



POST-COVID-19
Interdisciplinary Clinical Care Network
Provincial Health Services Authority

A Long COVID Update

May 8, 2024

VCH Family Medicine Rounds

Zachary Schwartz, Internal Medicine

I acknowledge with gratitude, that we are gathered on the traditional, ancestral and unceded territories of the x^wməθk^wəyəm (Musqueam), Sk̓wx̓wú7mesh (Squamish), and səlilwətał (Tsleil-Waututh) Nations who have nurtured and cared for the lands and waters around us for all time. I give thanks for the opportunity to live, work and support care here.



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Faculty Disclosure

- Faculty: **Zachary Schwartz**
- Relationships with financial sponsors:
 - Any direct financial relationships including receipt of honoraria: None
 - Memberships on advisory boards or speakers' bureau: none
 - Patents for drugs or devices: none
 - Other: financial relationships/investments none



Objectives

- Definition
- Burden of Disease
- Who is more likely to get it?
- Cause
- Management
- Active Trials
- Long Term Consequences
- Resources



Definition

WHO Definition

Delphi Consensus - 2021



- *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*

AKA

- Post COVID19 Syndrome
- Long-Haul COVID
- Chronic COVID
- Post-acute sequelae of SARS-CoV-2 (PASC)



Original Investigation

May 25, 2023

Development of a Definition of Postacute Sequelae of SARS-CoV Infection



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Defining Long COVID

- 10000 adults (9000 with COVID, 1000 without)
 - Looked at 30+ symptoms
 - The symptoms below most set apart those with C19 vs those without
 - Post-exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, issues with sexual desire or capacity, loss of smell or taste, thirst, chronic cough, chest pain, and abnormal movements.
 - Established a scoring system and were able to then identify a “meaningful threshold” for Long COVID



Burden of Disease



Burden of Disease

- Based on Census Bureau Household Survey from US CDC (2022)
 - ~ 6% of adults are suffering symptoms > 3 months after C19 infection
 - Of those, ~80% feel that their symptoms limit day-to-day activities (of which 25% say they are severely limited)
 - US estimates the total cost of PASC at ~ \$ 750 billion/year (reduced QOL, lost wages, lost earnings, increased medical spending)
- ****unfortunately still no great estimate of prevalence. Many quote 10% of patients have ongoing symptoms (seems to me an overestimate)**



Who is more likely to get it?



Risk factors

- Hospitalized/severe C19
- Pre-existing conditions (diabetes, asthma, autoimmune disease, obesity)
- Pre-Omicron Era
- Unvaccinated



