The Burden & Dynamic of Post-COVID Conditions: A Patient-Centric Perspective

Nathaniel Osgood

Includes Joint Work with Drs. Donna Goodridge, Gary Groot, Segun Oyedokun & Jenny Basran

Mythbusting: Common PCC/Long COVID Misconceptions

- Is psychosomatic in origin
- Is limited to those who experienced serious acute COVID-19 symptoms
- Is a single, monolithic condition
- Exhibits a unstructured, scattershot collection of symptoms
- Consists of symptoms that originate in acute phase and resolve over time
- Imposes burden limited to bearing with such symptoms
- Is a squishy set of nuisance symptoms medicalized by the privileged
- Is adequately captured in administrative databases and electronic health records

Pandemics disable people – the history lesson that policy makers ignore (Spinney, 2022. Nature)

- 1918 Spanish influenza outbreak considered the "mother of all pandemics" – 80% of all people who developed *encephalitis lethargica* went on to develop Parkinson-like symptoms

- 1955 20-85% of polio survivors relapsed

- 1957 and 1968 influenza pandemics followed by rises in encephalitis

- 2014 Post-Ebola syndrome recognized

Social costs are enormous when policymakers ignore the tail risk of pandemics

Source: Donna Goodridge

Long COVID could become a significant chronic disease

Both Hospitalized AND non-hospitalized impacted

Long COVID could become Finland's largest chronic disease, warns minister

A Tsunami of Disability Is Coming as a Result of 'Long COVID'

We need to plan for a future where millions of survivors are chronically ill

The NEW ENGLAND JOURNAL of MEDICINE

2021. Factoring in new infections in unvaccinated people, we can conservatively expect more than 15 million cases of long Covid resulting from this pandemic. And though data are still emerging, the average age of patients with long Covid is about 40, which means that the majority are in their prime working years. Given these demographics, long Covid is likely to cast a long shadow on our health care system and economic recovery.

Perspective

AUGUST 12, 2021

Confronting Our Next National Health Disaster — Long-Haul Covid

Steven Phillips, M.D., M.P.H., and Michelle A. Williams, Sc.D.

Images from
https://www.nejm.org/doi/pdf/10.1056/NEJMp2109285

Fig. 1: COVID-19-related neurological deficits.

From: Counting the neurological cost of COVID-19

The figure illustrates proposed routes of the spread of SARS-CoV-2 across the CNS and the possible mechanisms involved in neuronal injury in COVID-19. Mechanisms indicated by asterisks were proposed on the basis of data that emerged from hospitals in Wuhan, China in the first two months of 2020 (ref.3). SARS-CoV-2 produces viral loads in the oral cavity and nose (1) that cause infection of the olfactory mucosa and olfactory bulb4 to reach the brain (2–4). Viral budding from neuronal cells in the frontal lobe has been documented2. Vascular mechanisms that can cause neuronal damage are shown (3). Brain involvement (4) is thought to elicit specific clinical features (5) that are indicative of CNS injury. ACE2, angiotensin-converting enzyme 2 receptor; NRP1, neuropilin-1. Adapted with permission from ref.3.

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00324-2/fulltext
https://www.nature.com/articles/d41586-021-01693-6
https://www.reuters.com/article/us-health-coronavirus-finland-long-covid-idUSKBN2JH14W
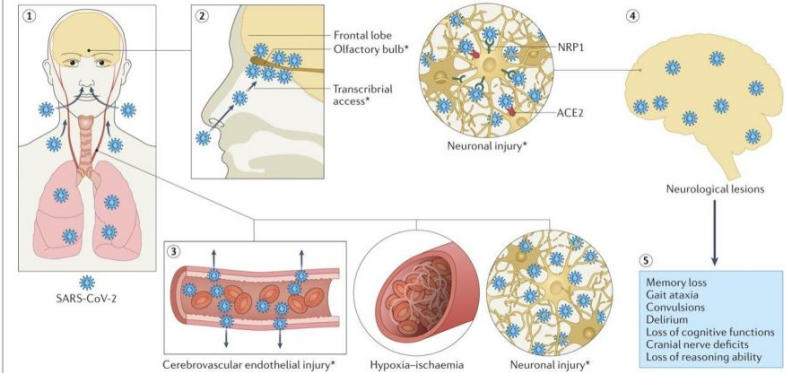https://www.nature.com/articles/s41582-021-00593-7?s=09
https://academic.oup.com/eurheartj/advancearticle/doi/10.1093/eurheartj/ehab914/6499078
https://www.scientificamerican.com/article/a-tsunami-of-disability-is-coming-as-a-result-of-lsquo-long-covid-rsquo/

Some Images adapted from partner Dr. J. Basran (SHA)

Update on Long COVID

(Hammond et al., SK COVID Evidence Support Team, March 2022)

- Common Case Definition: COVID-related symptoms that **persist or emerge beyond 4 weeks of infection** with 2 phases:
  - Ongoing symptomatic COVID-19 (OSC) - signs and symptoms from **4-12 weeks** from initial infection
  - Post-COVID-19 syndrome (PSC) – signs and symptoms **beyond 12 weeks** with respect to symptomatology, abnormal functioning, psychological burden and quality of life
  - **Long COVID includes both OCS and PCS**

Slide adapted from Donna Goodridge

COVID-19: Longer-term symptoms among Canadian adults - First report

Last updated: 2023-03-24   ⬇ PDF

The first report, Frequency and impact of longer-term symptoms following COVID-19 in Canadian adults, was published in the Fall of 2022

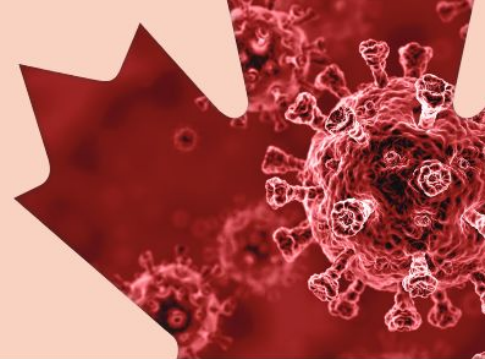Highlights   Second report: Spring 2023   **First report: Fall 2022**

Context

Coronavirus Disease 2019 (COVID-19), caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a substantial impact in Canada. As of September 3, 2022, about 4.2 million infections, confirmed by polymerase chain reaction (PCR), had been officially reported to the Public Health Agency of Canada by the provinces and territories. The severity of an acute SARS-CoV-2 infection can vary from being completely asymptomatic to severe

Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022

Context

Coronavirus Disease 2019 (COVID-19), caused by an infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a substantial impact in Canada. COVID-19 was the third leading cause of death in Canada in 2020 after cancer and heart disease, and significantly increased the demand for intensive care unit resources: from March 2020 to June 2021, there were almost 14,000 additional respiratory admissions in intensive care units compared with the pre-pandemic period (excluding Quebec). The indirect effects of the COVID-19 pandemic on other health conditions were also considerable with almost 560,000 fewer surgeries from March 2020 to June 2021 compared with the pre-pandemic period (excluding Quebec).

As of December 23, 2022, about 4.5 million infections, confirmed by polymerase chain reaction (PCR), had been officially reported to the Public Health Agency of Canada by the provinces and territories. This number, however, understates the true number of infected Canadians as it excludes those who test positive using rapid antigen tests (RAT) only, and those who did not get tested or may

"long COVID" when not resolved within three months of infection. Some of the more commonly reported symptoms include fatigue, coughing, shortness of breath, brain fog, and general weakness. With such a large number of infected Canadians, the potential burden of longer-term symptoms on individuals and their families, the healthcare system, and the economy through lost productivity, could be substantial.

Research published to date indicates that females and people who experience a more severe initial SARS-CoV-2 infection are at higher risk of developing longer-term symptoms. The virulence of the SARS-CoV-2 variant may also affect the risk of developing longer-term symptoms with Omicron variant infections being associated with a lower risk than earlier variants. With respect to protective factors, emerging evidence suggests that vaccination with two or more doses of COVID-19 vaccine prior to infection may reduce the risk of developing longer-term symptoms. Much, however, remains unknown regarding vulnerable populations, and risk and protective factors.

To address these and other information gaps, the Public Health Agency of Canada partnered with Statistics

Existing Long COVID in SK Study Ecosystem

- Entry point: Longitudinal smartphone based collection (rolling enrollment commenced February 2022); substantive respondents ~ 650
- Qualitative arm: Focus groups
- Long COVID mental health self-compassion app & data collection
- Dyspnea (pulmonary function tests, etc., exercise tolerance, etc.)
- Immunology

Survey

Questions include:

Whether or not you have had COVID
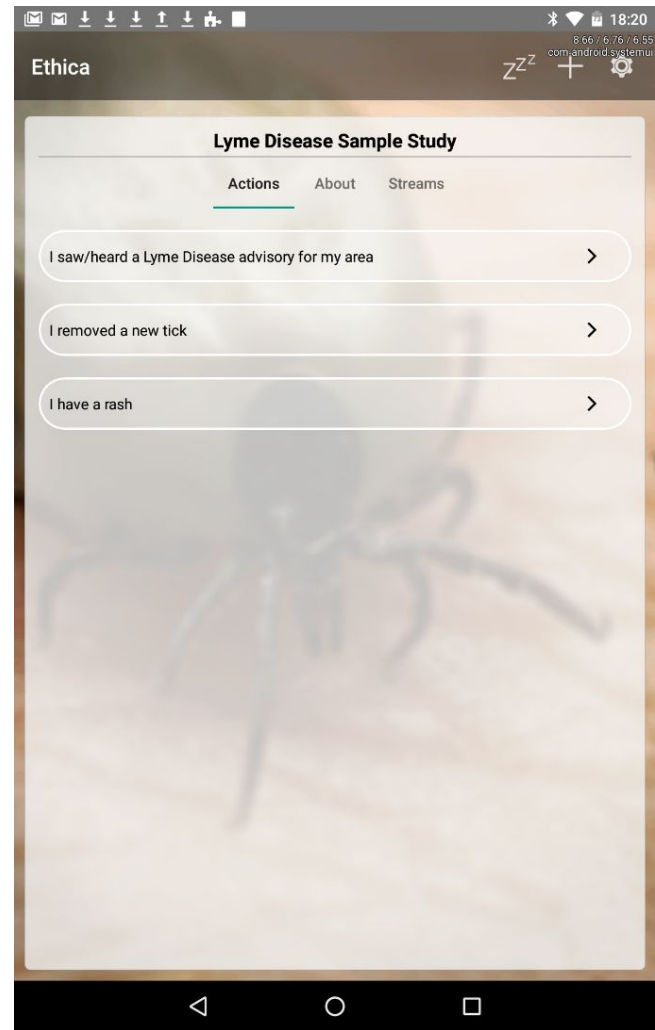
Vaccination status

Presence of 20 important symptoms known to be common with Long COVID

If a symptom is present, additional questions about that symptom, severity therapies used and satisfaction with care
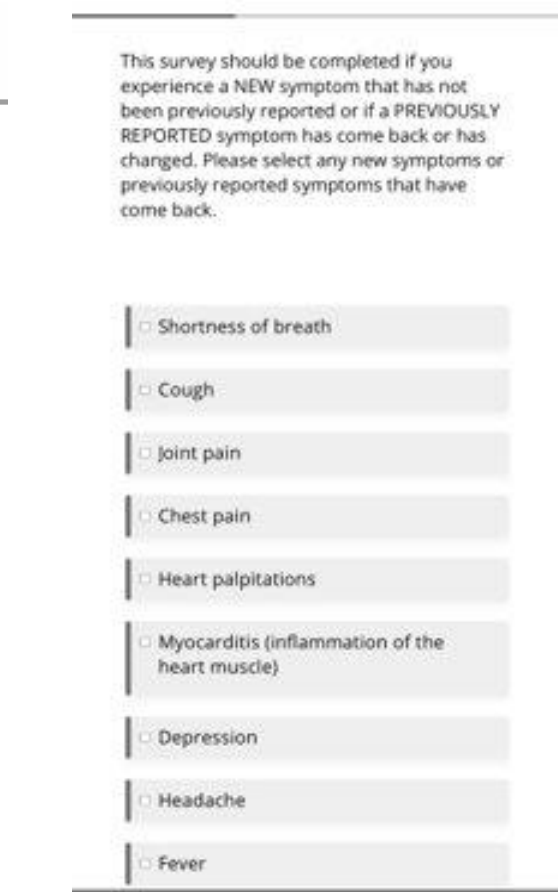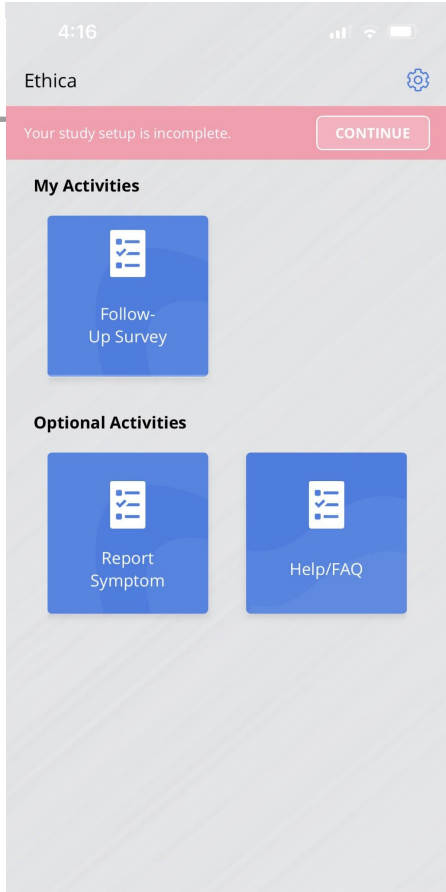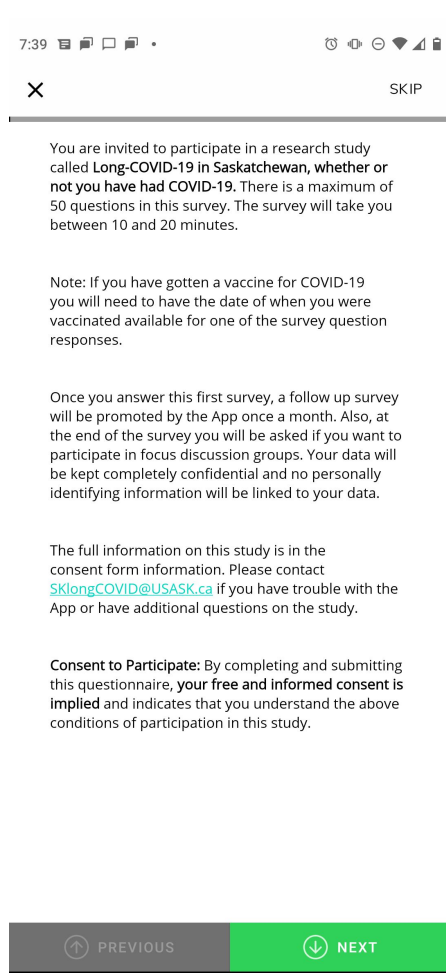
Questions on the presence of Post-Exertional Malaise and its impact on you

Adapted from source: Donna Goodridge

https://ethicadata.com

- Platform offering smartphone & web interfaces for participants, web administrative interfaces
- Interface, questionnaire types&content, triggering conditions & configuration modifiable in real-time
- Context-triggered questionnaires & EMAs
- Adaptive message delivery
- Monitoring sensors (steps, screen time, GPS, accel...)
- Interfaces for broad class of wearables
- Participant reachout in de-identified fashion
- Vast majority of studies require no programming
- Gamification interface (badges & point accrual)
- HIPAA & GDPR compliant
- CEPHIL origin, used in 100s of studies worldwide

Long COVID Study Interface Elements

You are invited to participate in a research study called **Long-COVID-19 in Saskatchewan, whether or not you have had COVID-19.** There is a maximum of 50 questions in this survey. The survey will take you between 10 and 20 minutes.

