POST COVID-19 CONDITION

OCSO BIWEEKLY SCAN OF EVIDENCE #27

July 2-July 15, 2022

SCOPE

This biweekly update presents an analysis of new evidence, guidance and issues related to post COVID-19 condition and synthesizes the current state of knowledge. Comprehensive lists of details and resources on this issue are available at the Office of the Chief Science Officer (OCSO).

CURRENT STATE OF KNOWLEDGE

According to the World Health Organization (WHO), post COVID-19 condition (PCC) refers to persistent symptoms occurring 12 weeks or more after an acute COVID-19 infection, which persist or reoccur for a minimum of 8 weeks. The most common symptoms that we know of in adults include: fatigue, memory problems, sleep disturbances, shortness of breath, anxiety and depression, general pain and discomfort, difficulty thinking or concentrating and post-traumatic stress disorder (PTSD). There is still a lot that we don't know about post COVID-19 condition in children.

PCC is also referred to as long COVID, post-acute sequelae, post COVID-19 symptoms, and post-acute COVID-19 syndrome. Prior to the WHO definition, a number of studies reported on post-acute sequelae (PAS) from 4 to 12 weeks post diagnosis. The Public Health Agency of Canada (PHAC) released a review of the current international evidence (November 2021). Over 100 symptoms or difficulties conducting usual activities of daily living were reported.

There is limited data suggesting that the condition may be more likely to develop in those:

- who were hospitalized during acute infection;
- had more than 5 COVID symptoms during the acute phase;
- have pre-existing respiratory disease;
- are older;
- are women; and
- have other co-morbidities or have higher BMI.

There's currently no universally agreed-upon approach to diagnose and treat post COVID-19 condition. Early evidence suggests that vaccination with 2 or more doses may help reduce the risk of developing post COVID-19 condition if infected. Emerging evidence points to the importance of multidisciplinary care given the heterogeneity of symptoms associated with PCC. Multidisciplinary teams in "long COVID" clinics have been set up to include professionals from the following fields: rehabilitation, respiratory and cardiac consultants, physiotherapists, occupational therapists, psychologists, etc.

People who have been hospitalized or who needed intensive care during recovery appear to be at greater risk of experiencing longer-term effects. However, recent research shows about 30% to 40% of people who weren't hospitalized for their initial COVID-19 infection still report symptoms beyond 12 weeks. Canadians suffering from PCC and who are unable to work because of their symptoms may be eligible for support through: Employment and Skills Development Canada's Employment Insurance (EI) Program and Canada Pension Plan Disability Benefits.

This week's scan includes a systematic review examining the link between diabetes and long COVID, as well as a study by Manhas et al. on a rehabilitation framework for post-COVID conditions (PCC) to support persons with PCC in Alberta, Canada.

GUIDELINES OR STANDARDS

- **WHO** developed a clinical case definition of PCC in October 2021. This first version was developed by patients, researchers and others with the understanding that the definition may change as new evidence emerges.
    - *"Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."*
    - **WHO:** Q&A page on Post-COVID-19 Condition (February 2022).

- **US CDC** describes Post-COVID conditions as a wide range of new, returning, or ongoing health problems that people experience after first being infected with the virus that causes COVID-19. The CDC posted Interim Guidance (Updated June 2021) for healthcare providers on Evaluating and Caring for Patients with Post-COVID Conditions. Post-COVID conditions can be considered a disability under the Americans with Disabilities Act (ADA). The CDC also released information on Caring for People with Post-COVID Conditions (Updated March 2022). CDC is using science to learn more about post-COVID conditions.

- UK **NICE**: Rapid guidelines for managing the long-term effects of COVID-19 (Updated March 2022).

- **Chartered Society of Physiotherapy** in UK published its COVID-19 rehabilitation standards (July 2021).

- Guidelines to help doctors manage long COVID patients published in *British Journal of General Practice* (August 2021).

- UK **NHS** guidance for Post-COVID syndrome assessment clinics (April 2021).

- Guidance for **Canadian Rehabilitation and Exercise Professionals** on Post COVID-19 condition and rehabilitation management strategies (August 2021).

- **Government of Canada**: COVID-19 for health professionals - Post COVID-19 condition (continuously updated)

- **Center for Effective Practice** – COVID-19: Clinical Guidance for Primary Care Providers - Long-term symptoms / Post-acute sequelae of COVID-19 (PASC) (last updated April 2022)

- *Wiener klinische Wochenschrift*: Guideline S1: Long COVID: Diagnostics and treatment strategies (December 2021)

- American Academy of Physical Medicine and Rehabilitation (**AAPM&R**): Cognitive Symptoms Guidance & Breathing Discomfort Guidance (December 2021).

