Update on Long COVID

Stanford MEDICINE

2025 AAIM Annual Meeting

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multidisciplinary clinical and research program

Disclosures

Research funding from Pfizer, Inc. for the STOP-PASC clinical trial

Impact of Long COVID

- Est. 400 million people impacted by Long COVID worldwide[1]
- Annual economic impact of approx. $1 trillion[1]
- **5% of all Adult Americans <u>still</u> experiencing Long COVID**[2]

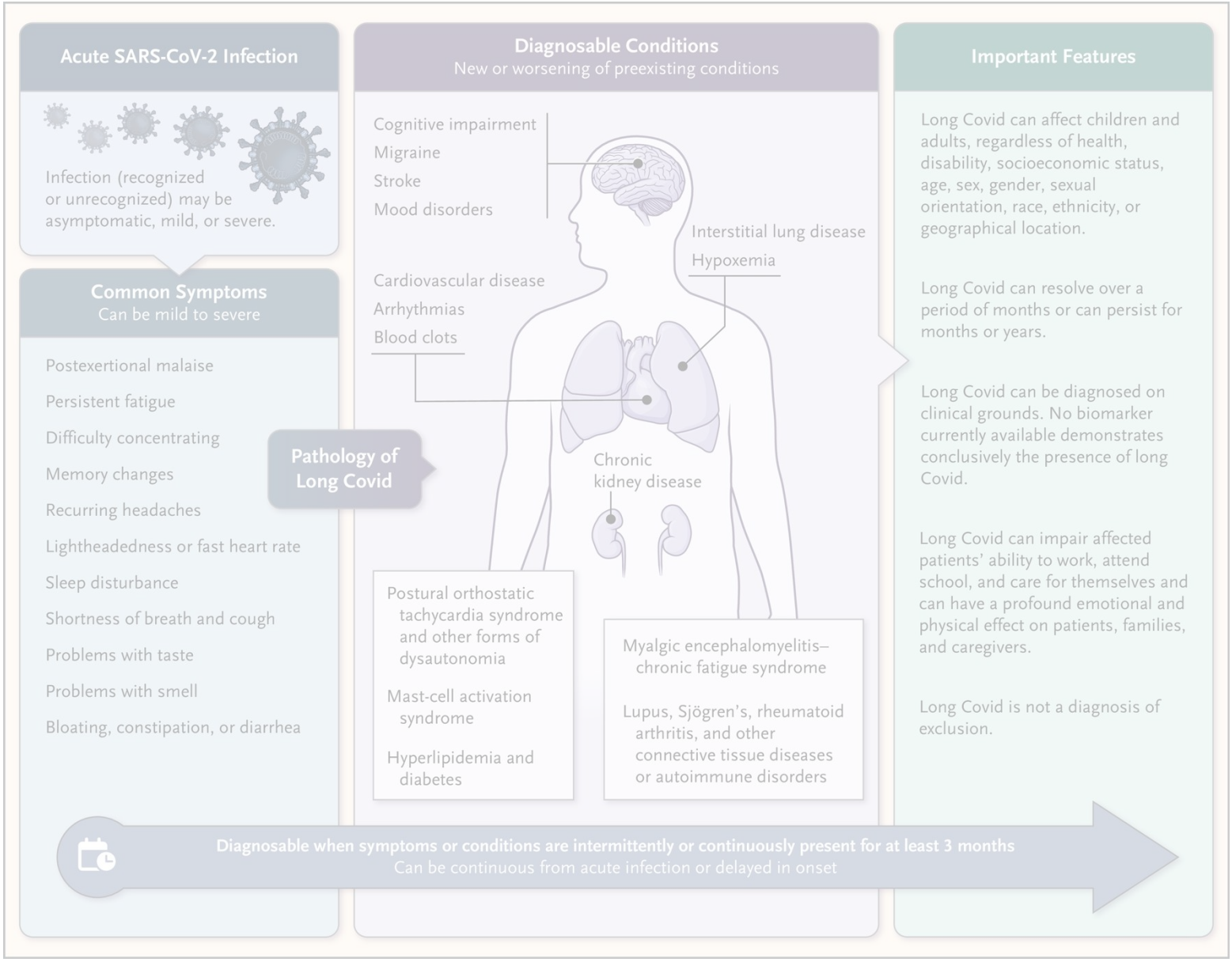
https://www.nbcnews.com/health/health-news/5-years-later-long-covid-still-medical-mystery-scientists-learned-rcna195608

1. Al-Aly et al. ***Nat. Med.*** (2024)
2. **CDC** National Center for Health Statistics (Aug 2024)

What is Long COVID?