Management



Rule out other causes/complications

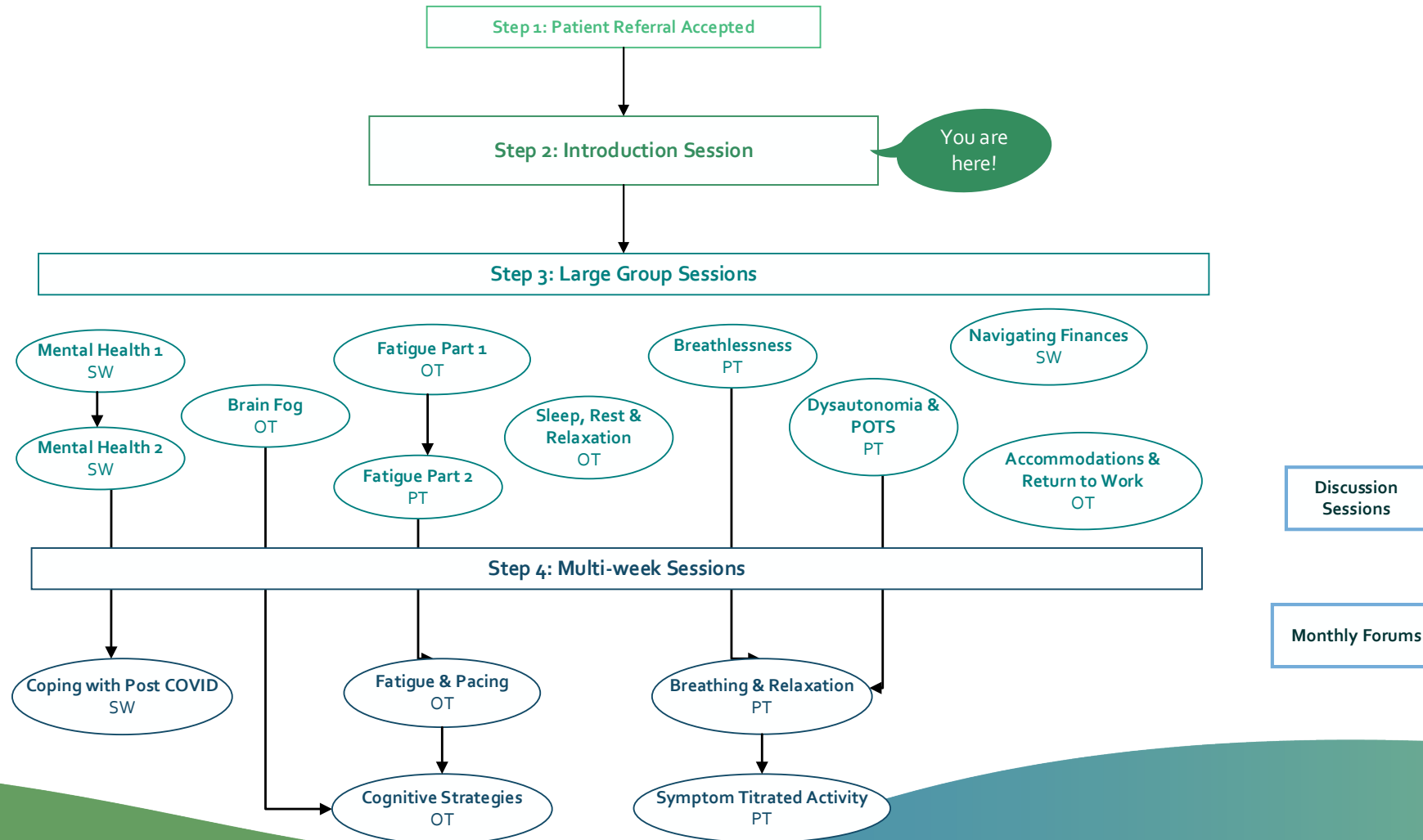
- **Fatigue/Brain Fog:** CBC, Ferritin, TSH, BNP, troponin, +/- Polysomnography, screen for anxiety/depression
- **Dyspnea:** CXR, spirometry
- **Palpitations:** ECG, Holter, +/- echo
- **Chest pain:** ECG, Troponin, BNP, CXR



Is Largely Supportive

- *Education, reassurance, and validation*
- Avoiding triggers (**especially post-exertional malaise)
- Referral to PC-ICCN (RN visits, +/- MD visit, group education classes)
 - Shortness of breath
 - Fatigue and Pacing
 - Mental Health
 - Sleep
 - Finances
 - Exercise

Self-Management Strategy





Does Paxlovid Help?





- Large observational trial from veteran affairs
- 281 793 people with SARS-CoV-2 infection who had at least 1 risk factor for progression to severe COVID-19 illness, compared with 246 076 who had no treatment
 - ~36000 received Paxlovid



- Those who were treated with Paxlovid, there was a reduced risk of PCC
 - Regardless of vaccination status
- Absolute risk reduction was about 4.5%
- About 13% vs 18% risk between treated vs untreated

There's always a but.....





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JOURNAL OF
MEDICAL VIROLOGY

RESEARCH ARTICLE |  **Open Access** |  

Association of nirmatrelvir for acute SARS-CoV-2 infection with subsequent Long COVID symptoms in an observational cohort study

Matthew S. Durstenfeld , Michael J. Peluso, Feng Lin, Noah D. Peyser, Carmen Isasi, Thomas W. Carton, Timothy J. Henrich, Steven G. Deeks, Jeffrey E. Olgin ... [See all authors](#) 

First published: 04 January 2024 | <https://doi.org/10.1002/jmv.29333> | Citations: 1

Matthew S. Durstenfeld and Michael J. Peluso are co-first authors.



- Among 666 treated who answered, rebound symptoms or test positivity were not associated with Long COVID symptoms



Resources

Tools and resources for patients



[MyGuide Long COVID](https://www.longcovidbc.ca/)

(<https://www.longcovidbc.ca/>)

- Launched in August 2023
 - Patient -specific care plan
 - Symptom management, resources, tools and next steps
 - Accessibility features (e.g. dark mode), multilingual (coming Nov '23)



[Website](https://phsa.ca/postcovid) (phsa.ca/postcovid)

- Self-management tools
- Symptom-specific resource page (handouts, videos)
- Links to external resources (support groups)

Education for Clinicians

- BC ECHO for Post-COVID Recovery (Jul 2021 – Jul 2022)
 - 12 virtual sessions
 - Instructive and case-based learning
 - <http://www.phsa.ca/health-professionals/education-development/bc-echo-for-post-covid-19-recovery>
- Post-COVID-19 Recovery Pathways
- COVID-19 clinical resources:
 - <http://www.phsa.ca/health-professionals/clinical-resources/post-covid-19-care>



Cause?