Note: If you have gotten a vaccine for COVID-19 you will need to have the date of when you were vaccinated available for one of the survey question responses.

Once you answer this first survey, a follow up survey will be promoted by the App once a month. Also, at the end of the survey you will be asked if you want to participate in focus discussion groups. Your data will be kept completely confidential and no personally identifying information will be linked to your data.

The full information on this study is in the consent form information. Please contact SKlongCOVID@USASK.ca if you have trouble with the App or have additional questions on the study.

Consent to Participate: By completing and submitting this questionnaire, **your free and informed consent is implied** and indicates that you understand the above conditions of participation in this study.

PREVIOUS   NEXT

4:16

Ethica

Your study setup is incomplete.   CONTINUE

My Activities

Follow-Up Survey

Optional Activities

Report Symptom

Help/FAQ

7:38

Have you had COVID-19? This can be medically confirmed COVID-19, or if you think you have contracted COVID-19 without a diagnosis or confirmation.

- Yes
- Not Sure
- No

PREVIOUS   NEXT

SKIP

This survey should be completed if you experience a NEW symptom that has not been previously reported or if a PREVIOUSLY REPORTED symptom has come back or has changed. Please select any new symptoms or previously reported symptoms that have come back.

- Shortness of breath
- Cough
- Joint pain
- Chest pain
- Heart palpitations
- Myocarditis (inflammation of the heart muscle)
- Depression
- Headache
- Fever

PREVIOUS   NEXT

Web-Based Administrative Dashboard

Long COVID-19 ▾

✳ License: Full

Participation (647)

INVITE PARTICIPANTS

Here you can view the list of participants in your study, and the summary of their adherence to the study requirements.

| 🏢 Enrollment Type: | Public | 🔗 Registration URL: | 📋 COPY LINK | ✏ EDIT |
| # Study Registration Code: | 1913 | ▦ Registration QR Code: | ⬇ DOWNLOAD | |

⬇ Download as CSV

	Ethica ID ▲	Label ▲	Last Recorded Data ▲	Joined In ▲	In Operation ▲	Session Stats ▲
☐	42176	Researcher	2022-06-05 08:00	2022-02-03 22:50		
☐	48258	Researcher	2022-02-04 11:28	2022-02-04 11:06		
☐	48532		2022-05-18 15:14	2022-02-08 12:21		
☐	10801		2022-02-08 08:07	2022-02-08 07:46		
☐	48533		2022-02-08 12:38	2022-02-08 12:26		
☐	48523		2022-03-10 13:14	2022-02-08 10:27		
☐	48524		2022-03-10 10:35	2022-02-08 10:31		
☐	48536		2022-05-10 03:37	2022-02-08 12:54		
☐	48543		2022-02-08 14:23	2022-02-08 14:14		
☐	48545		2022-04-10 08:00	2022-02-08 14:22		
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☐	48553		2022-02-08 15:03	2022-02-08 15:03		
☐	48556		2022-02-08 15:15	2022-02-08 15:04		

Long COVID Focus Groups: Methods

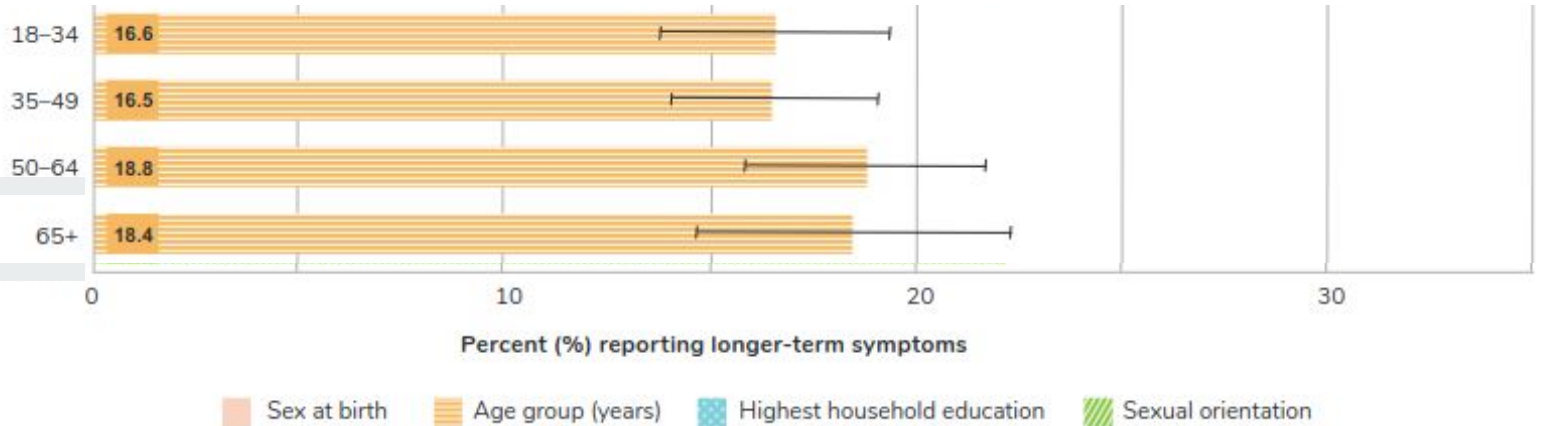Interpretive descriptive study using thematic analysis

Volunteer sample from consenting participants in Long COVID survey project

Long COVID Focus Group Findings

- 41 individuals from 8 Canadian provinces took part in 10 90 minutes focus groups conducted in Feb/Mar 2022

- Mean age 47.9 yrs, SD (10.4)

- 28 (68.3%) female

- Mean time elapsed since acute COVID infection 15.8 months, SD (6.4)

- 73.2% reported no pre-existing chronic illness

- 29 (70.7%) had not been hospitalized during acute infection

- 17 (41.4%) had to change employment as a result of persistent symptoms

Canada: Age-Specific Prevalence of Long Term Symptoms among those with Confirmed or Suspected Infection

Overall prevalence: 14.8% of infections -- about **1.4 million Canadians** (4.6% of Canadian adults)
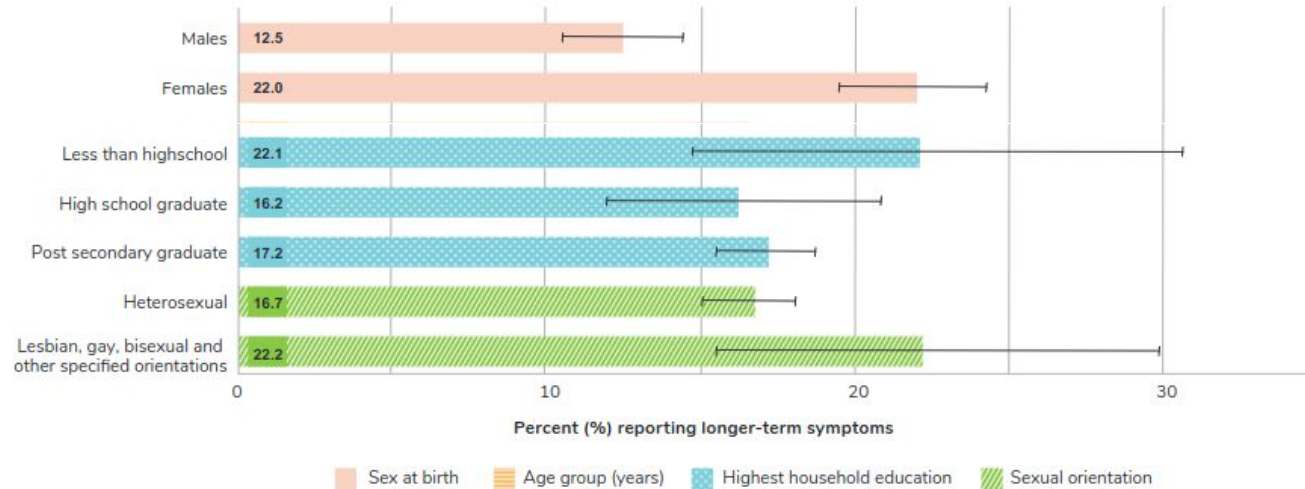

Age group	Percent (%) reporting longer-term symptoms
18–34	16.6
35–49	16.5
50–64	18.8
65+	18.4

Percent (%) reporting longer-term symptoms

Legend: Sex at birth · Age group (years) · Highest household education · Sexual orientation

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.
Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Education refers to the highest certificate, diploma, or degree completed by anyone in the household. Estimates exclude the territories. COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023)
https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

PCC Burden: Marked Birth Sex, SES & Sexual Orientation Disparities

Figure 2: Percent of Adults (Aged 18+) Self-reporting Longer-term Symptoms after a Positive COVID-19 Test or Suspected Infection by Sociodemographics, Canada, January 2020 to August 2022
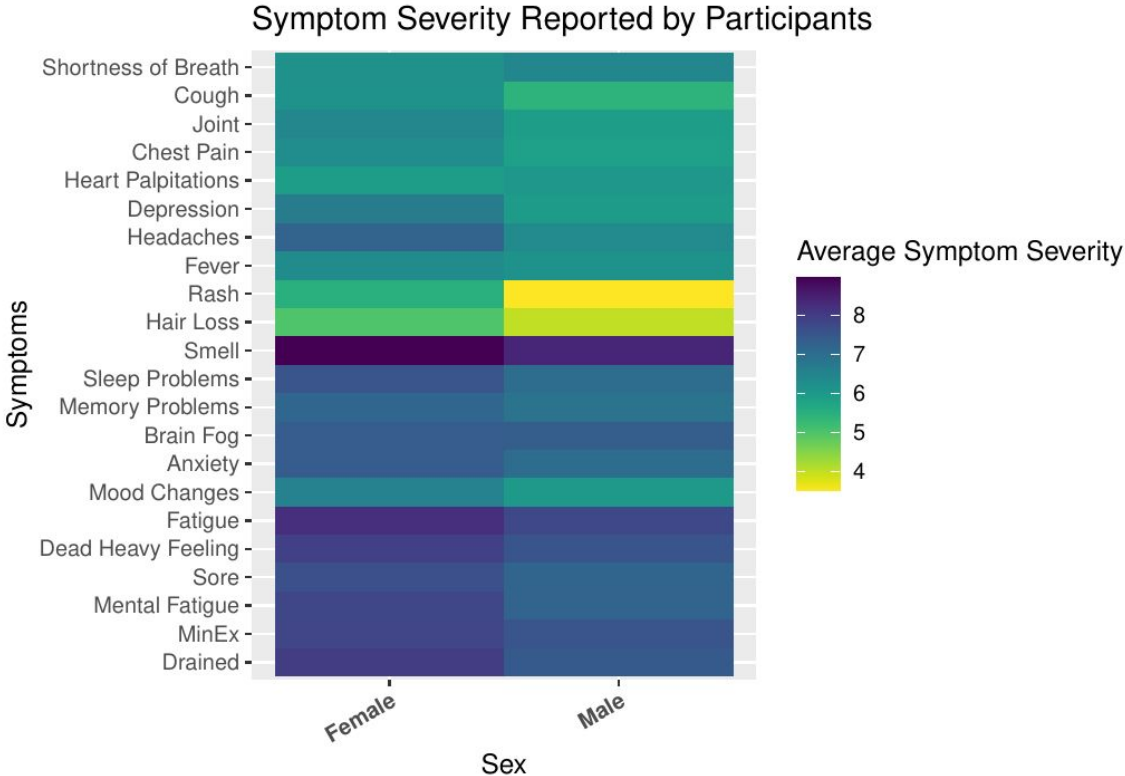
Category	Percent
Males	12.5
Females	22.0
Less than highschool	22.1
High school graduate	16.2
Post secondary graduate	17.2
Heterosexual	16.7
Lesbian, gay, bisexual and other specified orientations	22.2

Percent (%) reporting longer-term symptoms

Legend: Sex at birth | Age group (years) | Highest household education | Sexual orientation

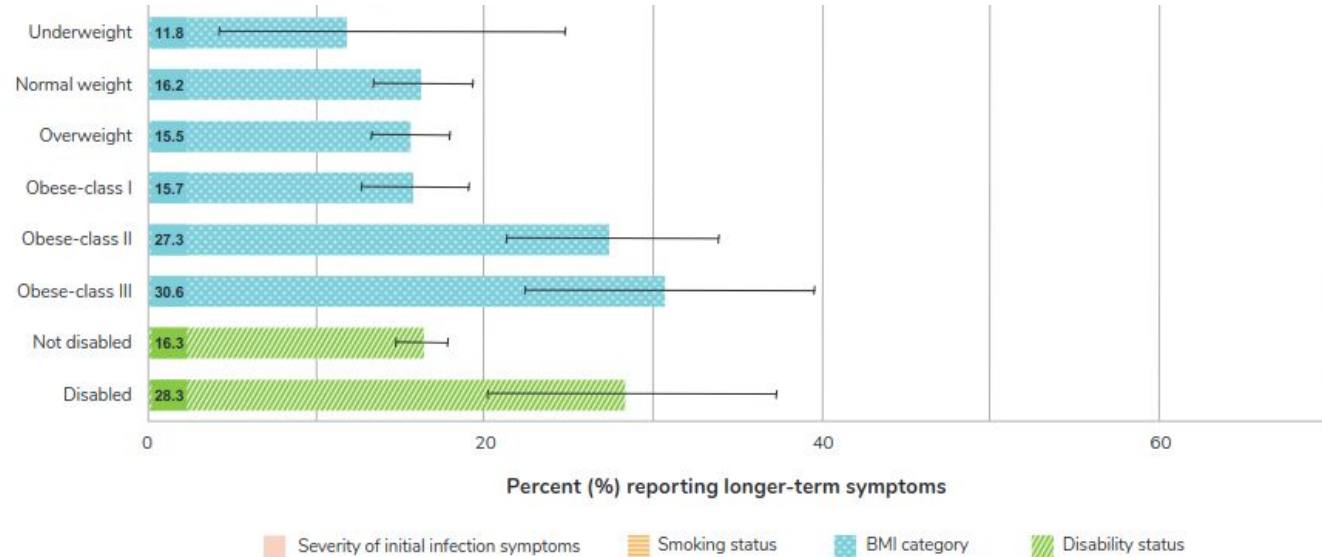**Source:** Canadian COVID-19 Antibody and Health Survey—Cycle 2.

Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Education refers to the highest certificate, diploma, or degree completed by anyone in the household. Estimates exclude the territories. COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023)
https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

Reported Symptom Severity bySex

Symptom Severity Reported by Participants

PCC by Weight & Disability Status

Underweight — 11.8
Normal weight — 16.2
Overweight — 15.5
Obese-class I — 15.7
Obese-class II — 27.3
Obese-class III — 30.6
Not disabled — 16.3
Disabled — 28.3

Percent (%) reporting longer-term symptoms

Severity of initial infection symptoms   Smoking status   BMI category   Disability status

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.

Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Estimates exclude the territories. BMI = body mass index, COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023) https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

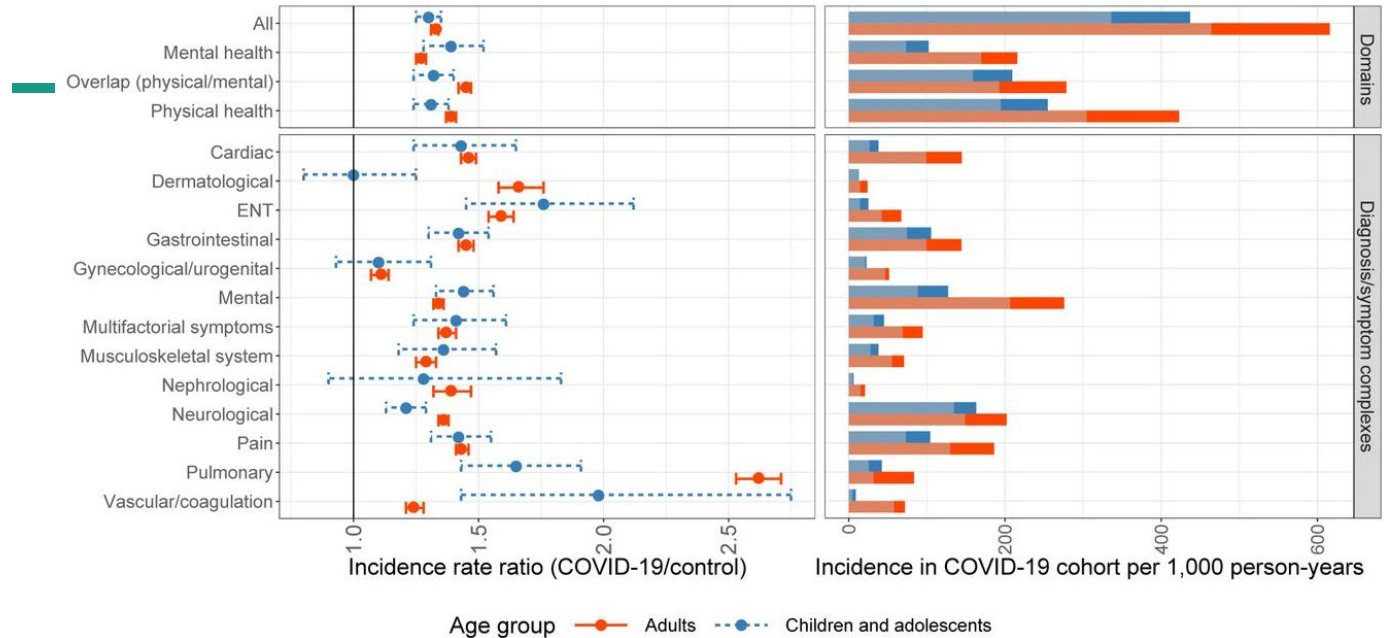# Long COVID & Health Disparities

- While data with sufficient confirmatory resolution remains elusive, the burden of Long COVID fall **strongly disproportionately** on
- **Women**
  - Higher risk of inflammatory Long COVID endotype/Post-COVID fatigue syndrome
- **Low SES populations**
  - Higher risk of infection (crowded housing, essential jobs, etc.)
  - Lower vaccination rates
  - Higher occurrence of severe acute-phase COVID-19 infection
  - Higher rates of comorbid risk factors (e.g., diabetes, autoimmune conditions, immune impairment, …)
  - Poor accessibility of care -- especially specialist & interdisciplinary care
  - Low health literacy & challenges navigating the health system
  - Higher pre-existing rates of mental health disorders
  - Infeasibility of securing medical leave, accommodate disability

Mythbusting: Common PCC/Long COVID Misconceptions

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- Is limited to those who experienced serious acute COVID-19 symptoms
- Is a single, monolithic condition
- Exhibits a unstructured, scattershot collection of symptoms
- Consists of symptoms that originate in acute phase and resolve over time
- Imposes burden limited to bearing with such symptoms
- ~~Is a squishy set of nuisance symptoms medicalized by the privileged~~
- Is adequately captured in administrative databases and electronic health records

Image from: Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P.A., Cuapio, A. and Villapol, S., 2021. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. Available at https://www.medrxiv.org/content/medrxiv/early/2021/01/29/2021.01.27.21250617.full.pdf

Image from: Baig, A.M., 2020. Chronic COVID syndrome: Need for appropriate medical terminology for long-COVID and COVID long-haulers. *Journal of medical virology.*

Elevated Risk of Diverse Symptoms After 3+ months (Adults&Kids)

Notable variable by
- Age
- Vaccination history
- Severity~

The elevation of risk of adults (red) and children (blue) suffering a wide variety of symptoms 3+ months after COVID- infection across diverse domains and organ systems.

This image is taken from: Roessler, M., Tesch, F., Batram, M., Jacob, J., Loser, F., Weidinger, O., Wende, D., Vivirito, A., Toepfner, N., Seifert, M. and Nagel, O., 2021. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19. MedRxiv. The article is accessible at the following address https://www.medrxiv.org/content/10.1101/2021.10.21.21265133v1.full?s=08

Prevalence of specific symptoms amongst Canadians w/PCCs

Symptoms	Percent reporting symptom (95% confidence interval)
fatigue, tiredness or loss of energy	72.1% (68.1%, 75.8%)
coughing	39.3% (35.0%, 43.8%)
shortness of breath or difficulty breathing	38.5% (34.2%, 43.0%)
difficulty thinking or problem solving (brain fog)	32.9% (28.9%, 37.0%)
general weakness	30.9% (27.1%, 34.9%)
headache	29.7% (26.1%, 33.5%)
loss of taste or smell	27.9% (23.3%, 33.1%)
stress or anxiety	24.2% (20.9%, 27.9%)
pain (e.g., muscular, abdominal, joint)	22.8% (19.6%, 26.3%)
sadness, pessimism, hopelessness or depression	18.8% (15.7%, 22.3%)
chest pain	17.0% (13.9%, 20.5%)
symptoms relating to the heart (e.g., fast, pounding or irregular heartbeat)	11.8% (9.1%, 15.1%)
fever	10.1% (8.1%, 12.5%)

Image from COVID-19: Longer-term symptoms among Canadian adults - First report (Fall 2022)
https://health-infobase.canada.ca/covid-19/post-covid-condition/fall-2022-report.html

Multi-organ complications of covid-19 and long covid.

Heart
- Chest pains
- Myocardial inflammation
- ↑ Serum troponin
- Palpitations

Lungs
- Dyspnea
- Chest pain
- Cough

Brain
- 'Brain fog'
- Delirium
- Fatigue
- Sleep disturbances
- Depression/anxiety/PTSD/OCS

Pancreas
- Pancreatic injury
- Pancreatitis

Spleen
- ↓ T & B lymphocyte
- Atrophy of lymphoid follicles

Liver
- Liver injury
- ↑ Aspartate aminotransferase
- ↑ Alanine aminotransferase

Kidney
- Renal impairment
- Acute kidney injury

Gastrointestinal tract
- Diarrhea
- Nausea
- Sore throat

Blood vessels
- Inflammation
- Vessel damage
- Coagulopathy
- Microangiopathy

ACE2

Harry Crook et al. BMJ 2021;374:bmj.n1648

theb**mj**

Neurological sequelae

Image & text from
Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of
COVID-19. *Nat Med* (2022).
https://doi.org/10.1038/s41591-022-02001-z

Strong concerns exist about the added burden of
dementia

Long-term neurologic outcomes of COVID-19

Evan Xu, Yan Xie & Ziyad Al-Aly ✉

Abstract

The neurologic manifestations of acute COVID-19 are well characterized, but a
comprehensive evaluation of postacute neurologic sequelae at 1 year has not been
undertaken. Here we use the national healthcare databases of the US Department of Veterans
Affairs to build a cohort of 154,068 individuals with COVID-19, 5,638,795 contemporary
controls and 5,859,621 historical controls; we use inverse probability weighting to balance the
cohorts, and estimate risks and burdens of incident neurologic disorders at 12 months
following acute SARS-CoV-2 infection. Our results show that in the postacute phase of
COVID-19, there was increased risk of an array of incident neurologic sequelae including
ischemic and hemorrhagic stroke, cognition and memory disorders, peripheral nervous
system disorders, episodic disorders (for example, migraine and seizures), extrapyramidal
and movement disorders, mental health disorders, musculoskeletal disorders, sensory
disorders, Guillain–Barré syndrome, and encephalitis or encephalopathy. We estimated that
the hazard ratio of any neurologic sequela was 1.42 (95% confidence intervals 1.38, 1.47) and
burden 70.69 (95% confidence intervals 63.54, 78.01) per 1,000 persons at 12 months. The
risks and burdens were elevated even in people who did not require hospitalization during
acute COVID-19. Limitations include a cohort comprising mostly White males. Taken
together, our results provide evidence of increased risk of long-term neurologic disorders in
people who had COVID-19.

Worsened Dysglycemia

Image & article from Barrett CE, Koyama AK, Alvarez P, et al. Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years — United States, March 1, 2020–June 28, 2021. MMWR Morb Mortal Wkly Rep 2022;71:59–65. DOI: http://dx.doi.org/10.15585/mmwr.mm7102e2external icon

Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years — United States, March 1, 2020–June 28, 2021

Catherine E. Barrett, PhD[1,2]; Alain K. Koyama, ScD[1,2]; Pablo Alvarez, MPH[1]; Wilson Chow[1]; Elizabeth A. Lundeen, PhD[1,2]; Cria G. Perrine, PhD[1]; Meda E. Pavkov, MD, PhD[2]; Deborah B. Rolka, MS[2]; Jennifer L. Wiltz, MD[1]; Lara Bull-Otterson, PhD[1]; Simone Gray, PhD[1]; Tegan K. Boehmer, PhD[1]; Adi V. Gundlapalli, MD[1]; David A. Siegel, MD[1]; Lyudmyla Kompaniyets, PhD[1]; Alyson B. Goodman, MD[1]; Barbara E. Mahon, MD[1]; Robert V. Tauxe, MD[1]; Karen Remley, MD[1]; Sharon Saydah, PhD[1] (View author affiliations)

View suggested citation

Summary

What is already known about this topic?

SARS-CoV-2 infection is associated with worsening of diabetes symptoms, and persons with diabetes are at increased risk for severe COVID-19. SARS-CoV-2 infection might also induce newly diagnosed diabetes.

What is added by this report?

Persons aged <18 years with COVID-19 were more likely to receive a new diabetes diagnosis >30 days after infection than were those without COVID-19 and those with prepandemic acute respiratory infections. Non–SARS-CoV-2 respiratory infection was not associated with an increased risk for diabetes.

What are the implications for public health practice?

The increased diabetes risk among persons aged <18 years following COVID-19 highlights the importance of COVID-19 prevention strategies in this age group, including vaccination for all eligible persons and chronic disease prevention and treatment.

Image & text from
Phetsouphanh, C., Darley, D.R., Wilson, D.B. *et al.*
Immunological dysfunction persists for 8 months
following initial mild-to-moderate SARS-CoV-2
infection. *Nat Immunol* (2022).
https://doi.org/10.1038/s41590-021-01113-x

Letter | Published: 13 January 2022

Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh ✉, David R. Darley, Daniel B. Wilson, Annett Howe, C. Mee Ling Munier, Sheila K. Patel, Jennifer A. Juno, Louise M. Burrell, Stephen J. Kent, Gregory J. Dore, Anthony D. Kelleher ✉ & Gail V. Matthews ✉

Abstract

A proportion of patients surviving acute coronavirus disease 2019 (COVID-19) infection develop post-acute COVID syndrome (long COVID (LC)) lasting longer than 12 weeks. Here, we studied individuals with LC compared to age- and gender-matched recovered individuals without LC, unexposed donors and individuals infected with other coronaviruses. Patients with LC had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Using a log-linear classification model, we defined an optimal set of analytes that had the strongest association with LC among the 28 analytes measured. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5–81.6% accuracy. This work defines immunological