2024 NASEM Definition:

Long COVID is an **infection-associated chronic condition** that occurs after SARS-CoV-2 infection and is present for **at least 3 months** as a continuous, relapsing and remitting, or progressive disease state that affects **one or more organ systems**.



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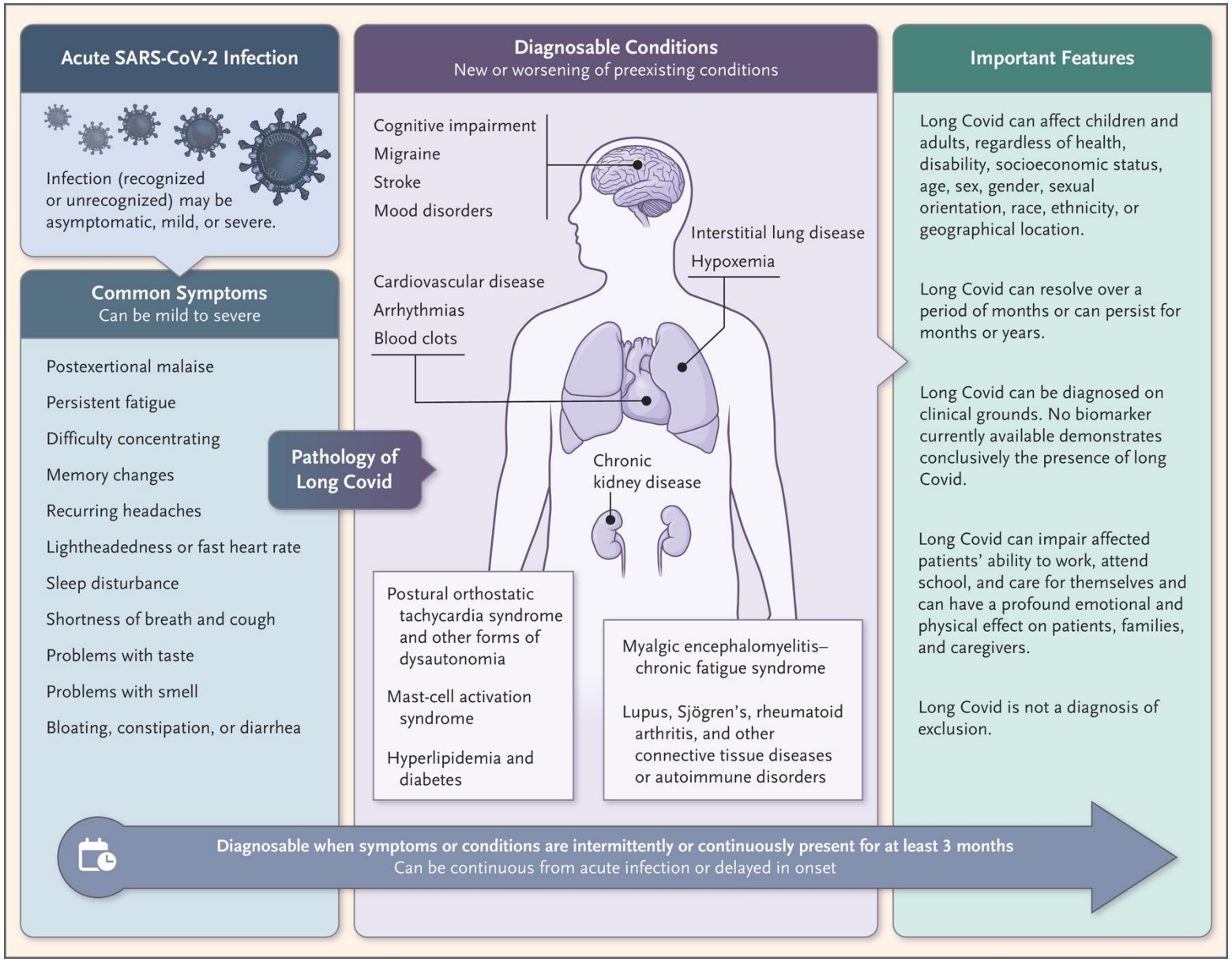