Pathophysiology

***It is unlikely there is just one common method by which the COVID-19 virus causes the symptoms and conditions associated with Long COVID.*



Pathophysiology

- Persistent SARS-CoV-2 in the blood and tissue months after infection (Viral reservoirs)
- Dysregulated immune response (activated T cells where/when they shouldn't be)
- Autoantibodies
- EBV reactivation
- Microthrombi
- Dysbiosis
- Unrepaired tissue damage

SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC)

Received: 30 March 2023

Accepted: 18 July 2023

Published online: 04 September 2023

 Check for updates

Amy D. Proal ¹✉, Michael B. VanElzaker^{1,2}, Soo Aleman³, Katie Bach^{1,4}, Brittany P. Boribong ^{5,6,7}, Marcus Buggert ⁸, Sara Cherry ⁹, Daniel S. Chertow ^{10,11}, Helen E. Davies ¹², Christopher L. Dupont ¹³, Steven G. Deeks¹⁴, William Eimer^{7,15,16,17}, E. Wesley Ely¹⁸, Alessio Fasano^{5,6,7}, Marcelo Freire ¹⁹, Linda N. Geng²⁰, Diane E. Griffin²¹, Timothy J. Henrich²², Akiko Iwasaki ^{23,24,25}, David Izquierdo-Garcia^{26,27}, Michela Locci²⁸, Saurabh Mehandru ^{29,30}, Mark M. Painter ³¹, Michael J. Peluso¹⁴, Etheresia Pretorius^{32,33}, David A. Price ^{34,35}, David Putrino³⁶, Richard H. Scheuermann ^{37,38,39}, Gene S. Tan^{13,40}, Rudolph E. Tanzi ^{7,15,16,17}, Henry F. VanBrocklin⁴¹, Lael M. Yonker ^{5,6,7} & E. John Wherry ³¹

The persistence of SARS-CoV-2 in tissues and its association with long COVID symptoms: a cross-sectional cohort study in China

Wenting Zuo, Di He*, Chaoyang Liang*, Shiyu Du, Zhan Hua, Qiangqiang Nie, Xiaofeng Zhou, Meng Yang, Haidong Tan, Jiuyang Xu, Yanbing Yu, Yuliang Zhan, Ying Zhang, Xiaoying Gu, Weijie Zhu, Hui Zhang, Hongyan Li, Weiliang Sun, Mingzhi Sun, Xiaolei Liu, Liguang Liu, Chuanzhen Cao, Rui Li, Jing Li, Yun Zhang, Yuting Zhang, Jing Guo, Ling Zhao, Chuan-Peng Zhang, Hongyu Liu, Shiyao Wang, Fei Xiao, Yeming Wang, Zai Wang, Haibo Li. Bin Cao*



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Viral persistence

- Single Centre Cross-sectional cohort (post Omicron Dec 2022)
- Enrolled those who were scheduled for procedures (and used residual surgical samples) and collected labs at regularly scheduled intervals
- Follow-up at 4 months to assess symptoms
- Detection of viral RNA highly correlated to symptoms (OR 5-6)



Remaining Questions

- Does this trigger autoimmunity?
- Does this trigger constant activation of immune system?
- Does it trigger “micro-clots”?




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New and Interesting Studies



Article | [Open access](#) | Published: 04 January 2024

Muscle abnormalities worsen after post-exertional malaise in long COVID

[Brent Appelman](#), [Braeden T. Charlton](#), [Richie P. Goulding](#), [Tom J. Kerkhoff](#), [Ellen A. Breedveld](#),
[Wendy Noort](#), [Carla Offringa](#), [Frank W. Bloemers](#), [Michel van Weeghel](#), [Bauke V. Schomakers](#),
[Pedro Coelho](#), [Jelle J. Posthuma](#), [Eleonora Aronica](#), [W. Joost Wiersinga](#), [Michèle van Vugt](#)  &
[Rob C. I. Wüst](#) 

[Nature Communications](#) **15**, Article number: 17 (2024) | [Cite this article](#)