- Royal Australian College of General Practitioners (**RACGP**) guidance for GPs caring for patients with post–COVID-19 conditions (December 2021).

- European Society of Clinical Microbiology and Infectious Diseases (**ESCMID**): Rapid guidelines for assessment and management of long COVID (February 2022)

- **ACAS** (UK-based Advisory, Conciliation and Arbitration Service): Long COVID – advice for employers and employees (last reviewed April 2022)

- **Ontario Health** Post COVID-19 Condition - Guidance for Primary Care (PDF)

- **Scottish Government Guidelines:** Managing the long-term effects of COVID-19

NATIONAL AND INTERNATIONAL DEVELOPMENTS *(JULY 2 – JULY 15)*

CANADA

- (NEW) On July 7th, the Government of Canada announced they will be investing $10 million to create a pan-Canadian platform to advance research into the effectiveness and clinical challenges of new COVID-19 treatments in non-hospitalized patients. The Canadian ADAptive Platform Trial of COVID-19 Therapeutics in Community Settings (Can-ADAPT COVID) will be led by Dr. Andrew Pinto. Dr. Pinto will investigate outpatient medications for COVID-19 such as nirmatrelvir/ritonavir and provide key insights into whether treatments prevent hospitalization and post COVID-19 condition ("long COVID").
- (NEW) A study by Manhas et al. describes the development and composition of a codesigned, multidisciplinary, integrated, systematic rehabilitation framework for post-COVID conditions (PCC) that spans the care continuum to streamline and standardize rehabilitation services to support persons with PCC in Alberta, Canada.
- (NEW) The new post-COVID rehab program at The Ottawa Hospital combines physiotherapy and occupational therapy, but also includes an important core of mental health supports

UK

- (NEW) According to recent UK ONS data, of triple-vaccinated adults, 4.5%, 4.2% and 5.0% self-reported having long COVID 12 to 16 weeks after a first laboratory-confirmed coronavirus (COVID-19) infection compatible with the Omicron BA.1, Omicron BA.2 or Delta variants, respectively, using data to 27 May 2022. There was no statistical evidence of differences in the odds of reporting long COVID between infections compatible with the Omicron BA.1, Omicron BA.2 and Delta variants among adults who were triple vaccinated when infected; this was after statistically adjusting for socio-demographic characteristics for all comparisons, and for time since last vaccine dose when comparing Omicron BA.1 and BA.2.

US

- (NEW) CDC published a checklist designed to help patients and caregivers get the most out of appointments with healthcare providers for post-COVID conditions.

EMERGING SCIENTIFIC EVIDENCE *(JULY 2 – JULY 15)**

EVIDENCE PRODUCTS

TITLE AND AUTHOR	EVIDENCE TYPE	SUMMARY
Post COVID-19 complications, adjunct therapy explored, and steroidal after effects (Sonkar et al)	Review (Available in *Can J Chem)*	Review discusses various post-COVID-19 complications observed and adjunctive therapies used along with common COVID-19 treatment and spotlights their side effects and consequences. This review provides the latest literature on COVID-19, which emphasizes the subsequent complications in various organs, side effects of drugs, and alternative regimens used to treat COVID-19.
Association of COVID-19 with Diabetes: A Systematic Review and Meta-Analysis	Systematic Review *(Available in*	Emerging evidence suggests that long COVID-19 may lead to a wide range of post-acute sequelae outcomes, including new onset of diabetes. Aim of this meta-analysis was to estimate the incidence of newly diagnosed diabetes in survivors of COVID-19. Multiple electronic databases

(Ssentongo et al)	*Research Square)*	(MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and the World Health Organization Global Literature on Coronavirus Disease) and clinical trial registries were searched to June 25, 2022, for studies reporting the association of COVID-19 and diabetes. Two investigators independently assessed studies for inclusion. Risk of bias was assessed using the Newcastle-Ottawa Scale. We estimated the effect of COVID-19 on incident diabetes by random-effects meta-analyses using the generic inverse variance method. We identified 5 eligible studies consisting of 1,130,773 COVID-19 patients and 16,630,187 controls. Median age was 43 years and 34.8 % were female. COVID-19 was associated with a 74% higher risk of incident diabetes. Average risk of bias assessment was 7.5. In this systematic review and meta-analysis, COVID-19 was associated with higher risk for developing new onset diabetes among survivors.