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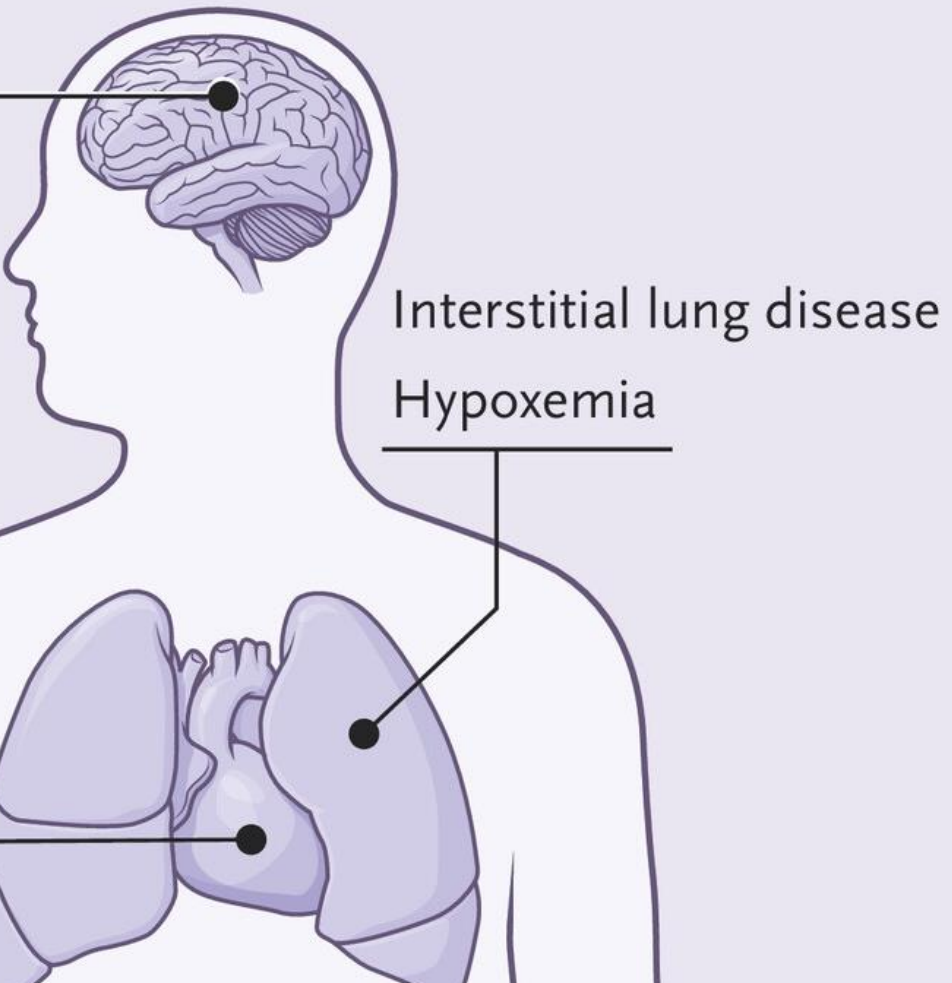
osable Conditions
ing of preexisting conditions