Marked Mortality Differential within 1ˢᵗ Year Post-infection
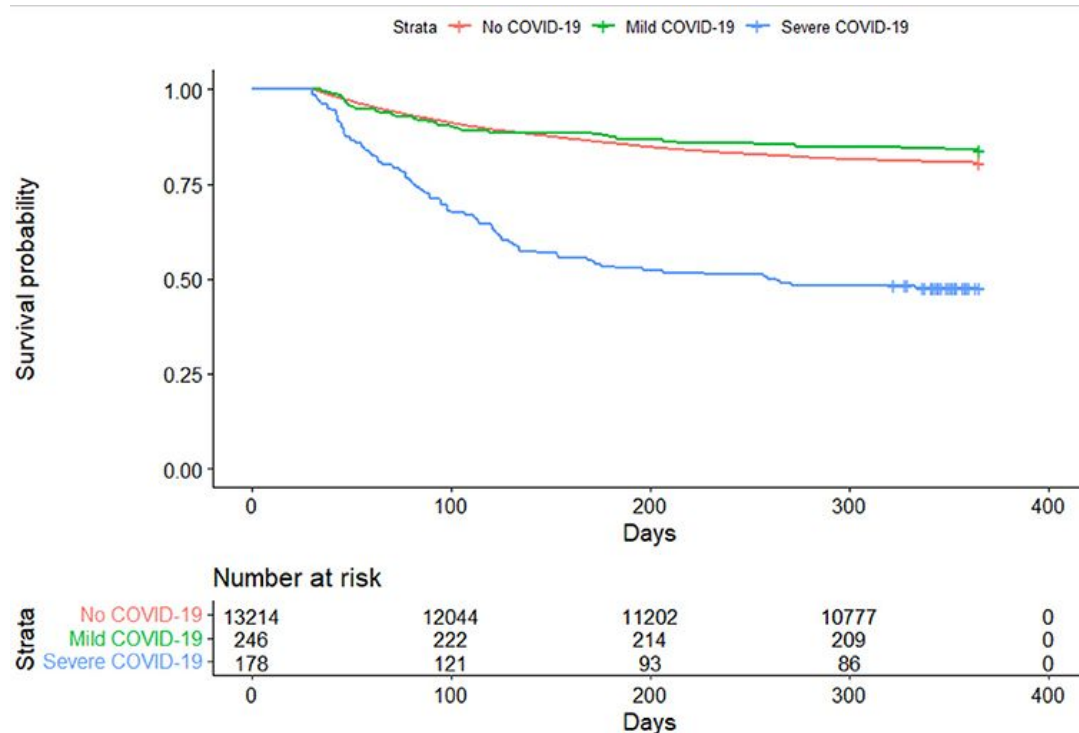
Source: Mainous III, A.G., Rooks, B.J., Wu, V. and Orlando, F.A., 2021. COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk. Frontiers in Medicine, p.2351.
https://www.frontiersin.org/articles/10.3389/fmed.2021.778434/full

Mythbusting: Common PCC/Long COVID Misconceptions

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Another proposed six subtypes based on the existing literature:
1. non-severe COVID-19 multi-organ sequelae (NSC-MOS)
2. pulmonary fibrosis sequelae (PFS)
3. chronic fatigue syndrome (ME/CFS)
4. Postural orthostatic tachycardia syndrome (POTS)
5. post-intensive care syndrome (PICS)
6. medical or clinical sequelae (MCS)

Yong and Liu, *Rev Med. Vir.* (Dec 2021)

Omitted from slide: Microbiome disruption

Image from Hector Fabio Bonilla & Linda N. Geng. Long COVID: An Update and the Stanford PACS Clinic. Stanford University Department of Medicine Grand Rounds. Jan 12 2022 https://youtu.be/jbc_NhIRgcM

Symptom Severity

Symptom labels (rows):
SOB, Cough, JointPain, ChestPain, HeartPalpitations, Depression, Headaches, Fever, Rash, HairLoss, LossOfSmell, SleepIssues, MemoryIssues, BrainFog, Anxiety, MoodIssues, PhysicalFatigue, DeadHeavyFeeling, Soreness, MentalFatigue, ExhaustionAfterMin..., FeelingDrained

Principal Components: Factor Loadings & Variance explained

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8
Standard deviation	2.981	1.28664	1.18036	1.08008	0.97998	0.96534	0.91826	0.90632
Proportion of Variance	0.404	0.07525	0.06333	0.05303	0.04365	0.04236	0.03833	0.03734
Cumulative Proportion	0.404	0.47923	0.54256	0.59559	0.63924	0.68160	0.71993	0.75726

Broad, particularly fatigue & brain fog
Memory without respiratory&cardiac
Mental Health&Affective

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8
SOB	0.1860101	-0.331353058	-0.035783093	0.3869155901	-0.0439615909	0.10722839	-0.0863059178	0.041969414
Cough	0.0957892	-0.429408939	-0.012301606	0.1211855536	-0.2370570673	0.56842010	-0.2810989585	0.011419775
JointPain	0.1961486	-0.223059209	0.003380971	-0.1311745818	-0.2541909603	-0.18691673	0.0102959333	-0.392364147
ChestPain	0.1896466	-0.439921170	-0.024004604	0.2155995089	0.1512032349	-0.18492141	-0.1001264324	0.103714344
HeartPalpitations	0.1663005	-0.222794870	0.062868471	0.0986604108	0.4618412558	-0.48446381	-0.2104501106	0.086504022
Depression	0.1972633	0.116893507	0.434037746	0.1361222265	-0.0171567485	0.10305590	0.2304376235	0.125507250
Headaches	0.2025930	-0.049578509	0.045841718	-0.2520330553	-0.0765720582	-0.25988468	-0.0628113256	-0.503928817
Fever	0.1497972	-0.355505931	0.122214883	-0.2483859139	-0.0351462576	0.07836071	0.4206283816	0.004257941
Rash	0.1344617	-0.181135232	0.270190120	-0.4366791191	-0.0089911908	0.05909273	0.3106814446	0.277165495
HairLoss	0.1079522	0.023703031	0.071569382	-0.5656730691	0.3460968455	0.25965968	-0.4959289493	0.118123394
LossOfSmell	0.1109121	-0.001604897	-0.236803572	-0.1983915732	-0.5943440740	-0.34943030	-0.2536415768	0.527573798
SleepIssues	0.2242126	-0.042247818	0.170223076	-0.0541496285	-0.0547156136	0.02630673	-0.1183727727	-0.174814893
MemoryIssues	0.2423882	0.273435837	0.103624877	0.0961683274	-0.0265564798	0.06963359	-0.2428550909	-0.091166585
BrainFog	0.2667048	0.215867654	0.045769517	0.0673187859	-0.0936471301	0.14355985	-0.1690658544	-0.058807207
Anxiety	0.2171701	0.097652159	0.391968439	0.1133761743	0.0004428418	-0.15171328	-0.0978244309	0.167162127
MoodIssues	0.2322922	0.186984691	0.293061164	0.1846592760	-0.0660573393	-0.02888072	0.0864887847	0.164889875
PhysicalFatigue	0.2802530	0.124049039	-0.101398872	0.0001929006	0.0267607322	0.07899934	-0.0007339593	-0.178230820
DeadHeavyFeeling	0.2140912	0.038636303	-0.334257800	-0.0130278450	0.3600027057	0.09393661	0.1298743820	0.214861842
Soreness	0.2704886	0.075423843	-0.247619225	-0.0494358908	-0.0551237184	-0.06861797	0.1385160274	-0.082887022
MentalFatigue	0.2748061	0.200862878	-0.083577520	-0.0079923589	-0.0555352475	0.05030161	0.0256038129	0.021083546
ExhaustionAfterMinimalExercise	0.2810838	0.053106445	-0.304592028	-0.0091600218	0.0624135920	0.09057739	0.1918658676	0.032754713
FeelingDrained	0.2763203	0.060187809	-0.299968121	0.0444995632	0.0585486966	0.06111320	0.1618333309	0.057578634

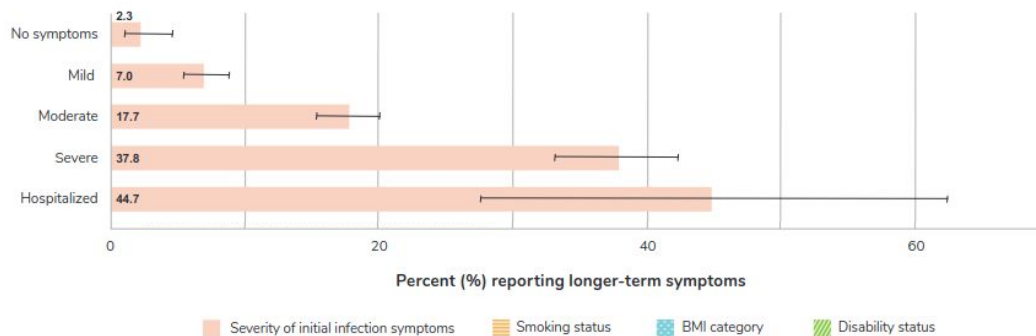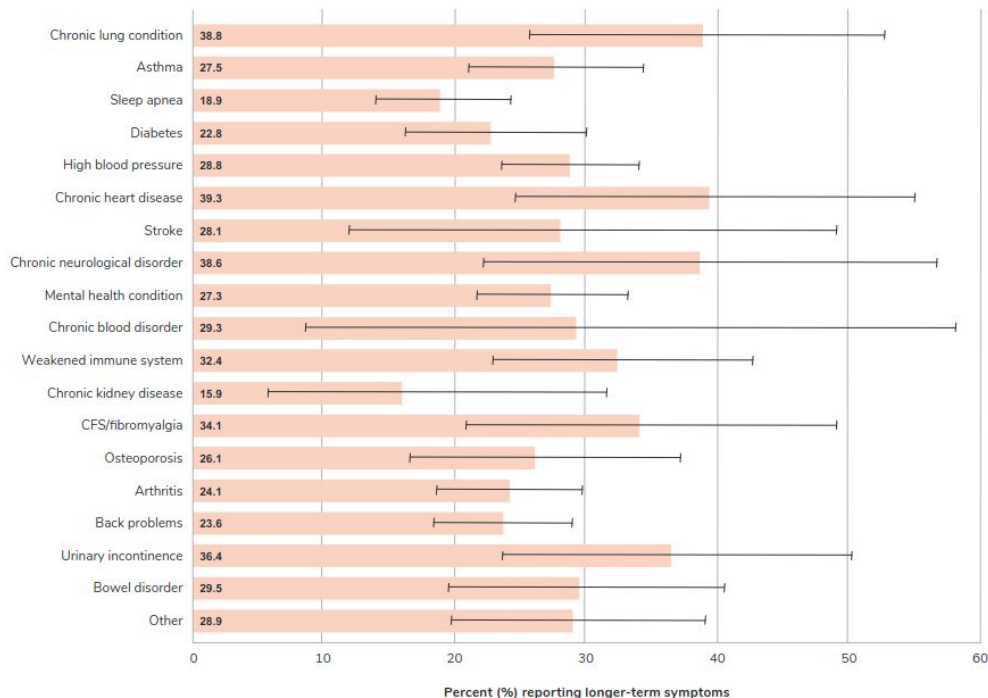# Acute Infection Severity based on Symptom Severity PCA
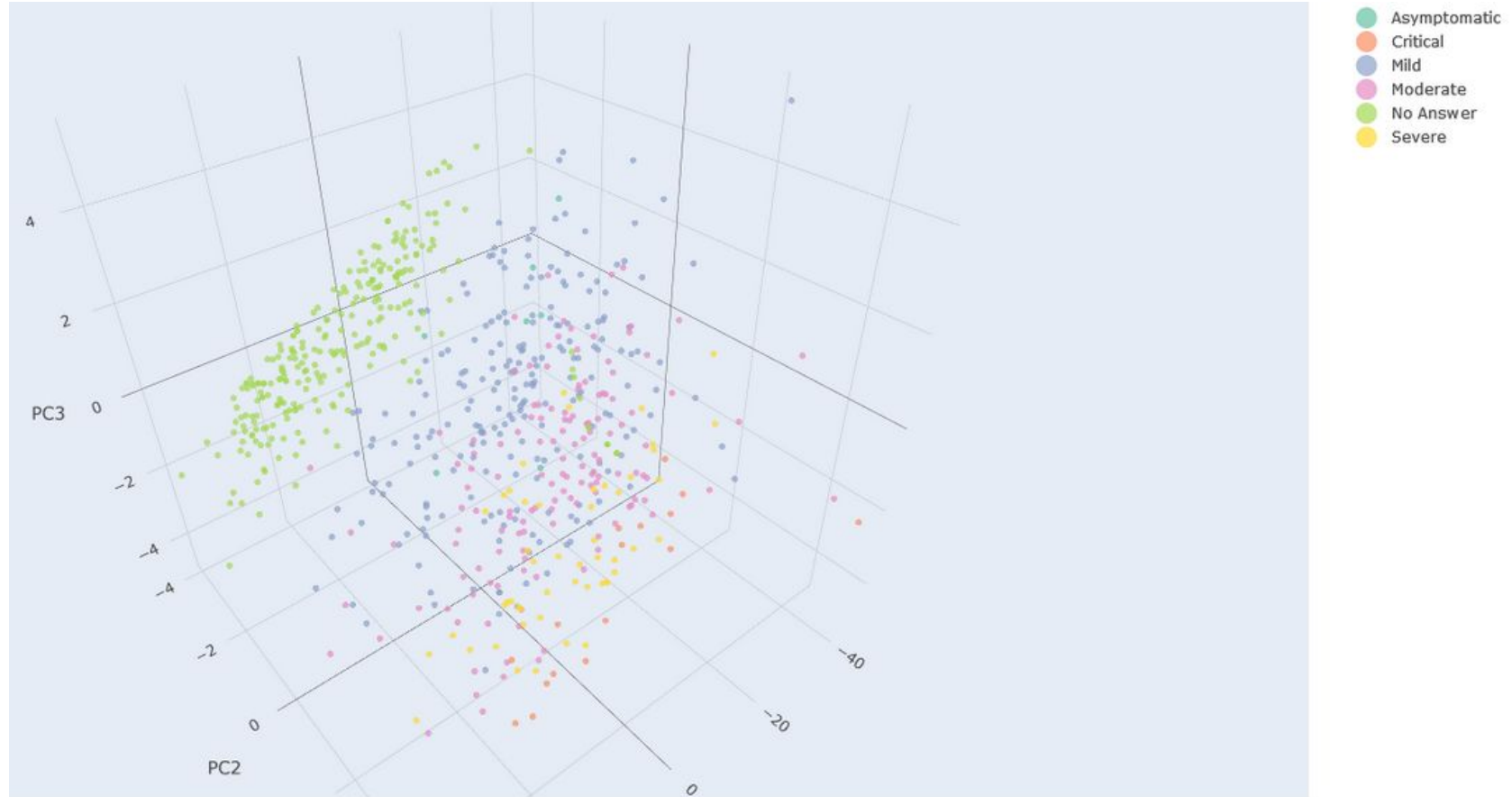
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Canada: Impact of Acute COVID Severity on Risk of PCC

Figure 6: Percent of Adults (Aged 18+) Self-reporting Longer-term Symptoms after a positive COVID-19 Test or Suspected Infection by Selected Risk Factors, Canada, January 2020 to August 2022

Percent (%) reporting longer-term symptoms

Legend: Severity of initial infection symptoms, Smoking status, BMI category, Disability status

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.

Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Estimates exclude the territories. BMI = body mass index, COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023) https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

Symptom Severity by Reported Acute Severity
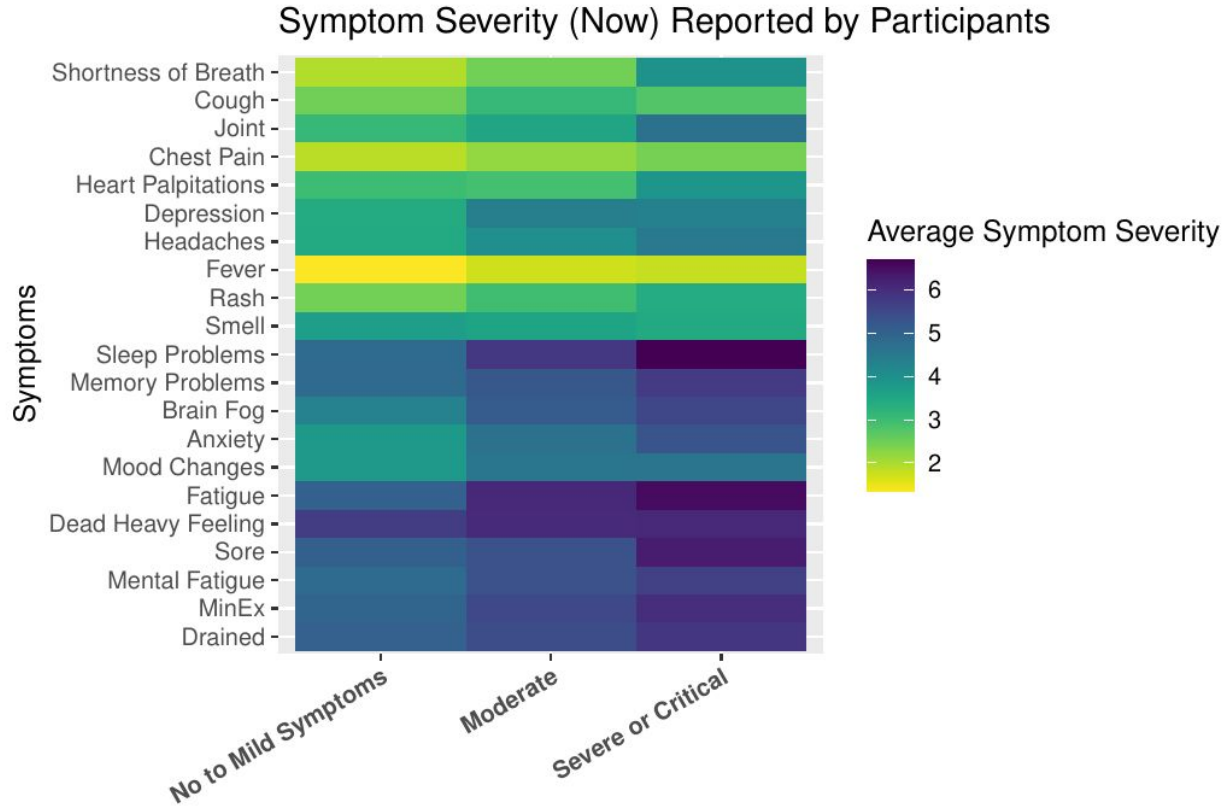
Symptom Severity (Now) Reported by Participants

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% of Canadians with Pre-Existing Conditions Experiencing PCC after COVID-19 Infection

Condition	Percent
Chronic lung condition	38.8
Asthma	27.5
Sleep apnea	18.9
Diabetes	22.8
High blood pressure	28.8
Chronic heart disease	39.3
Stroke	28.1
Chronic neurological disorder	38.6
Mental health condition	27.3
Chronic blood disorder	29.3
Weakened immune system	32.4
Chronic kidney disease	15.9
CFS/fibromyalgia	34.1
Osteoporosis	26.1
Arthritis	24.1
Back problems	23.6
Urinary incontinence	36.4
Bowel disorder	29.5
Other	28.9

Percent (%) reporting longer-term symptoms

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.
Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Chronic conditions were defined as health conditions expected to last or lasting 6 months or more that were diagnosed by a health professional. Respondents can report more than one chronic condition. A total of 21 chronic conditions were examined. Chronic conditions with too few respondents to report include: Alzheimer's disease or other dementia, and liver disease. Estimates exclude the territories.
CFS = chronic fatigue syndrome, COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023)
https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

Multiple early factors anticipate post-acute COVID-19 sequelae

Graphical abstract

Authors

Yapeng Su, Dan Yuan, Daniel G. Chen, ..., Mark M. Davis, Jason D. Goldman, James R. Heath

Correspondence

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In brief

By correlating patient symptoms with in-depth profiling of blood cells and plasma components throughout COVID-19 infection, this study identifies factors that may predict sustained disease.

Highlights

- Longitudinal multi-omics associate PASC with auto-antibodies, viremia, and comorbidities

- Reactivation of latent viruses during initial infection may

% of Canadians with Counts of Pre-Existing Conditions Experiencing PCC after COVID-19 Infection

Figure 3: Percent of Adults (Aged 18+) Self-reporting Longer-term Symptoms after a Positive COVID-19 Test or Suspected Infection by Number of Selected Chronic Conditions Present Pre-infection, Canada, January 2020 to August 2022
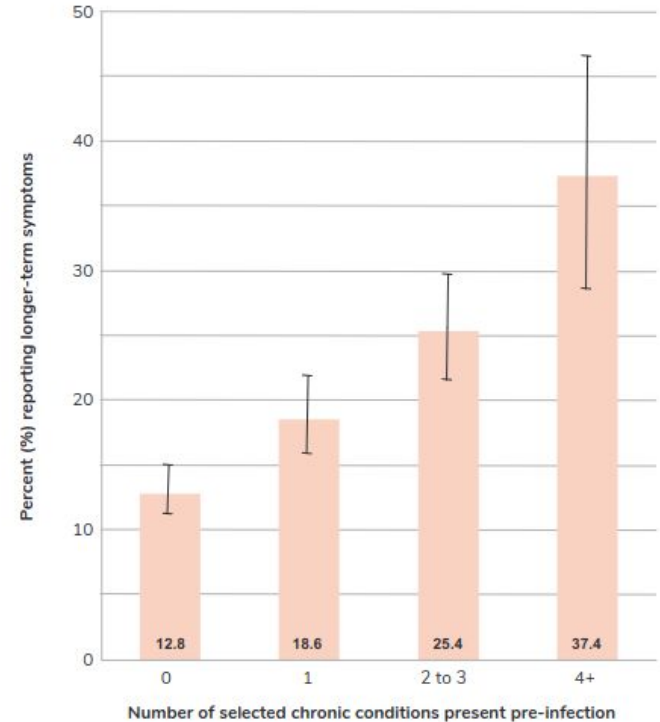
Number of selected chronic conditions present pre-infection

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.
Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Chronic conditions were defined as health conditions expected to last or lasting 6 months or more that were diagnosed by a health professional. See the technical notes for the list of 21 conditions examined. Estimates exclude the territories. COVID-19 = Coronavirus Disease 2019.

Activity Limitations amongst Canadians with PCC

How often daily activities were limited	Percent reporting level of limitation (95% confidence interval)
never	16.9% (14.1%, 20.2%)
rarely	29.4% (25.5%, 33.7%)
sometimes	32.3% (28.6%, 36.3%)
often	15.7% (12.9%, 18.9%)
always	5.6% (4.1%, 7.6%)

Amongst those with paid job or attending school, 74.1% (95% CI: 69.3%, 78.3%) reported absences

Image from COVID-19: Longer-term symptoms among Canadian adults - First report (Fall 2022)
https://health-infobase.canada.ca/covid-19/post-covid-condition/fall-2022-report.html

Functional Limitations of LC Participants by Reported Acute COVID Severity

Limitations of Functioning by Perceived Severity
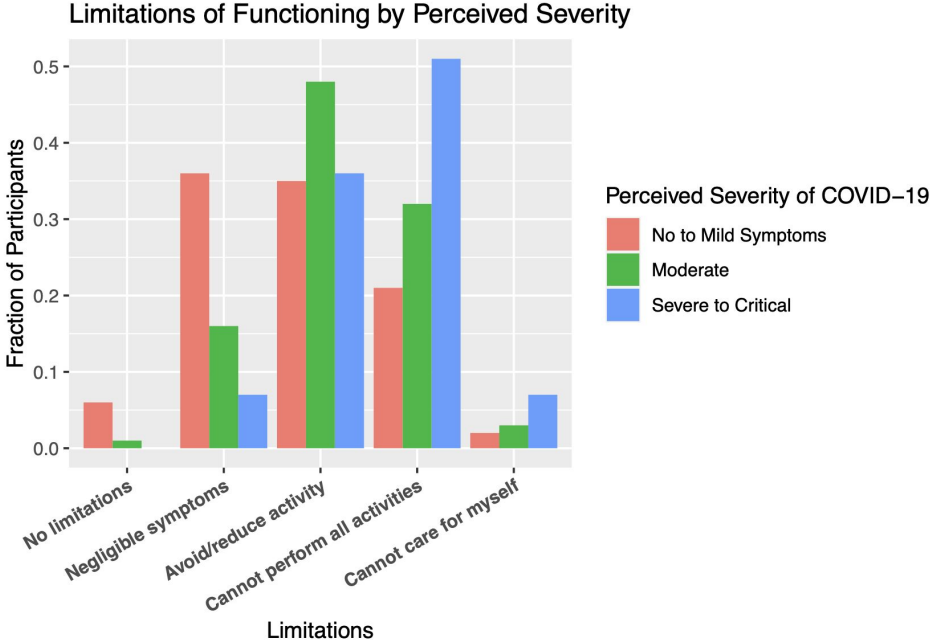
Debilitating Conditions

Fatigue	"I could do …a kids' puzzle for 15 minutes, and I would have to rest physically and cognitively for 14 hours and try again the next day." (F6)
Tachycardia/ Hypotension	"Any time I rise or change position, my heart rate goes really high, 140 usually, and then my blood pressure drops…every time I stand up, every time I get moving. And then it causes dizziness, nausea, all those fun symptoms." (F1)
Dyspnea	"It would take me an hour to walk up the flight of stairs and back down…'cause I was so short of breath" (F5)
Sleep Problems	"I'll sleep for 20 minutes and then I'll be awake …when you add that all up, it's like three hours of sleep I've had, but all broken up." (F10)

Adapted from Donna Goodridge

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Association with Vaccination History (Count)

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023)
https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

Figure 8: Percent of Adults (Aged 18+) Self-reporting Longer-term Symptoms after a Positive COVID-19 Test or Suspected Infection by Number of COVID-19 Vaccine Doses Received Prior to Infection, Canada, January 2020 to August 2022
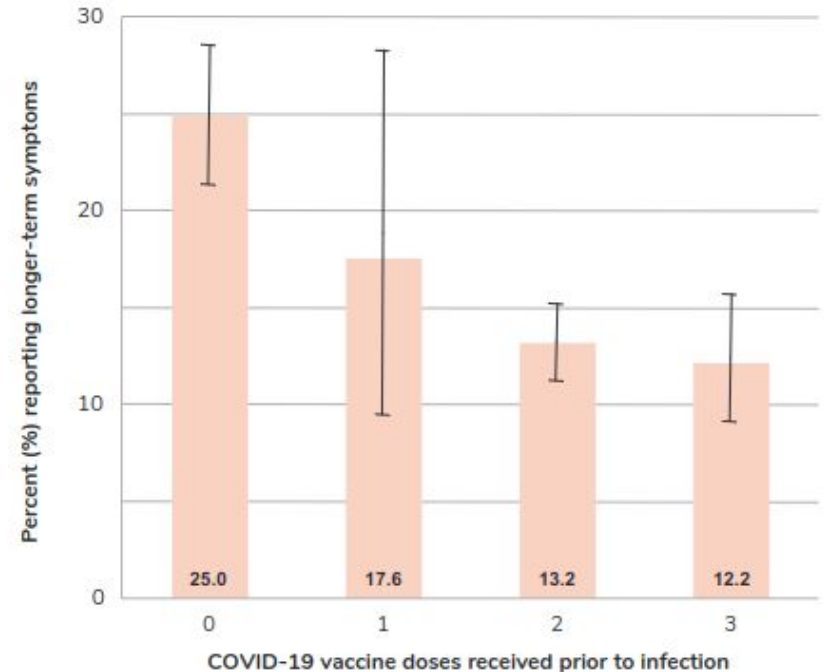
Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.
Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Estimates exclude the territories. COVID-19 = Coronavirus Disease 2019.
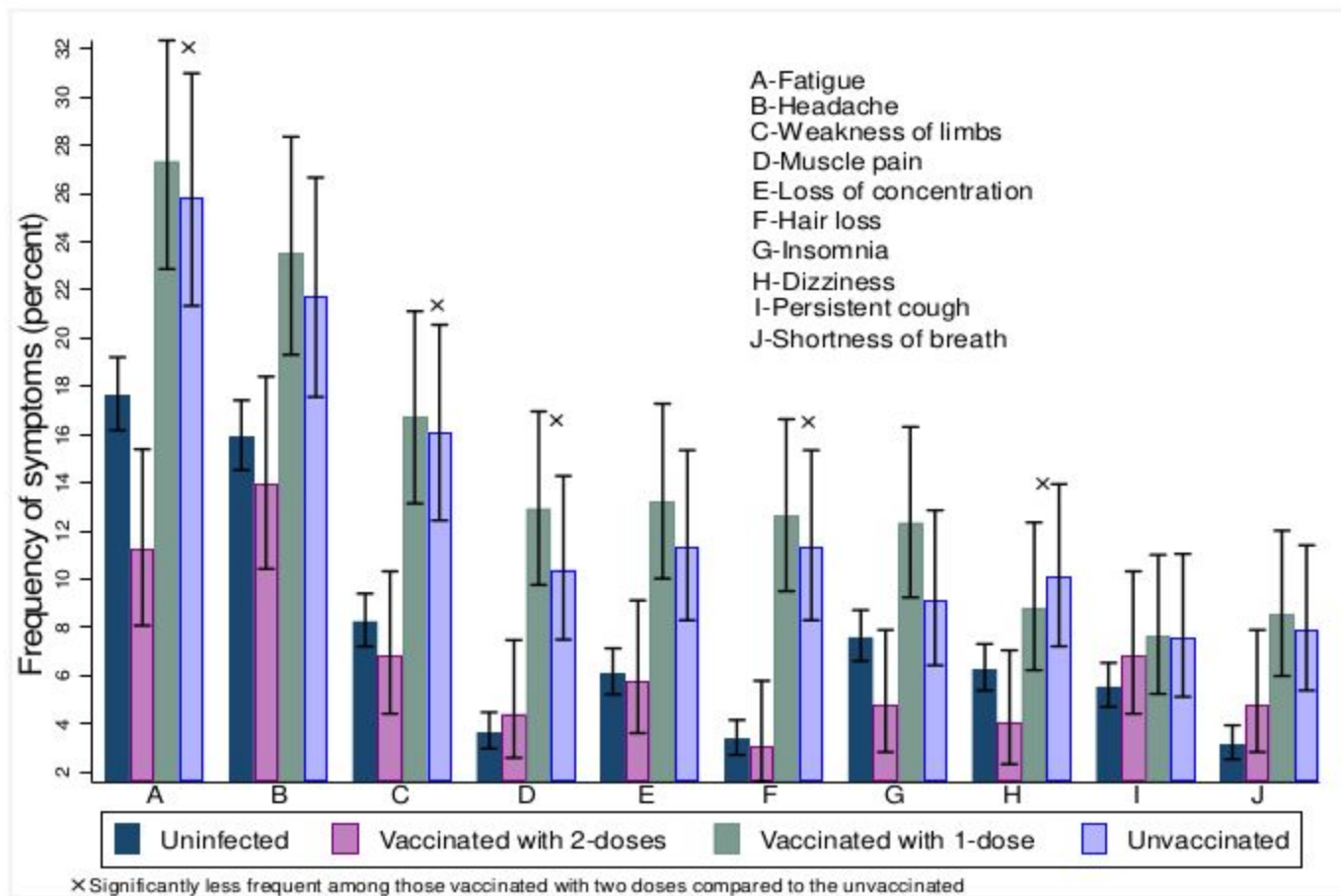
Figure 1. Frequency of most reported symptoms among the uninfected, the vaccinated and the unvaccinated

Image from: Kuodi, P., Gorelik, Y., Zayyad, H., Wertheim, O., Wiegler, K.B., Jabal, K.A., Dror, A., Nazzal, S., Glikman, D. and Edelstein, M., 2022. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected between March 2020 and November 2021. *medRxiv*.