SELECTED LITERATURE

TITLE AND AUTHOR	SOURCE	SUMMARY
Searching for Factors Influencing the Severity of the Symptoms of Long COVID (Mińko et al)	*Int J Environ Res Public Health*	The purpose of this study was to look for factors that influence the type and severity of Long COVID symptoms. In total, 932 individuals with a history of COVID-19 were qualified for the study using an original questionnaire based on the COVID-19 Yorkshire Rehab Screen (C19-YRS) questionnaire. Older adults were more likely to report problems with mobility and in performing daily activities. Those with a higher BMI showed significantly more symptoms such as dyspnea at rest and on exertion, feelings of chronic fatigue, problems with mobility and in performing daily activities. The data show that those with Long COVID should receive multidisciplinary help including additional medical and psychological support. Particular attention should be paid to elderly and obese persons.
Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study (O'Kelly et al)	*Brain Behav Immun Health*	In this single centre interventional pre post study, the safety of Low Dose Naltrexone (LDN) was explored in patients with Post COVID-19 Syndrome (PCS). Patients were recruited through a Post COVID clinic, had a baseline quality of life questionnaire in symmetrical Likert format, were prescribed 2 months of LDN and repeated the same questionnaire at the end of the second month. Patients were monitored to adverse events. 52 patients participated of whom 40 (76.9%) were female. Median age was 43.5 years. Healthcare workers represented the largest occupational cohort n = 16(34.8%). Median time from diagnosis of COVID-19 until enrolment was 333 days. 38 participants (73.1%) were known to commence LDN, two of whom (5.3%) stopped taking LDN post commencement due to new onset diarrhoea and also described fatigue. In total 36(69.2%) participants completed the questionnaire at the end of the two-month period. Improvement was seen in 6 of 7 parameters measured; recovery from COVID-19, limitation in activities of daily living, energy levels, pain levels, levels of concentration and sleep disturbance, improvement in mood approached but was not significant. LDN is safe in patients with PCS and may improve well-being and reduce symptomatology in this cohort.
Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated	*Research Square prepub*	Our aim was to investigate these aspects in SARS-CoV-2 positive individuals with and without a post COVID-19 condition diagnosis. We conducted a population-based cohort study of adults in the entire Stockholm Region, Sweden, with a positive SARS-CoV-2 test from 1 March

factors, and healthcare use by severity of acute infection (Hedberg et al)		2020 to 31 July 2021, stratified by severity of the acute infection. The study outcome was a post COVID-19 condition diagnosis registered any time 90 to 360 days after positive test. We performed Cox regression models to assess baseline characteristics associated with post COVID-19. Individuals with post COVID-19 were then propensity-score matched to individuals without post COVID-19 to assess healthcare use beyond the acute infection. Among 204 805 SARS-CoV-2-positive individuals, the proportion receiving a post COVID-19 diagnosis was 1% among individuals not hospitalized for their COVID-19 infection, 6% among hospitalized, and 32% among ICU-treated individuals. Female sex was associated with post COVID-19 among non-hospitalized and hospitalized individuals, with interactions between age and sex. Among individuals with post COVID-19, the monthly proportion with outpatient care visits after the infection compared to before the infection was substantially elevated up to one year after the acute infection, with substantial proportions of this care attributed to care related to post COVID-19.
Long COVID and symptom trajectory in a representative sample of Americans in the first year of the pandemic (Wu et al)	*Sci Rep*	We use a sample representing the U.S. community population from the Understanding America Study COVID-19 Survey, which surveyed around 8000 respondents bi-weekly from March 2020 to March 2021. Our final sample includes 308 infected individuals who were interviewed one month before, around the time of, and 12 weeks after infection. About 23% of the sample experienced new-onset symptoms during infection which lasted for more than 12 weeks, and thus can be considered as having long COVID. The most common new-onset persistent symptoms among those included in the study were headache (22%), runny or stuffy nose (19%), abdominal discomfort (18%), fatigue (17%), and diarrhea (13%). Long COVID was more likely among obese individuals and those who experienced hair loss, headache and sore throat) during infection. There was a lack of evidence relating risk to age, gender, race/ethnicity, education, current smoking status, or comorbid chronic conditions. This work provides national estimates of long COVID in a representative sample after accounting for pre-infection symptoms.
Remodeling of T Cell Dynamics During Long COVID Is Dependent on Severity of SARS-CoV-2 Infection (Wiech et al)	*Front immunol*	We performed longitudinal studies of mild, moderate and severe COVID-19-convalescent patients, at two time points (3 and 6 months from the infection), to assess the dynamics of T cells immune landscape, integrated with patients-reported symptoms. We show that alterations among T cell subsets exhibit different, severity- and time-dependent dynamics, that in severe convalescents result in a polarization towards an exhausted/ senescent state of CD4+ and CD8+ T cells and perturbances in CD4+ Tregs. CD8+ T cells exhibit a high proportion of CD57+ terminal effector cells, together with significant decrease of naïve cell population, augmented granzyme B and IFN-γ production and unresolved inflammation 6 months after infection. Mild convalescents showed increased naïve, and decreased central memory and effector memory CD4+ Treg subsets. Patients from all severity groups can be predisposed to the long COVID symptoms, and fatigue and cognitive dysfunctions are not necessarily related to exhausted/senescent state and T cell dysfunctions, as well as unresolved inflammation that was found only in severe convalescents. In conclusion, post-COVID-19 functional remodeling of T cells could be seen as a two-step process, leading to distinct convalescent immune states at 6 months after infection. Our data imply that attenuation of the functional