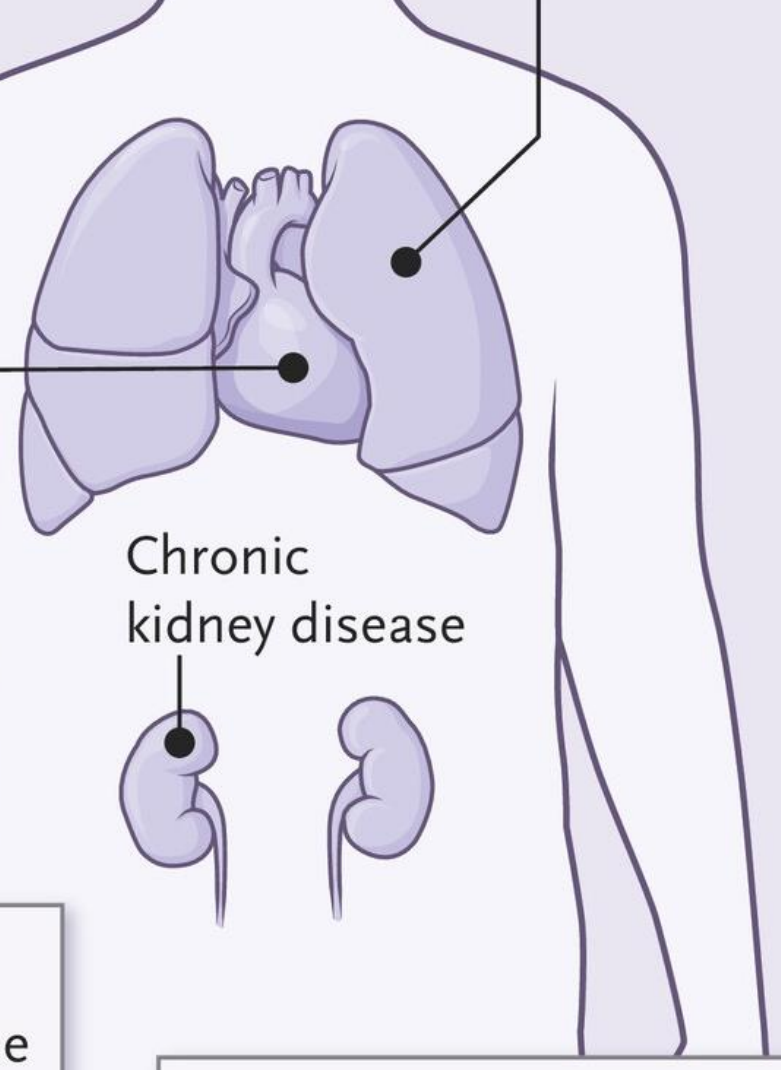
Important Features

Long Covid can affect children and adults, regardless of health, disability, socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographical location.

Long Covid can resolve over a period of months or can persist for months or years.

Long Covid can be diagnosed on clinical grounds. No biomarker currently available demonstrates

Ely et al. ***NEJM*** (2024)



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Long Covid can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of long Covid.

Long Covid can impair affected patients' ability to work, attend school, and care for themselves and can have a profound emotional and physical effect on patients, families, and caregivers.

Long Covid is not a diagnosis of exclusion.

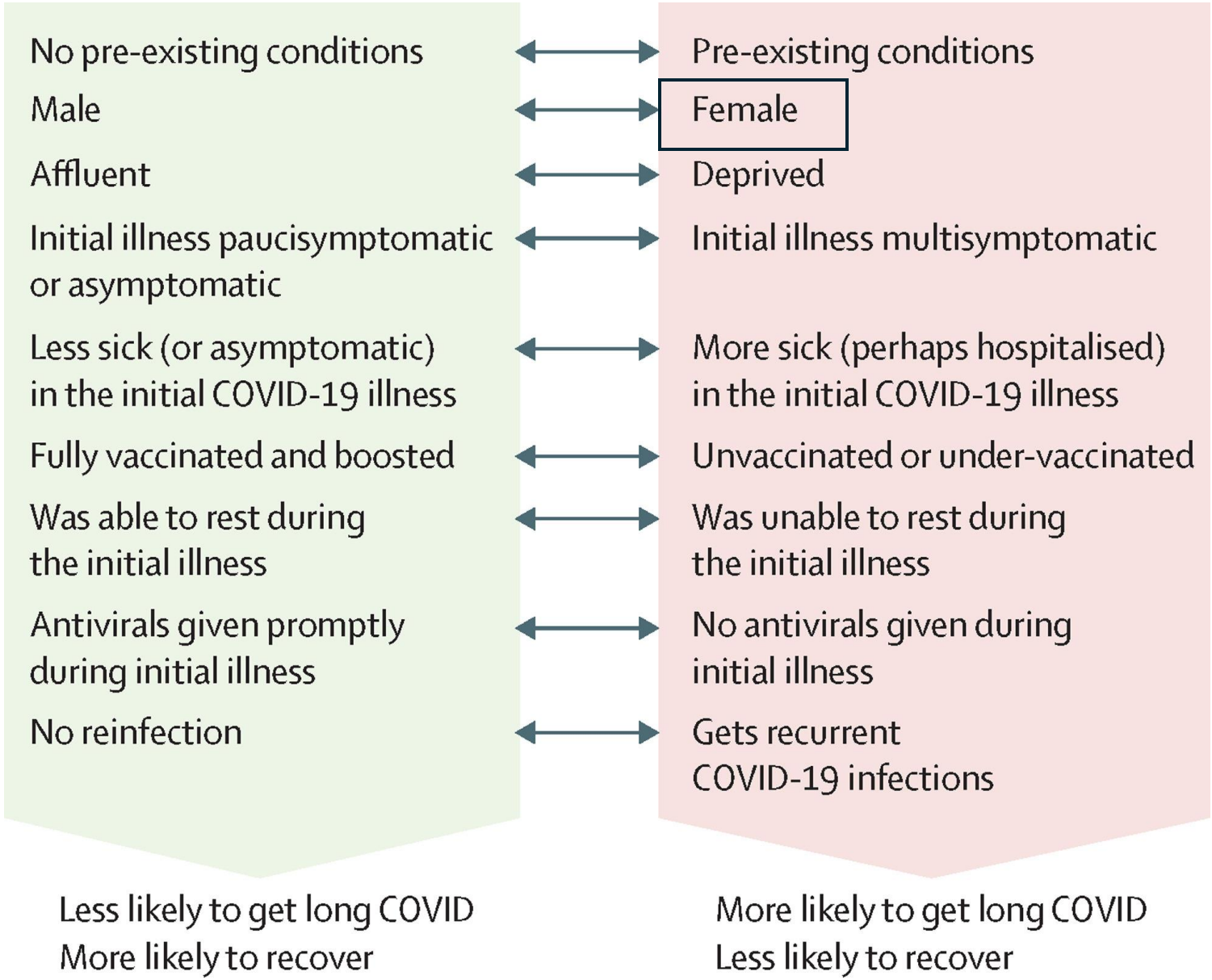
Myalgic encephalomyelitis–chronic fatigue syndrome