Long COVID after breakthrough SARS-CoV-2 infection
(al-Aly et al. Nature Med , May 25, 2022)

US Veterans Affairs cohort (n=33,940) including vaccinated persons with breakthrough infections and controls without evidence of SARS-CoV-2 infection

6 months post-infection, compared to controls, higher risk of death (HR 1.75, CI 1.59-1.93), incident post-acute sequalae ICV, coagulation and hematological, GI, kidney, mental health, MSK and neurological disorders)

Compared to unvaccinated persons with SARS-CoV-02, those with BTI exhibited lower risk of death (HR 0.66, CI 0.58-.074) and incident post-acute sequelae (HR 0.85, CI 0.82-.89)

Vaccination before infection confers only partial protection in the post-acute phase of the disease – Must optimize prevention of BTI and develop post-acute care pathways

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Figure 7: Percent of Adults (Aged 18+) Self-reporting Longer-term Symptoms after a Positive COVID-19 Test or Suspected Infection by Time Period of Infection, Canada, January 2020 to August 2022
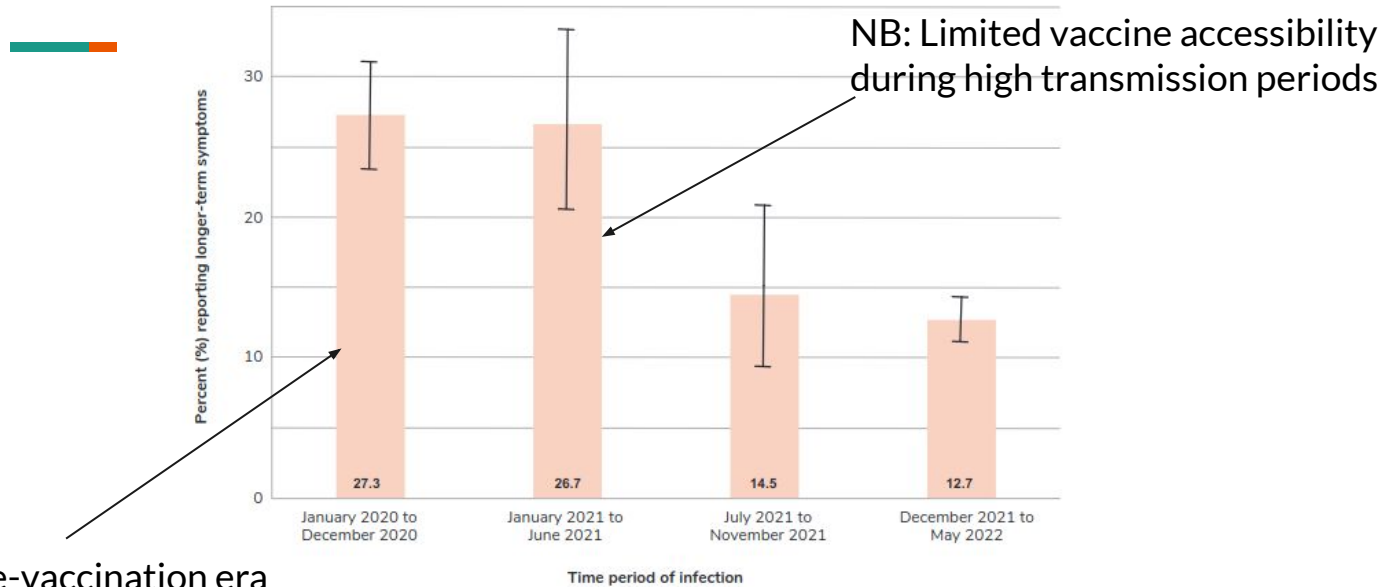
NB: Limited vaccine accessibility during high transmission periods

NB: Pre-vaccination era

Source: Canadian COVID-19 Antibody and Health Survey—Cycle 2.

Note: Longer-term symptoms are defined as self-reported persistent, recurring, or new symptoms 3 or more months after a positive COVID-19 test or suspected infection. Infections occurring within 3 months of August 31, 2022 are excluded because of an insufficient post-infection period to assess longer-term symptoms. Estimates exclude the territories. COVID-19 = Coronavirus Disease 2019.

Source: PHAC, StatsCan & CITF, Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022 (March 2023) https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf

Symptom Duration amongst PCC Canadians Infected ≥ 1 yr

Duration of symptoms	Percent reporting duration (95% confidence interval)
less than 2 months	11.3% (7.1%, 17.5%)
between 2 months and less than 3 months	8.6% (5.3%, 13.6%)
between 3 months and less than 6 months	21.9% (16.3%, 28.6%)
between 6 months and less than 1 year	11.1% (7.9%, 15.2%)
1 year or longer	47.3% (40.3%, 54.3%)

Amongst those with paid job or attending school, 74.1% (95% CI: 69.3%, 78.3%) reported absences

Image from COVID-19: Longer-term symptoms among Canadian adults - First report (Fall 2022)
https://health-infobase.canada.ca/covid-19/post-covid-condition/fall-2022-report.html

Disability is likely to account for the lion's share of COVID-19's burden, and might disproportionately affect women, especially those who were infected young.

SMITH MP. ESTIMATING TOTAL MORBIDITY BURDEN OF COVID-10: RELATIVE IMPORTANCE OF DEATH AND DISABILITY. *J CLIN EPI* 2022:142;54-59.

Source: Donna Goodridge

Only SALC Participants
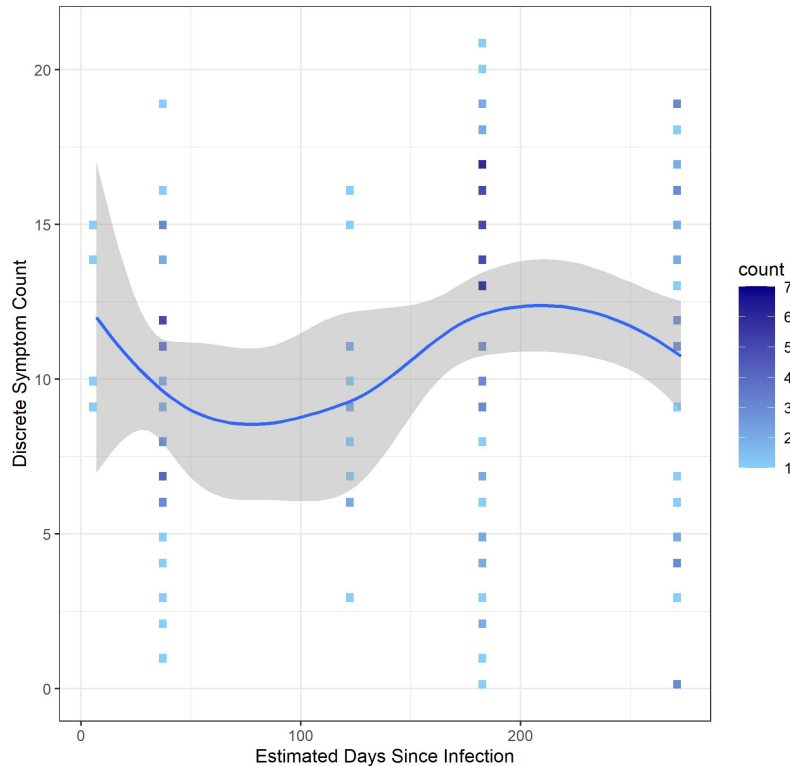
Base symptoms only
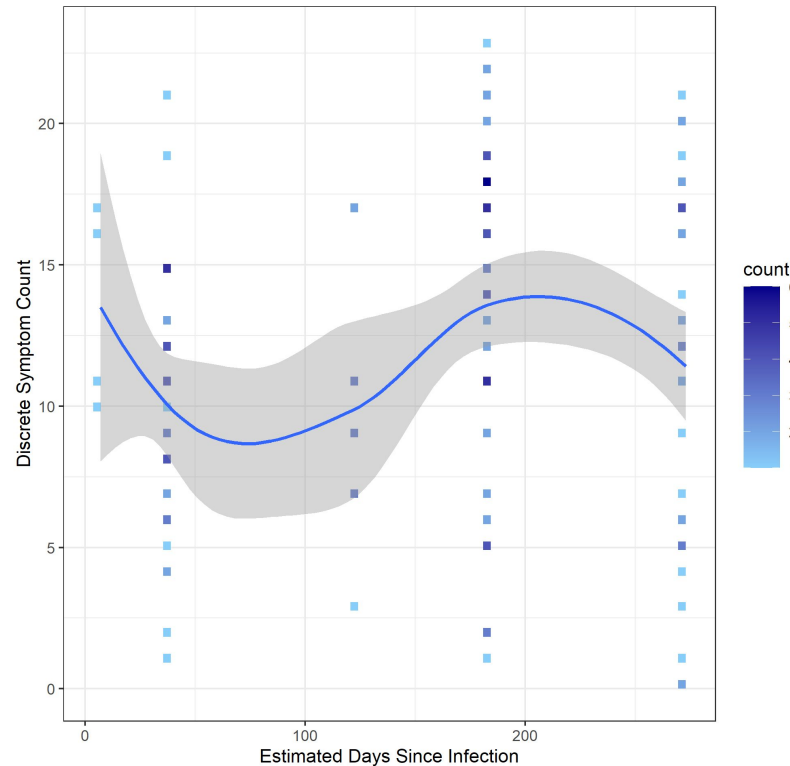
Additional symptoms Included

Boxplots of Participants' Self-Reported Severity of Depression Over Estimated Months Since Infection
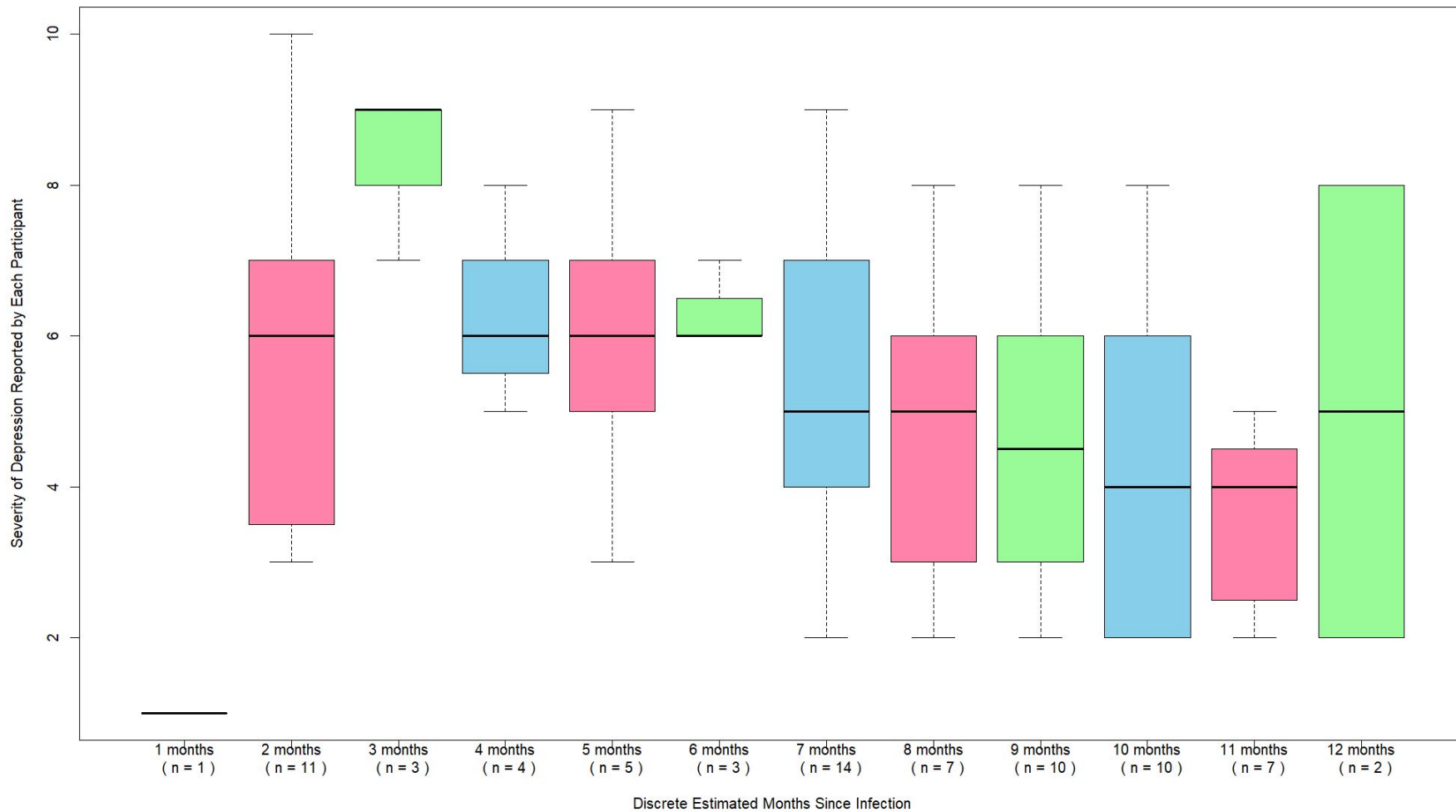
The Process of Adaptation

- Grieving Losses *"I'm missing out on being a mom, like for my 18-month-old. I can be a mom, bits and pieces. I've missed out on so many activities."* (F1)

- Considering the Prospect of Permanent Disability *"Some of the questions my mom has posed to me is like trying to get me thinking about what happens if this doesn't go away. What happens if I'm at 60% forever?"* (F2)

- **Living with Relapses** ***"It cycles. You're good for a couple of days and then I walk too far because I'm trying to get more exercise because that's what my doctor said to do, and it sets me back for two days, your joints hurt, it hurts to sit, it hurts to stand up."* (F10)**

- Transformed identities *"I have always defined myself for working and volunteering and being there for everybody else, and now I can't, and it's been very hard for me." (F6)*

Adapted from: Donna Goodridge

Cumulative Impacts of Reinfection Risks

Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 28, 2398–2405 (2022).
https://doi.org/10.1038/s41591-022-02051-3
https://www.nature.com/articles/s41591-022-02051-3

Acute and postacute sequelae associated with SARS-CoV-2 reinfection

Benjamin Bowe, Yan Xie & Ziyad Al-Aly ✉

Abstract

First infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with increased risk of acute and postacute death and sequelae in various organ systems. Whether reinfection adds to risks incurred after first infection is unclear. Here we used the US Department of Veterans Affairs' national healthcare database to build a cohort of individuals with one SARS-CoV-2 infection ($n = 443{,}588$), reinfection (two or more infections, $n = 40{,}947$) and a noninfected control ($n = 5{,}334{,}729$). We used inverse probability-weighted survival models to estimate risks and 6-month burdens of death, hospitalization and incident sequelae. Compared to no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.17, 95% confidence intervals (CI) 1.93–2.45), hospitalization (HR = 3.32, 95% CI 3.13–3.51) and sequelae including pulmonary, cardiovascular, hematological, diabetes, gastrointestinal, kidney, mental health, musculoskeletal and neurological disorders. The risks were evident regardless of vaccination status. The risks were most pronounced in the acute phase but persisted in the postacute phase at 6 months. Compared to noninfected controls, cumulative risks and burdens of repeat infection increased according to the number of

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Good advice is hard to come by...