		polarization together with blocking granzyme B and IFN-γ in CD8+ cells might influence post-COVID alterations in severe convalescents.
Detection of Post-COVID-19 Patients Using Medical Scent Detection Dogs—A Pilot Study (Twele et al)	*Front Med*	Previous research proved dogs' ability to detect acute SARS-CoV-2 infections, but has not yet shown if dogs also indicate samples of patients with post-COVID-19 condition (Long COVID). Nine dogs, previously trained to detect samples of acute COVID-19 patients, were confronted with samples of Long COVID patients in two testing scenarios. In test scenario I (samples of acute COVID-19 vs. Long COVID) dogs achieved a mean sensitivity (for acute COVID-19) of 86.7% and a specificity of 95.8%When dogs were confronted with Long COVID and negative control samples in scenario IIa, dogs achieved a mean sensitivity (for Long COVID) of 94.4 and a specificity of 96.1%. In comparison, when acute SARS-CoV-2 positive samples and negative control samples were comparatively presented (scenario IIb), a mean sensitivity of 86.9 and a specificity of 88.1% was attained. This pilot study supports the hypothesis of volatile organic compounds (VOCs) being long-term present after the initial infection in post-COVID-19 patients. Detection dogs, trained with samples of acute COVID-19 patients, also identified samples of Long COVID patients with a high sensitivity when presented next to samples of healthy individuals.
Development of a Novel Care Rehabilitation Pathway for Post-COVID Conditions (Long COVID) in a Provincial Health System in Alberta, Canada (Manhas et al)	*Phys Ther*	The purpose of this study was to describe the development and composition of a codesigned, multidisciplinary, integrated, systematic rehabilitation framework for post-COVID conditions (PCC) that spans the care continuum to streamline and standardize rehabilitation services to support persons with PCC in Alberta, Canada. A collaborative, consensus-based approach was used, involving 2 iterative provincial taskforces in a Canadian provincial health system. The first taskforce (59 multidisciplinary stakeholders) sought to clarify the requisite facets of a sustainable, provincially coordinated rehabilitation approach for post-COVID rehabilitation needs, based on available research evidence. The second taskforce (129 multidisciplinary stakeholders) translated that strategy and criteria into an operational framework for provincial implementation. Both taskforces sought to align with operational realities of the provincial health system. The summation of this collaborative, consensus approach resulted in the Provincial Post COVID-19 Rehabilitation Response Framework (PCRF). The PCRF includes 3 care pathways across the care continuum, specifically targeting in-hospital care, continuing care, and community-based care, with 3 key elements: (1) the use of specific symptom screening and assessment tools to systematically identify PCC symptoms and functional impairments; (2) pathways to determine patients' rehabilitation trajectory and to guide their transition between care settings; and, (3) self-management and education resources for patients and providers.
Chronic fatigue, depression and anxiety symptoms in Long COVID are strongly predicted by neuroimmune and neuro-oxidative pathways which are caused by the inflammation during acute infection (Al-Hakeim et al)	*medRxiv*	The severity of the Long COVID physio-affective phenome is largely predicted by peak body temperature (BT) and lowered oxygen saturation (SpO2) during the acute infectious phase. This study aims to delineate whether the association of BT and SpO2 during the acute phase and the Long COVID physio-affective phenome is mediated by neurotoxicity (NT) resulting from activated immune-inflammatory and oxidative stress pathways. We recruited 86 patients with Long COVID (3-4 months after the acute phase) and 39 healthy controls and assessed serum C-reactive protein (CRP), caspase-1, interleukin (IL)-1β, IL-18, IL-10, myeloperoxidase (MPO), advanced oxidation protein products (AOPP), total antioxidant