Lupus, Sjögren's, rheumatoid arthritis, and other

Ely et al. ***NEJM*** (2024)

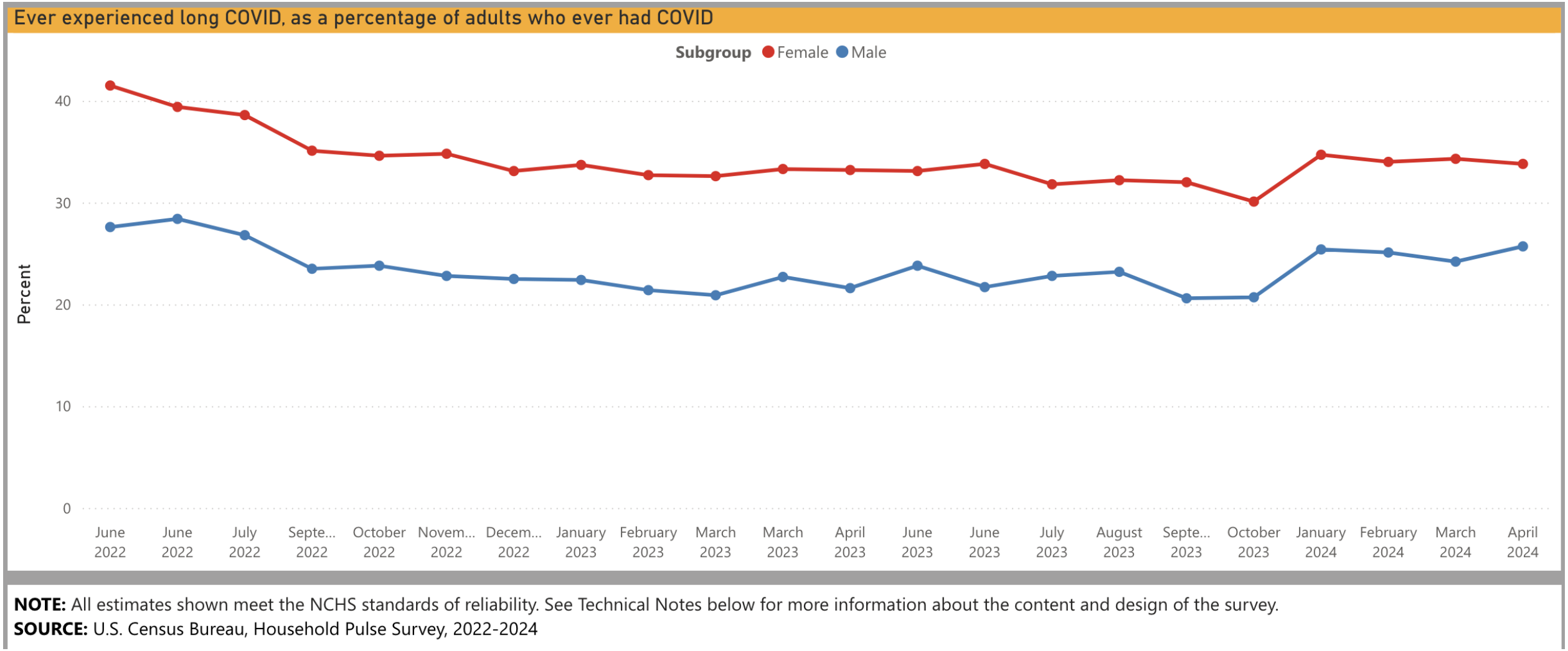
Who gets Long COVID?