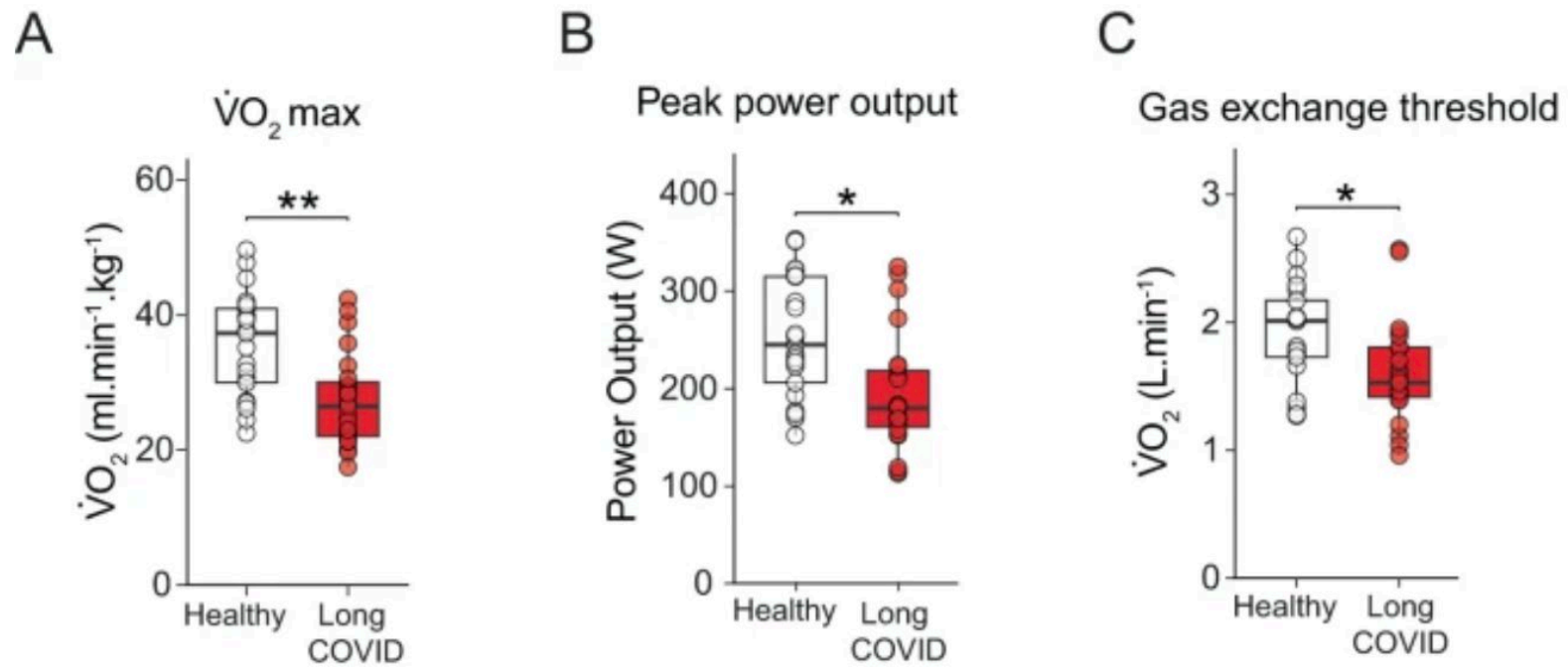
221k Accesses | **17** Citations | **5180** Altmetric | [Metrics](#)



- They induced PEM in 25 patients with Long COVID and PEM
- Obtained labs and skeletal muscle biopsies before and after exercise
- Matched results to 21 healthy patients without PEM



Fig. 1: Lower exercise capacity in patients with long COVID.



- Succinate dehydrogenase activity was not reduced in healthy controls one day after exercise, but was reduced in the long COVID patients, suggesting that the combination of a reduced maximal mitochondrial respiration and decreased mitochondrial content are part of the pathophysiology of post-exertional malaise.
- We conclude that severe exercise-induced muscle damage and subsequent regeneration are associated with the pathophysiology of post-exertional malaise, and can possibly explain muscle pain, fatigue, and weakness in patients with long COVID experiencing post-exertional malaise.