		capacity (TAC), and calcium (Ca), as well as peak BT and SpO2 during the acute phase. Cluster analysis revealed that a significant part (34.9%) of Long COVID patients (n=30) show a highly elevated NT index computed based on IL-1β, IL-18, Caspase-1, CRP, MPO and AOPP. Partial Least Squares analysis showed that 61.6% of the variance in the physio-affective phenome of Long COVID is explained by the NT index, lowered Ca, peak BT/SpO2 in the acute phase, and prior vaccinations with Astra-Zeneca or Pfizer. The most important predictors of the physio-affective phenome are Ca, CRP, IL-1β, AOPP and MPO. The infectious-immune-inflammatory core of acute COVID-19 strongly predicts the development of physio-affective symptoms 3-4 months later, and these effects are partly mediated by neuro-immune and neuro-oxidative pathways.
Using Logistic Regression to Predict Long COVID Conditions in Chronic Patients (Kulenovic et al)	*Stud Health Technol Inform*	This paper presents a method for predicting selected long COVID conditions in chronic and multimorbidity patients. It produces a logistic regression model for each long COVID condition by examining electronic medical records (EMRs) of COVID-19 patients and taking their chronic conditions as predictors. The models were developed and tested using the Jumpstart EMR database, provided in the COVID-19 Research Environment of Hopkins University, containing about 250,000 EMRs of the outpatient and ambulatory COVID-19 patients across the US. They are illustrated by predictions of 20 prevalent acute and chronic long-COVID conditions in patients diagnosed with frequent pre-COVID chronic diseases. These models can aid in investigating long COVID impacts on various chronic patients, finding their underlying pathophysiology, and establishing guidelines for their treatment and prevention.
The Role of Acupuncture for Long COVID: Mechanisms and Models (Williams & Moramarco)	*Med Acupunct*	Objective was to establish an evidence-based role for acupuncture as a safe and effective treatment for managing Long COVID in the integrative medical setting. Background: COVID-19 progresses to a chronic state, termed Long COVID, in about 30% of cases with estimates as high as 40% for prolonged illness. Symptoms are diverse and range over several body systems, including unrelenting fatigue, persistent malaise, chronic pain, and mood changes. Early clinical reports suggest acupuncture can effectively address both symptoms and the underlying causes of Long COVID. Historically, acupuncture is well defined in Traditional Chinese Medicine writings to treat influenza-like febrile illnesses. Contemporary scientific literature and case studies support the value of acupuncture for symptoms associated with acute and chronic respiratory viral infections, such as influenza, including SARS and COVID-19. Recent reports provide early evidence of acupuncture's effectiveness in managing Long COVID symptoms and may also have disease-modifying benefits.
Deriving and validating a risk prediction model for long COVID-19: protocol for an observational cohort study using linked Scottish data (Daines et al)	*BMJ Open*	In this protocol, we describe plans to develop a prediction model to identify individuals at risk of developing long-COVID.We will use the national Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform, a population-level linked dataset of routine electronic healthcare data from 5.4 million individuals in Scotland. We will identify potential indicators for long-COVID by identifying patterns in primary care data linked to information from out-of-hours general practitioner encounters, accident and emergency visits, hospital admissions, outpatient visits, medication prescribing/dispensing and mortality. We will investigate the potential indicators of long-COVID by performing a matched analysis between those with a positive reverse transcriptase PCR (RT-PCR) test for SARS-CoV-2 infection and two control