- The scarcity of good advice has often left people with LONG COVID feeling isolated and frustrated in the search for therapies

- Self-prescribing practices in Long COVID are unsurprisingly high

- A vast range of OTC medicines, remedies, supplements, and dietary practices are being used because people are willing to try almost anything

- Advice on the internet and social media can be conflicting and a source of misinformation

Brown et al. Long COVID and self-management. Lancet 2022. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902798-7

Source: Donna Goodridge

High-Burden Symptom: Brain Fog

Brain Fog

	COVID and LC (n= 290)	COVID No LC (n= 76)	Don't Know LC (n= 26)	No COVID (n= 247)
Prevalence	80.56% (n= 288)	36.49% (n= 74)	61.11% (n= 18)	23.24% (n= 241)
Worse after COVID	96.98% (n= 232)	62.96% (n= 27)	27.27% (n= 11)	1.79% (n= 56)
Worst Severity Average	7.36 (n= 232)	4.74 (n= 27)	5.36 (n= 11)	4.14 (n= 56)
Severity Now Average	4.94 (n= 232)	2.30 (n= 27)	3.73 (n= 11)	2.36 (n= 56)
Seen HCP	44.83% (n= 232)	14.81% (n= 27)	9.09% (n= 11)	16.07% (n= 56)
Satisfied with care	27.88% (n= 104)	75.00% (n= 4)	0.00% (n= 1)	66.67% (n= 9)

High-Burden Symptom: Memory Issues

Memory Issues

	COVID and LC (n= 290)	COVID No LC (n= 76)	Don't Know LC (n= 26)	No COVID (n= 247)
Prevalence	82.35% (n= 289)	39.19% (n= 74)	50.00% (n= 18)	30.71% (n= 241)
Worse after COVID	95.78% (n= 237)	51.72% (n= 29)	22.22% (n= 9)	1.35% (n= 74)
Worst Severity Average	7.07 (n= 237)	4.14 (n= 29)	6.33 (n= 9)	4.07 (n= 74)
Severity Now Average	5.23 (n= 237)	2.34 (n= 29)	4.89 (n= 9)	2.66 (n= 74)
Seen HCP	44.30% (n= 237)	24.14% (n= 29)	11.11% (n= 9)	20.27% (n= 74)
Satisfied with care	34.29% (n= 105)	71.43% (n= 7)	100.00% (n= 1)	86.67% (n= 15)

Post-Exertional Malaise

Tired After Minimal Exercise

	COVID and LC (n= 290)	COVID No LC (n= 76)	Don't Know LC (n= 26)	No COVID (n= 247)
Prevalence	73.52% (n= 287)	29.73% (n= 74)	27.78% (n= 18)	13.69% (n= 241)
Worse after COVID	99.05% (n= 211)	77.27% (n= 22)	20.00% (n= 5)	3.03% (n= 33)
Worst Severity Average	7.75 (n= 211)	4.68 (n= 22)	5.00 (n= 5)	4.85 (n= 33)
Severity Now Average	5.45 (n= 211)	1.91 (n= 22)	3.00 (n= 5)	2.58 (n= 33)
Seen HCP	49.76% (n= 211)	13.64% (n= 22)	40.00% (n= 5)	24.24% (n= 33)
Satisified with care	31.43% (n= 105)	100.00% (n= 3)	50.00% (n= 2)	62.50% (n= 8)

After performing activities...

	COVID and LC (n= 290)	COVID No LC (n= 76)	Don't Know LC (n= 26)	No COVID (n= 247)
Recovered within an hour	47.90% (n= 286)	93.15% (n= 73)	94.44% (n= 18)	88.75% (n= 240)
Worsened fatigue	68.88% (n= 286)	15.07% (n= 73)	38.89% (n= 18)	5.44% (n= 239)
Worsened mental capability	67.48% (n= 286)	16.44% (n= 73)	50.00% (n= 18)	12.13% (n= 239)

Focus Groups for People with Symptoms of Long COVID

41 individuals from 8 Canadian provinces participated in 10 focus groups in February/March 2022.

●Sample quotes:

He was a young emergency doctor filling in to do this assessment. Took five minutes and didn't – hadn't even read my chart, didn't look at my echo result. Was just like, "I think antidepressants are the answer." And so right then, I was, like, you absolutely are incorrect and this isn't a depression. You know, I've monitored my heart rate, monitored my oxygen. And it's almost like POTS-like symptoms. I'm like, I'm not making it up in my head. And yeah, it's been terrible.

I find my whole nervous system is just feels like jacked up, like lights, lights are too bright, sounds are too loud. Everything smells too – it's just, the whole – I feel like my whole nervous system is jacked right up to the nines.

Source: Donna Goodridge

Provider and Relational Factors Contributing to Erosion of Trust

- Feelings of Abandonment *"Just imagine you're in the middle of the ocean without a life jacket and you're struggling to keep your head afloat. And a boat comes by and start clapping at you and says, "Man, you're doing a good job," and drives off." That's sort of what I feel like right now. "* (F4)

  - *"We're drowning and we are alone"* (F6)
- Expectations that providers know the answers *"Physicians here are not equipped to deal with this, and I know we don't know what we don't know, we're living in real time, but it's frustrating as a person when they're supposed to be the experts."* (F9)
- *"They kind of ameliorate things, but you know, no one seems to know anything about really getting down to how do we cure this"* (F8)

  - Concerns dismissed *"I've been on my own and the doctors have done nothing but gaslight me."* (F6)

Source: Donna Goodridge

Factors Affecting the Complex Work of Recovery

- Family support *"I've had to have my husband come to all my doctors' appointments because **I just can't process quick enough and answer questions and remember things**."* (F4)

- Frustration of having Symptoms Discredited *"I'm struggling with the lack of belief. People think I'm faking all the time and I'm like, seriously? Look at my thermometer, it's 104. I'm not faking!"*(F4)

- Need for Self-Advocacy

  "I've been doing a lot of research, a lot of investigating because I've been on my own and the doctors have done nothing but gaslight me." (F6)

- *"A lot of times, we're guiding what [providers] are doing, right? We're – especially because I have a medical background, so I'm researching and I'm looking and I'm doing anything I can to try to help my situation, right? Which, again, when you're going through long COVID is extremely exhausting. **A lot of people don't even have the energy to be their own advocate, right?**" (F8)*

Adapted from Donna Goodridge

Existing EHRs & administrative data risk missing much of the PCC burden
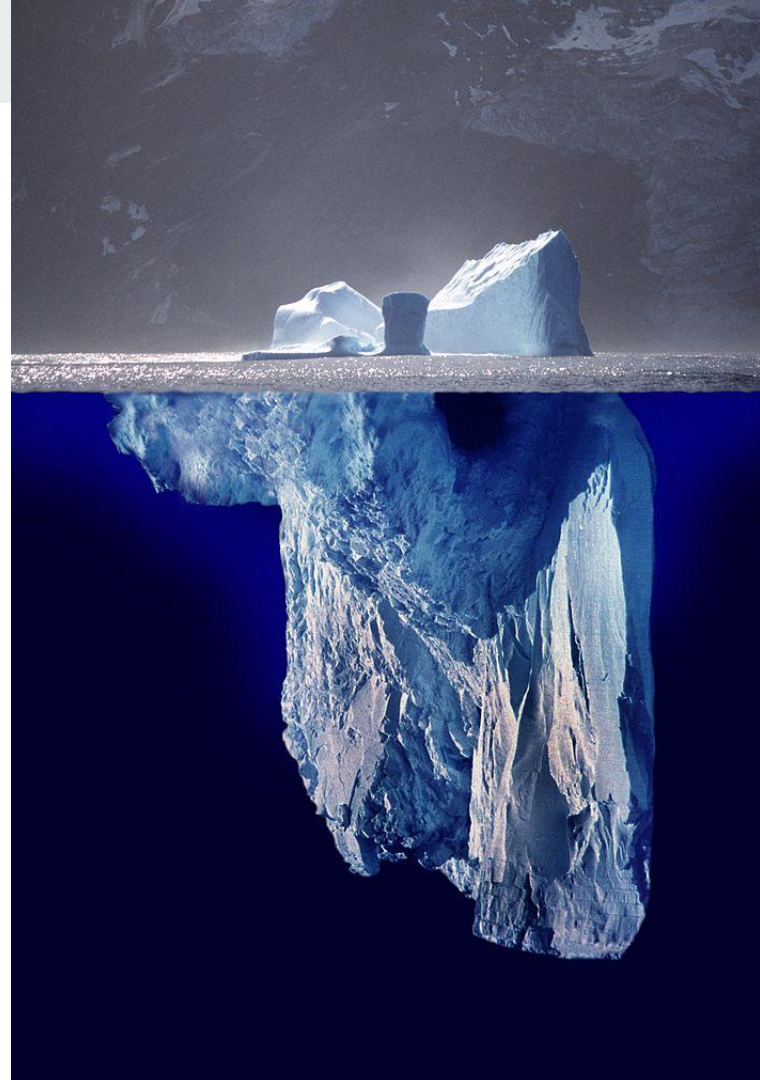
Mythbusting: Common PCC/Long COVID Misconceptions

- ~~Is psychosomatic in origin~~
- ~~Is limited to those who experienced serious acute COVID-19 symptoms~~
- ~~Is a single, monolithic condition~~
- ~~Exhibits a unstructured, scattershot collection of symptoms~~
- ~~Consists of symptoms that originate in acute phase and resolve over time~~
- ~~Imposes burden limited to bearing with such symptoms~~
- ~~Is a squishy set of nuisance symptoms medicalized by the privileged~~
- ~~Is adequately captured in administrative databases and electronic health records~~

Prognostic Machine Learning Models

- We have been explore the predictive accuracy of a variety of types of machine learning models
- Model classes explored include deep neural networks, Bayesian, Statistical learning & kernel methods

Effectiveness of Parsimonious Predictive Models

- Extremely simple machine learning models can offer strong power in predicting Long COVID outcomes
- Example: **4 variable** model: **Acute** Severity, Sex, Vaccination status, count preexisting conditions

	AUC	**Accuracy**	**Precision**	**F1-score**
SVC	0.801	0.746	0.771	0.753
XGBM	0.757	0.592	0.704	0.604
Deep Neural Network	0.787	0.732	0.724	0.727

Our Long COVID Dynamic Modeling Work

- Dynamic modeling work
  - Summer 2021 & onwards: COVID-19 Multi-jurisdiction ABM
  - Refined Long COVID-specific ABM (Nastaran Jamali)
  - Work with Ellen Rafferty et al. (Institute for Health Economics)
  - Work with Alex Doroshenko, Karsten Hempel for Alberta WCB

Long COVID Agent-Based & Hybrid Modeling

- Saskatchewan intervention & projection-focused hybrid, spatially explicit COVID-19 ABM (summer 2021-): Clinical need progression (self-management, interdisciplinary care, specialty care)
- Long COVID ABM (CEPHIL student Nastaran Jamali)
- Joint w/Ellen Rafferty et al. (IHE): Long COVID resource utilization ABM
- Joint w/PHAC (RJ Edjoc) et al.: Cardiac Long COVID outcomes ABM

Long COVID ABM

- Infection pathways, including reinfection
- Pre-existing conditions
- Vaccination
- For each patient, principal components-guided families of post-COVID conditions, each with
  - Severity
  - Diagnosis status
  - Treatment pathways
  - Separate timing of resolution
  - Active/inactive distinction
- Custom characterization of high-burden outcomes with unique dynamics & risk factors (e.g., diabetes, cardiovascular, depression)
- History information