Article | [Open access](#) | Published: 25 September 2023

Distinguishing features of long COVID identified through immune profiling

[Jon Klein](#), [Jamie Wood](#), [Jillian R. Jaycox](#), [Rahul M. Dhodapkar](#), [Peiwen Lu](#), [Jeff R. Gehlhausen](#),
[Alexandra Tabachnikova](#), [Kerrie Greene](#), [Laura Tabacof](#), [Aryn A. Malik](#), [Valter Silva Monteiro](#),
[Julio Silva](#), [Kathy Kamath](#), [Minlu Zhang](#), [Abhilash Dhal](#), [Isabel M. Ott](#), [Gabrielee Valle](#), [Mario](#)
[Peña-Hernández](#), [Tianyang Mao](#), [Bornali Bhattacharjee](#), [Takehiro Takahashi](#), [Carolina Lucas](#), [Eric](#)
[Song](#), [Dayna McCarthy](#), ... [Akiko Iwasaki](#) 

+ Show authors

[Nature](#) **623**, 139–148 (2023) | [Cite this article](#)



Letter | [Open access](#) | Published: 08 April 2024

Large-scale phenotyping of patients with long COVID post-hospitalization reveals mechanistic subtypes of disease

[Felicity Liew](#), [Claudia Efstathiou](#), [Sara Fontanella](#), [Matthew Richardson](#), [Ruth Saunders](#), [Dawid Swieboda](#), [Jasmin K. Sidhu](#), [Stephanie Ascough](#), [Shona C. Moore](#), [Noura Mohamed](#), [Jose Nunag](#), [Clara King](#), [Olivia C. Leavy](#), [Omer Elneima](#), [Hamish J. C. McAuley](#), [Aarti Shikotra](#), [Amisha Singapuri](#), [Marco Sereno](#), [Victoria C. Harris](#), [Linzy Houchen-Wolloff](#), [Neil J. Greening](#), [Nazir I. Lone](#), [Matthew Thorpe](#), [A. A. Roger Thompson](#), [PHOSP-COVID collaborative group](#) & [ISARIC investigators](#)

+ Show authors



Decoding Post-Viral Fatigue: The Basal Ganglia's Complex Role in Long-COVID

by **Thorsten Rudroff** ^{1,2}  

¹ Department of Health and Human Physiology, University of Iowa, Iowa City, IA 52242, USA

² Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242, USA

Neurol. Int. **2024**, 16(2), 380-393; <https://doi.org/10.3390/neurolint16020028>

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Published: 28 March 2024

- Aberrant Metabolic Patterns on MR spectroscopy
 - Altered choline and lactate (suggestive of neuroinflammation) when compared to controls
 - However, could be related to hypoperfusion or other physiological processes



Active trials

Local trials (enrolling soon)

- **RECLAIM**

- Recovering from CCOVID-19
Lingering symptoms Adaptive
Integrative Medicine
- 6-month duration
- Requires at least **2** in-person visits
at BC Women's Hospital
- 3 arms
 - 2 interventions, 1 placebo

- **LDN**

- Low Dose Naltrexone
- 16-week duration
- Fully virtual
- 2 arms
 - 1 intervention, 1 placebo



Some International trials

- RECOVER VITAL (NIH)
 - Paxlovid vs placebo

- RECOVER-NEURO (NIH)

(ways to improve memory/attention/brain processing speed)

- Transcranial direct current stimulation (tDCS)
- online goal management training program for people with PASC



Long Term Consequences

(most of data from “pre-vaccine” era)



OPEN

Long-term cardiovascular outcomes of COVID-19

Yan Xie ^{1,2,3}, Evan Xu ^{1,4}, Benjamin Bowe^{1,2} and Ziyad Al-Aly ^{1,2,5,6,7} 

February 2022



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Summary of VA study

- Pre-vaccination era
- Compared 155 thousand COVID19 patients with 5 million contemporary and 5 million historical controls
- They looked at excess burden of disease at 1 year per 1000 people

CVD	A. Fib	Ischemic Heart disease	NICMO	Thrombotic disorders
4.03	10.7	5.35	3.56	5.47

Cardiac complications following respiratory illnesses not “new”

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H., Hannah Chung, M.P.H., Natasha S. Crowcroft, M.D., Timothy Karnauchow, Ph.D., Kevin Katz, M.D., Dennis T. Ko, M.D., Allison J. McGeer, M.D., Dayre McNally, M.D., Ph.D., David C. Richardson, M.D., Laura C. Rosella, Ph.D., M.H.Sc., et al.