		groups: (1) individuals with at least one negative RT-PCR test and never tested positive; (2) the general population (everyone who did not test positive) of Scotland. Cluster analysis will then be used to determine the final definition of the outcome measure for long-COVID. We will then derive, internally and externally validate a prediction model to identify the epidemiological risk factors associated with long-COVID.
Long COVID in K18-hACE2 mice causes persistent brain inflammation and cognitive impairment (Sriramula et al)	*Research Square prepub*	We establish an animal model of long COVID by eliciting mild disease in K18-hACE2 mice. Following recovery from infection with a low dose of SARS-CoV-2, K18-hACE2 mice show the characteristic lung fibrosis associated with SARS-CoV-2 infection, which correlates with increased expression of the pro-inflammatory kinin B1 receptor (B1R). These mice also have elevated expression of B1Rs and inflammatory markers in the brain and exhibit cognitive impairments such as elevated anxiety and attenuated exploratory behavior. Our data demonstrate that K18-hACE2 mice exhibit persistent effects of SARS-CoV-2 infection on brain tissue, revealing the potential of this model for investigating long COVID. The results further imply that elevated B1R expression may drive the long-lasting inflammatory response associated with SARS-CoV-2 infection.
Race, Ethnicity, and Utilization of Outpatient Rehabilitation for Treatment of Post COVID-19 Condition (Hentschel et al)	*PM&R*	Objective was to examine factors associated with outpatient rehabilitation use following COVID-19 and to ascertain whether differential incidence of sequelae explain variation in post-COVID rehabilitation utilization by race and ethnicity. U.S. adults with COVID-19 during 2020 in the TriNet X database were participants. From 406,630 laboratory-confirmed COVID-19 cases, we identified 8,724 individuals who received outpatient rehabilitation and matched 28,719 controls. Of rehabilitation users, 43.3% were 40 years old or younger, 54.8% were female, 58.2% were white, 17.9% were African American/Black, 2.1% were Asian, 13.0% were Hispanic, 39.2% had no comorbidities, and 40.3% had been hospitalized for COVID-19. Dyspnea (20.4%), fatigue (12.4%), and weakness (8.2%) were the most frequently identified symptoms. Although there were no racial differences in the incidence of the 6 post COVID-19 condition symptoms considered, African American/Black individuals were significantly less likely to receive outpatient rehabilitation than their white counterparts. Hispanic individuals had higher outpatient rehabilitation utilization and a significantly higher incidence of post-COVID fatigue.
Neurological long-COVID in the outpatient clinic: Two subtypes, two courses (Grisanti et al)	*J Neurol Sci*	In this study, we evaluated a population of patients with prior COVID-19 infection who showed signs and symptoms consistent with neurological long-COVID. We prospectively collected demographic and acute phase course data from patients with prior COVID-19 infection who showed symptoms related to neurological involvement in the long-COVID phase. Firstly, we performed a multivariate logistic linear regression analysis to investigate the impact of demographic and clinical data, the severity of the acute COVID-19 infection and hospitalization course, on the post-COVID neurological symptoms at three months follow-up. Secondly, we performed an unsupervised clustering analysis to investigate whether there was evidence of different subtypes of neurological long COVID-19. 109 patients referred to the neurological post-COVID outpatient clinic. Clustering analysis on the most common neurological symptoms returned two well-separated and well-balanced clusters: long-COVID type 1 contains the subjects with memory disturbances, psychological impairment, headache, anosmia and ageusia, while long-COVID type 2

		contains all the subjects with reported symptoms related to PNS involvement. The analysis of potential risk-factors among the demographic, clinical presentation, COVID 19 severity and hospitalization course variables showed that the number of comorbidities at onset, the BMI, the number of COVID-19 symptoms, the number of non-neurological complications and a more severe course of the acute infection were all, on average, higher for the cluster of subjects with reported symptoms related to PNS involvement.
A Case-Crossover Phenome-wide Association Study (PheWAS) for Understanding Post-COVID-19 Diagnosis Patterns (Haupert et al)	*medRxiv*	Objective was to assess which diagnoses appear more frequently after a COVID-19 infection and how they differ by COVID-19 severity and vaccination status. We applied a case-crossover phenome-wide association study (PheWAS) in a retrospective cohort of COVID-19 survivors, comparing the occurrences of 1,649 diagnosis-based phenotype codes (PheCodes) pre- and post-COVID-19 infection periods in the same individual using a conditional logistic regression. Patients tested for or diagnosed with COVID-19 at Michigan Medicine from March 10, 2020 through May 1, 2022. We compared the rate of occurrence of 1,649 disease classification codes in "pre-" and "post-COVID-19 periods". We studied how this pattern varied by COVID-19 severity and vaccination status at the time of infection. Using a case-crossover PheWAS framework, we found mental, circulatory, and respiratory disorders to be strongly associated with the "post-COVID-19 period" for the overall COVID-19-positive cohort. A total of 325 PheCodes reached phenome-wide significance and top hits included cardiac dysrhythmias, respiratory failure, insufficiency, arrest and anxiety. In the patients with severe disease, we found stronger associations with many respiratory and circulatory disorders, such as pneumonia and acute pulmonary heart disease and the "post-COVID-19 period," compared to those with mild/moderate disease. Our results confirm that patients experience myriad symptoms more than 28 days after SARS-CoV-2 infection, but especially mental, circulatory, and respiratory disorders.

*Note: Content may have been published prior to this scan period but was only available through applying our search strategies during this period.

