19 and its sequelae: A platform for optimal patient care, discovery and training. *Journal of Thrombosis and Thrombolysis, 10.*

[41] Canstanares Zapatero, D., Hanquet, G., & Van Den Heede, K. (January, 2021). *Epidemiology of long COVID: A pragmatic review of the literature*. Brussels: Belgian Health Care Knowledge Centre.

[42] De Sire, A., Andrenelli, E., Negrini, F., Patrini, M., Lazzarini, S.G., Ceravolo, M.G., et al. (February, 2021). Rehabilitation and COVID-19: A rapid living systematic review by Cochrane rehabilitation field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020. *European Journal of Physical and Rehabilitation Medicine*.

[43] De Sire, A., Andrenelli, E., Negrini, F., Patrini, M., Lazzarini, S.G., Ceravolo, M.G., et al. (February, 2021). Rehabilitation and COVID-19: Supplementary Digital Material. *European Journal of Physical and Rehabilitation Medicine*.

[44] Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P.A., Cuapio, A., et al. (January, 2021). More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. *medRxiv (preprint).*

[45] Michelen, M., Manoharan, L., Elkheir, N., Cheng, V., Dagens, D., Hastie, C., et al. (December 9, 2020). Characterising long-term COVID-19: A rapid living systematic review. *medRxiv (preprint).*

[46] National Institute for Health and Care Excellence (December, 2020). *COVID 19 rapid guidelines: Managing the long-term effects of COVID-19 - evidence reviews 2 and 3: Prevalence.* London: NICE; 2020. Report No.: NG188.

[47] Soni, S.N., & Nimbalkar, S.M. (February, 2021). Long COVID syndrome following infection with SARS-CoV-2: A devastating influence on health status in some affected individuals. *Journal of Clinical and Diagnostic Research*, *15* (2): LE17-LE21.

[48] National Institute for Health Research. (March 16, 2021). Living with COVID-19. A dynamic review of the evidence around ongoing COVID-19 - Second Review. *National Institute for Health Research.*

[49] Willi, S., Ruthhold, R., et al. (March/April, 2021). COVID-19 sequelae in adults aged less than 50 years: A systematic review. *Travel Medicine and Infectious Disease, 40.*

[50] Ludvigsson, J. (March, 2021). Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatricia, 110* (3).

[51] Akbarialiabad, H., Taghrir, M.H., et al. (March, 2021). Long COVID: A comprehensive systematic scoping review. *Preprints*. 2021030490.

[52] Iwu, C., et al. (January, 2021). The occurrence of long COVID: A rapid review. *Pan African Medical Journal, 38*.

[53] Hoshijima, H., et al. (April 8, 2021). Incidence of long-term post-acute sequelae of SARS-CoV-2 infection related to pain and other symptoms: A living systematic review and meta-analysis. *medR$_x$iv.*

[54] Alinaghi, S., et al. (January 2021). Late complications of COVID-19: A systematic review of current evidence. *Archives of Academic Emergency Medicine, 9* (1), e14.

[55] Al Ramadan, A., et al. (March 2021). Acute and post-acute neurological complications of COVID-19. *Neurology International, 13* (1), 102-119.

[56] British Medical Journal. (September, 2020). Long COVID: How to define it and how to manage it (webinar). *British Medical Journal, 370*, m3489.

[57] British Medical Journal. (September, 2020). Long COVID: How to define it and how to manage it (webinar). *British Medical Journal, 370*, m3489.

[58] Raveendran, A.V., et al. (2021). Long COVID: An overview. *Diabetes & Metabolic Syndrome: Clinical Research & Review, 15*, 869-875.

[59] Sudre, C., et al. (March 10, 2021). Attributes and predictors of long COVID. *Nature Medicine, 27*, 626–631.

[60] Dennis, A., et al. (March 2021). Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: A prospective, community-based study. *British Medical Journal Open, 11* (3), e048391.

[61] Moreno-Perez, O., et al. (March 2021). Post-acute COVID-19 syndrome incidence and risk factors: A Mediterranean cohort study. *Journal of Infection, 82* (3), 378-383.

[62] Huang, C., et al. (January 16, 2021). 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *The Lancet, 397* (10270), 220-232.