January 2018



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Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales

Circulation, September 2022

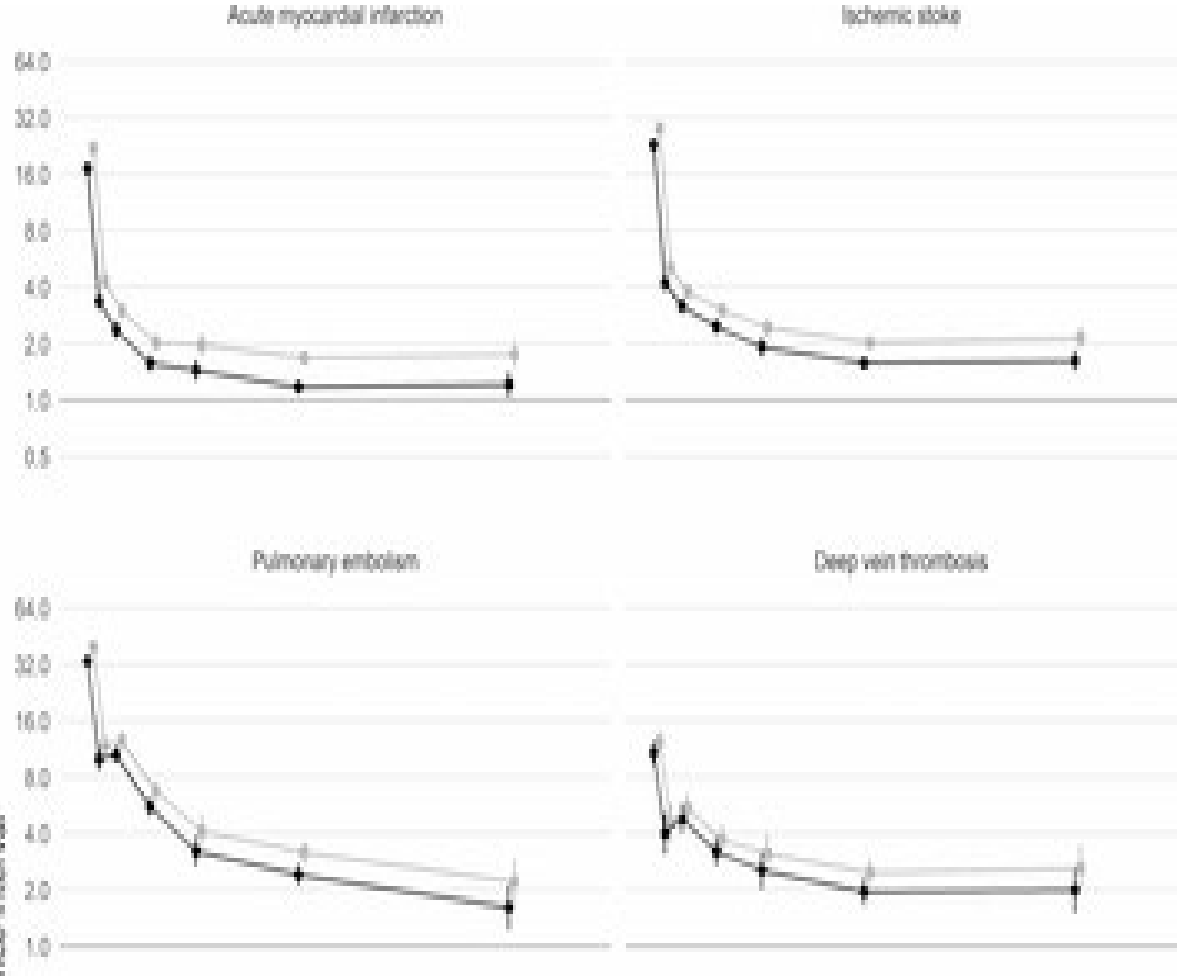
- Once again, data collected from January-December 2020
- Hospitalized risk > community risk

	Week 1	Week 27-49
Arterial Thromboses (HR)	21.7	1.34
VTE (HR)	33.2	1.80

7200 additional arterial thromboses and 3500 additional VTE events after 1.4 million COVID-19 diagnoses.



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Rochelle Knight. Circulation. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales, Volume: 146, Issue: 12, Pages: 892-906, DOI: (10.1161/CIRCULATIONAHA.122.060785)

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Pearls

- This condition exists, despite lack of diagnostic clarity and tests
- Your first job is to rule out other “organic” causes
- Treatment remains largely supportive
- Most will demonstrate recovery over time
- We will hopefully have more answers, evidence, and therapeutics soon

Thank you for your time

- Zachary.schwartz@vch.ca



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