COMMENTARIES, LETTERS AND OPINION PIECES *(JULY 2 – JULY 15)*

- **Call for action: Health services in the European region must adopt integrated care models to manage Post-Covid-19 Condition (*Lancet*):** With the emergence of Post-Covid-19 Condition there is now a further increase in the overall rehabilitation needs within health systems. In a call for action, the recommendation is to: 1) Build capacity for early identification and recognition of symptoms of Post-Covid-19 Condition, 2) Strengthen primary health care to manage Post-Covid-19 Condition when medically indicated, and to be the point of referral for more severe cases, 3) Acknowledge the need for individualized long-term rehabilitative care for persons with Post-Covid-19 Condition, and 4) Strengthen the health system to be able to provide an individualised multidisciplinary care pathway in which patient's multi-system symptoms and rehabilitation needs are assessed and managed, informed by real world outcome data and patient experience.

- **Long COVID: A New Challenge for Prevention of Obesity in Women *(American Journal of Lifestyle Medicine):*** Long COVID affects individuals that do not recover for several weeks or months following the onset of symptoms of COVID-19. Obesity could play a role in the long COVID syndrome. During the pandemic, various factors contributed greatly to aggravating obesity in women leading to a pro-inflammatory and prothrombotic status. This commentary explores the relationship between long COVID and obesity in women.

MEDIA HIGHLIGHTS *(JULY 2 – JULY 15)*

CANADA

- **Montreal study looks for ways to treat COVID-19 long-haulers crippled by lingering symptoms (CBC News):** Dr. Thao Huynh is a researcher and epidemiologist-cardiologist with the McGill University Health Centre (MUHC) and she is conducting a study on the long-haul impacts of COVID-19 with the aim of better understanding the disease and treating its symptoms. Huynh said her research has so far uncovered clear indicators of heart damage in patients who have these long-COVID symptoms. Her study is uncovering active heart inflammation or heart scarring. There are also heart palpitations and other abnormalities, she said. In fact, a third of patients have heart problems, she said. The brain is also affected, she added, and the brain and heart are closely related. She said about 80% long-COVID patients are women and she believes it is an autoimmune issue. However, she admits, not everybody agrees with her on that. What is clear is that many people, including doctors and nurses, are crippled by the symptoms, she said. Huynh's Impact Quebec COVID-19 Long Haul Study launched a year ago.
- **Rehab program gives hope to 'long COVID' sufferers (CBC News):** A ground-breaking rehab program at The Ottawa Hospital is offering hope to people suffering from "long COVID." Its estimated that about four million Canadians have been infected, which means some 400,000 may have long COVID. Many sufferers report intense fatigue, trouble catching their breath, brain fog, anxiety and depression. The new post-COVID rehab program at The Ottawa Hospital combines physiotherapy and occupational therapy, but also includes an important core of mental health supports.

GLOBAL

- **Long Covid: what we know about it and how best to treat it (The Guardian):** Being vaccinated and boosted seems to protect against long Covid. Estimates of those with Covid who will develop long Covid range from 5% to 30%, but applying this prevalence to the general population is problematic. Prof Gail Matthews from the Kirby Institute is a lead investigator on the Adapt study examining patients for long Covid, which has been running since mid 2020. While there are some children who experienced more severe symptoms affecting function, most children who have symptoms after three months “are doing well and improve over time”.

POST COVID-19 CONDITION RESOURCES

- (NEWLY ADDED) Recovery & Rehabilitation After COVID-19: Resources for Health Professionals (Alberta Health Services)
- (NEWLY ADDED) ZB MED preprint Viewer: Website includes 45.543 COVID-19 related preprints from medRxiv and bioRxiv, ChemRxiv, ResearchSquare, arXiv and from Preprints.org. They have recently developed and incorporated a long COVID classifier based on state-of-the-art methods and manually curated data by experts
- Long COVID Physio: Long COVID Physio is an international peer support, education and advocacy, patient-led association of Physiotherapists living with Long COVID and allies. They post various educational videos on long COVID.
- John Hopkins Medicine - Long-Term Effects of COVID-19
- C19 Recovery Awareness (US): The mission of the Long Haul COVID Fighters is to provide support for those whose health has been affected by COVID-19, promote public awareness and education regarding lengthy COVID recovery, and advocate for the medical, mental health, and social interests of long haul COVID survivors.
- COVID-19 Virtual Library of Health Data and Evidence (Canada): Resources to knowledge products, data and evidence on the impacts of COVID-19, which includes post COVID-19 condition. This is a searchable collection of products funded and published by the Government of Canada.
- Lullabies for long COVID (UK): An online program developed in collaboration with the English National Opera could help with rehabilitation, by improving mental health and symptoms of breathlessness.
- Solve Long Covid Initiative (US): The Solve ME/CFS Initiative is a non-profit organization that serves as a catalyst for critical research into diagnostics, treatments, and cures for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Long Covid and other post-infection diseases.
- PASC Guide (University of Michigan): A resource for people with PASC/long COVID.