Person
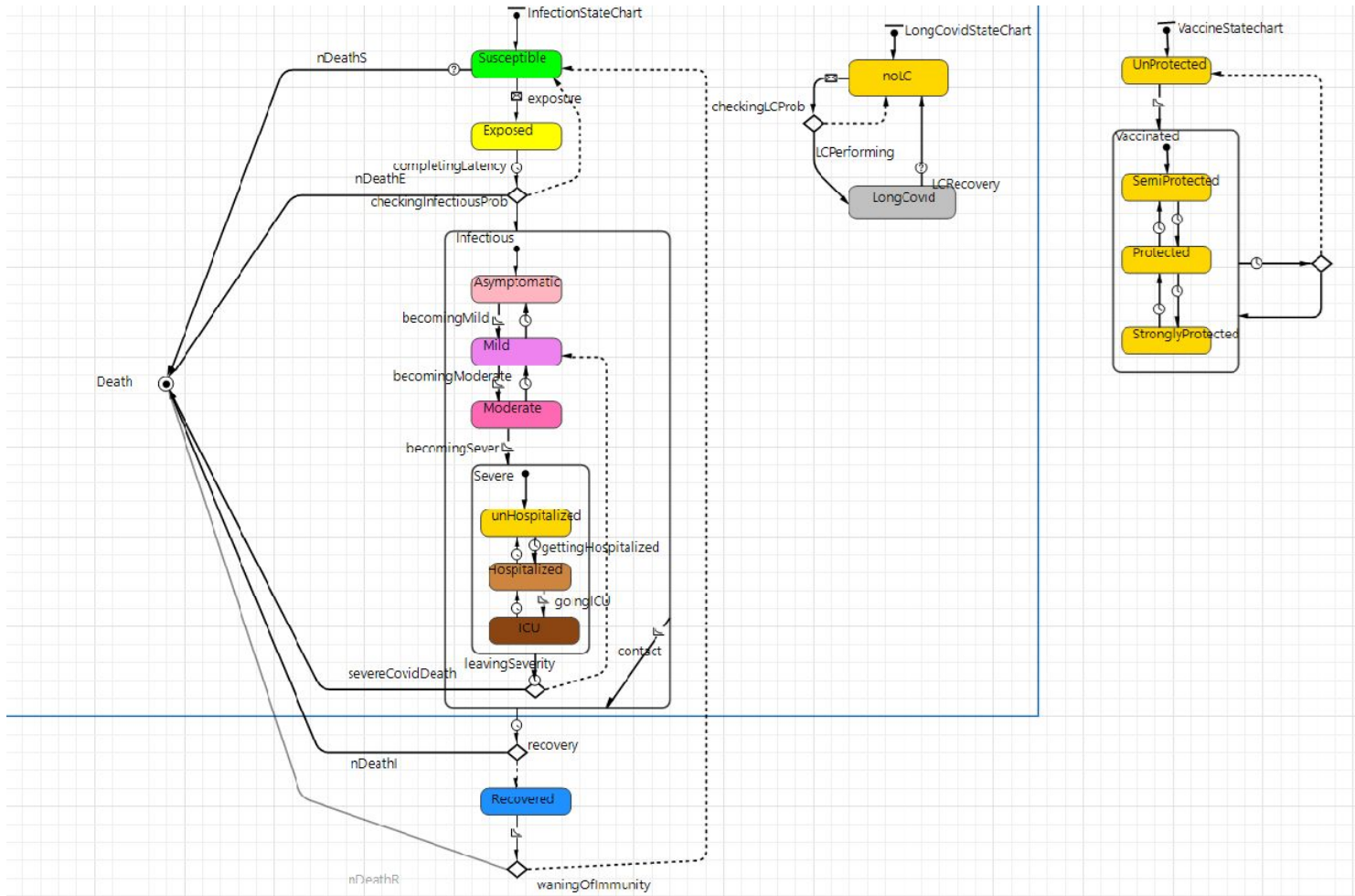
Diabetes Statechart with initial diabetes distribution
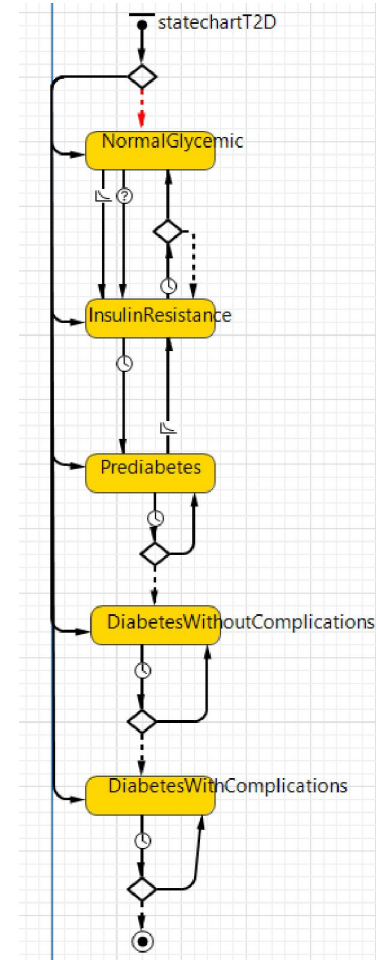
Example Outcomes 1
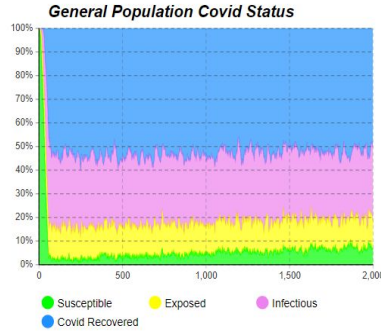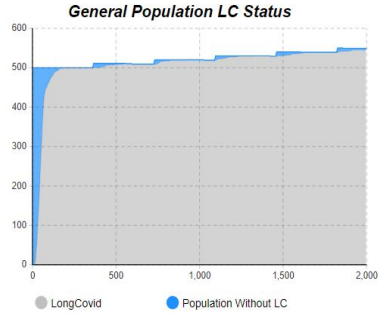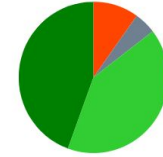
Example Outcomes 2

General Population LC Depression

PreDep 141   MinorDep 196
DiabetesWithoutComplications 46

General Population LC Problems

Healthy 81   Fatigue 200
Depression 386   Prediabetes & DiabetesT2 205
Cardio 442   Coughing 160
ObsessiveCompulsiveD 113   Anxiety 226
PostTraumaticStress 152

General Population LC DiabetesT2

Undiagnosed 1   Prediabetes 10
DiabetesWithoutComplications 52   DiabetesWithComplications 143

General Population LC CardioProblems

Undiagnosed 5   MinorCardioSymp 213   PreHeartFailure 140
SymptamaticHF 67   AdvancedHF 22

cumulative Infectived People
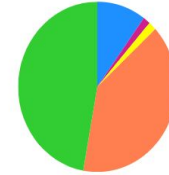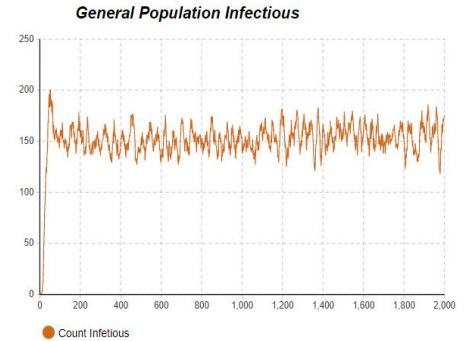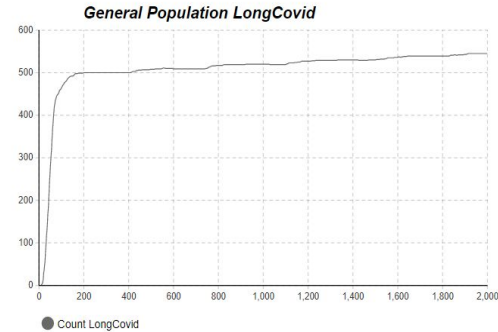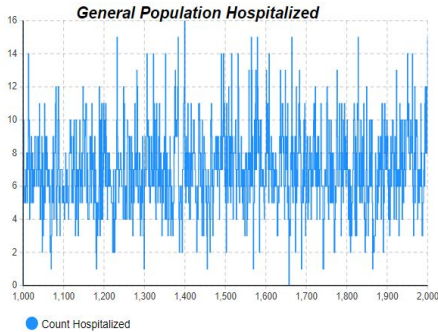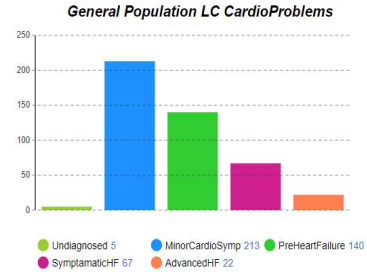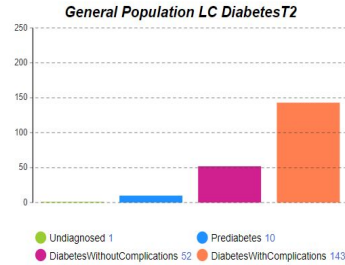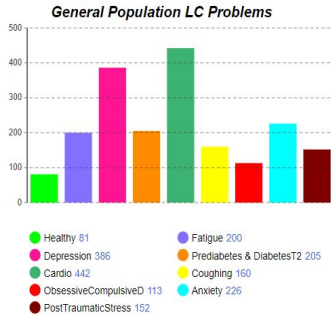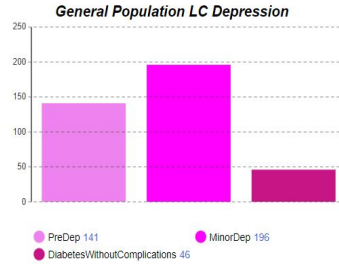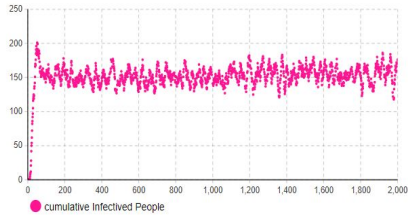
Modeling Challenges

- Reliable infection data
- Vast array of symptoms & incompletely elucidated latent classes
- Symptom-specific dynamics
- Diversity of biological pathways underlying symptoms (neurologic, dysbiosis, organ damage, immune dysregulation, psychiatric, autonomic nervous system, etc.)
- Unclear impact of reinfection
- Non-monotonic nature of evolution
- Diversity of risk factors
- Undiagnosed nature of much (most) of PCC?
- Lack of (ICD) medical coding standards
- Inter-provincial fragmentation
- Evolving & Non-additive healthcare burdens
- Limitations in longitudinal data availability

Short-Term Study Evolution

- Incorporation into Metis-Nation of Saskatchewan population-wide survey instruments
- SPOR-supported deployment of adapted & updated study with Long COVID registries across 4 western provinces
  - Administrative data linkage to smartphone-based reporting
  - Citizen science portals

A Call to Action

- We are witness to imposition of a new high-burden chronic disease
- Like many others, the heaviest disease burden falls on vulnerable groups
- Post-covid condition patients experience high difficulty in seeking care
- This disease is preventable, has possible prophylaxis but high burden once emerged
- While exhibiting myriad manifestations, there is high structure that dynamic modeling can exploit
- Modeling of such conditions from the immunological through the population level is key to lower the burden and deliver effective care

Key References

- Su, Y., Yuan, D., Chen, D.G., Ng, R.H., Wang, K., Choi, J., Li, S., Hong, S., Zhang, R., Xie, J. and Kornilov, S.A., 2022. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell, 185(5), pp.881-895.
- Merad, M., Blish, C.A., Sallusto, F. and Iwasaki, A., 2022. The immunology and immunopathology of COVID-19. Science, 375(6585), pp.1122-1127.
- Mainous III, A.G., Rooks, B.J., Wu, V. and Orlando, F.A., 2021. COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk. Frontiers in Medicine, p.2351. https://www.frontiersin.org/articles/10.3389/fmed.2021.778434/full
- Phetsouphanh, C., Darley, D.R., Wilson, D.B. et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2infection. Nat Immunol (2022). https://doi.org/10.1038/s41590-021-01113-x
- Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. Nat Med (2022). https://doi.org/10.1038/s41591-022-02001-z
- Roessler, M., Tesch, F., Batram, M., Jacob, J., Loser, F., Weidinger, O., Wende, D., Vivirito, A., Toepfner, N., Seifert, M. and Nagel, O., 2021. Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19. MedRxiv. The article is accessible at the following address https://www.medrxiv.org/content/10.1101/2021.10.21.21265133v1.full?s=08
- Barrett CE, Koyama AK, Alvarez P, et al. Risk for Newly Diagnosed Diabetes >30 Days After SARS-CoV-2 Infection Among Persons Aged <18 Years — United States, March 1, 2020–June 28, 2021. MMWR Morb Mortal Wkly Rep 2022;71:59–65. DOI: http://dx.doi.org/10.15585/mmwr.mm7102e2external icon
- Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 28, 2398–2405 (2022). https://doi.org/10.1038/s41591-022-02051-3 https://www.nature.com/articles/s41591-022-02051-3
- Brown et al. Long COVID and self-management. Lancet 2022. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902798-7

Canadian Resources

- Associations between Longer-term Symptoms after COVID-19 and Sociodemographics, Health Characteristics, Period of Infection, and Vaccination Status in Canadian Adults, January 2020 to August 2022
https://health-infobase.canada.ca/src/doc/post-covid-condition/Association-Between-Longer-term-Symptoms-after-COVID-19.pdf
- COVID-19: Longer-term symptoms among Canadian adults
  - Report:
https://health-infobase.canada.ca/src/doc/post-covid-condition/COVID-19-longer-term-symptoms-among-Canadian-adults.pdf
  - Highlights: https://health-infobase.canada.ca/covid-19/post-covid-condition/
- Long-term symptoms in Canadian adults who tested positive for COVID-19 or suspected an infection, January 2020 to August 2022
https://www150.statcan.gc.ca/n1/daily-quotidien/221017/dq221017b-eng.htm
- Canadian COVID-19 Antibody and Health Survey (CCAHS)
https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5339

Other Notable Vaccination-Related Studies

Al-Aly, Z., Bowe, B. and Xie, Y., 2022. Long COVID after breakthrough SARS-CoV-2 infection. Nature medicine, 28(7), pp.1461-1467.

Azzolini, E., Levi, R., Sarti, R., Pozzi, C., Mollura, M., Mantovani, A. and Rescigno, M., 2022. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. Jama, 328(7), pp.676-678.

Daniel Ayoubkhani, Charlotte Bermingham, Koen B Pouwels, Myer Glickman, Vahé Nafilyan, Francesco Zaccardi, Kamlesh Khunti, Nisreen A Alwan, A Sarah Walker. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort

Kuodi, P., Gorelik, Y., Zayyad, H., Wertheim, O., Wiegler, K.B., Jabal, K.A., Dror, A., Nazzal, S., Glikman, D. and Edelstein, M., 2022. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected between March 2020 and November 2021. medRxiv.

Antonelli, M., Penfold, R.S., Merino, J., Sudre, C.H., Molteni, E., Berry, S., Canas, L.S., Graham, M.S., Klaser, K., Modat, M. and Murray, B., 2022. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. The Lancet Infectious Diseases, 22(1), pp.43-55.

Vaccination post-infection
   V.-T. Tran, E. Perrodeau, J. Saldanha, I. Pane, P. Ravaud,SSRN[Preprint] (2021); http://doi.org/10.2139/ssrn.3932953.
   M. A. Simon, R. D. Luginbuhl, R. Parker, medRxiv2021.2011.2017.21263608 [Preprint] (2021); doi: 10.1101/2021.11.17.21263608.

Acknowledgements