- Health Education England (HEE) e-learning modules: long COVID programme
- Voices of Long COVID (US): Voices of Long Covid campaign features testimonials from a diverse group of people ages 18-29 who are suffering from long-term complications of COVID-19 infection.
- Dignity Health (US): COVID-19 and Chronic Illness Recovery Program based in the U.S. has helped over 2,000 people struggling with COVID long-term effects ("COVID long haulers"). Treatment is exercise-based for lingering or long-term conditions (sequelae) from having the virus.
- Altea (Switzerland): A network for sharing evidence-based information on the long-term effects of COVID-19.
- Pandemic-Aid Networks: Long COVID research library.
- Post-COVID-19 Functional Status Scale: An overview of a patient self-reported scale that helps to support assessment of functional status and recovery after the SARS-CoV-2 infection.
- Ontario College of Family Physicians: Resources on Post-COVID Condition.
- Agency for Clinical Innovation (Australia): Living Evidence - post acute sequelae of COVID-19.
- Pre-populated literature searches: Long COVID search (LitCovid) and Long COVID search (NIH)
- PAHO Webinar Series on Post COVID-19 Condition launched 17 February, 2022, from 10:30 am to 12:30 pm (EST).
- Body Politic COVID-19 Support Group (Global): Housed on the Slack app, group members have access to dozens of different channels, which give space for more personal discussion. Some of the channels include those specifically for medical professionals, parents of children with Covid-19, LGBTQ+ individuals, BIPOC+, and different regions around the world.
- Patient-Led Research Collaborative (Global): Self-organized group of Long COVID patients working on patient-led research around the Long COVID experience.
- British Heart Foundation (UK): UK-based foundation with resources on long COVID.
- COVID Long Haul (Canada): Canada's largest online platform for COVID survivors, their family members and anyone searching for the most up-to-date information about the pandemic. There is a COVID long-haulers support group and a Report on Pan-Canadian Long COVID Impact Survey (PDF) (June 2021)
- BC ECHO for Post-COVID-19 Recovery (Canada): BC ECHO for Post-COVID-19 Recovery is a learning community of specialists and community health-care providers who use case-based learning to improve care for those recovering from symptoms post-COVID-19.
- Long Covid Support (UK): Peer support and advocacy group aiming to facilitate international peer support and campaigning in the UK for recognition, rehabilitation and research into treatments.
- Long COVID SOS (UK): Long-term sufferers formed the LongCovidSOS campaign to put pressure on the UK government to recognise the needs of those with Long Covid, and to raise awareness among the general public and employers.
- Survivor Corps (US): One of the largest and fastest growing grassroots movements connecting, supporting, and mobilizing COVID-19 Survivors to support research. They have a list of Post-COVID Care Centers (PCC) and a PCCC Best Practices Guide.
- The Center for Chronic Illness (US): Aims to promote well-being and decrease isolation for those impacted by chronic illness through support and education. Their online support groups are professionally-facilitated and offer psychoeducational tools for coping.
- Blooming Magnolia (US): Mission is to empower others by providing a platform to strengthen & protect mental health and support those afflicted with Long-Covid through education and funding of therapeutic research. They have a list of support groups and resources on their website.

- Long COVID Alliance (US): US-based network of patient-advocates, scientists, disease experts, and drug developers who have joined together to leverage their collective knowledge and resources to educate policy makers and accelerate research to transform our understanding of post-viral illness.

- Long COVID Kids (UK/US/Canada): Parent & patient led advocacy & support group based in the UK.

- Long COVID Physio (US & UK): International peer support, education and advocacy group of Physiotherapists living with Long COVID, founded in November 2020 by Physiotherapists living with Long COVID from the UK and US.

- Patient-Led Research Collaborative (Global): Group of Long COVID patients working on patient-led research around the Long COVID experience.

- CANCOV- Patient resources (Canada): CANCOV is a research platform grounded in a prospective longitudinal 1-year cohort study of patients infected with COVID-19.

- COVID Patient Recovery Alliance (CPRA) (US): CPRA aims to bring together leaders in business, health care, research, academia, data and analytics, and patient advocacy to develop solutions that coordinate diverse data sources, inform models of care, and ensure adequate payment for long-COVID patients. Their report outlines recommendations for federal policymakers to promote recovery.

- British Lung Foundation (UK): UK-based charity sharing resources on navigating the NHS, breathlessness support, movement and energy support for long COVID patients.

- Living with Long COVID (US): COVID-19 Long-Haulers and Post-COVID Support Community.

***Note**: Previous OCSO Post COVID-19 Condition Scans can be found here.*