ANYONE can get Long COVID, but certain factors may decrease or increase risk of developing it.



Greenhalgh et al. *The Lancet* (2024)

Female adults who ever had COVID have higher rates of Long COVID than males



NOTE: All estimates shown meet the NCHS standards of reliability. See Technical Notes below for more information about the content and design of the survey.
SOURCE: U.S. Census Bureau, Household Pulse Survey, 2022-2024

https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

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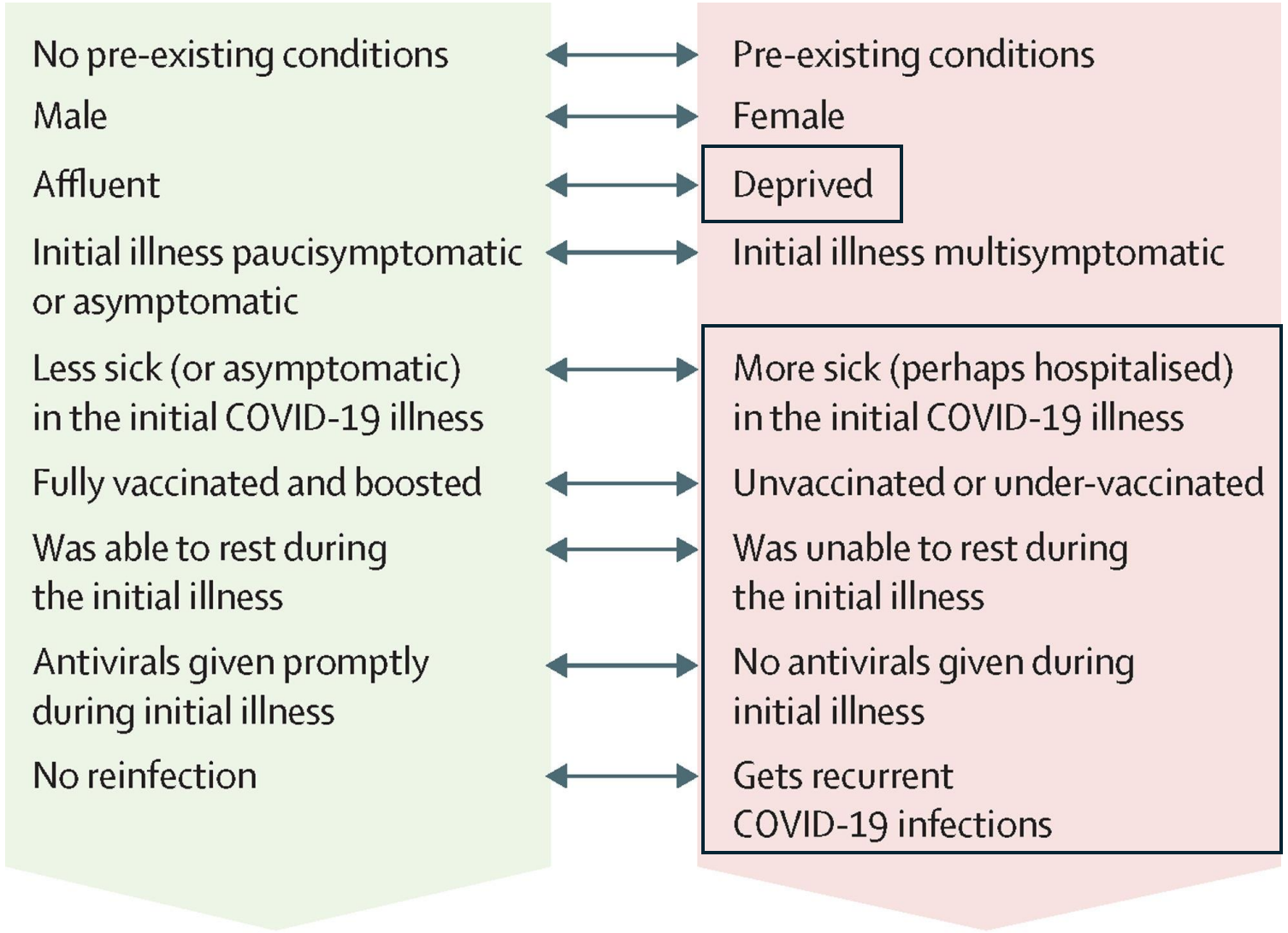

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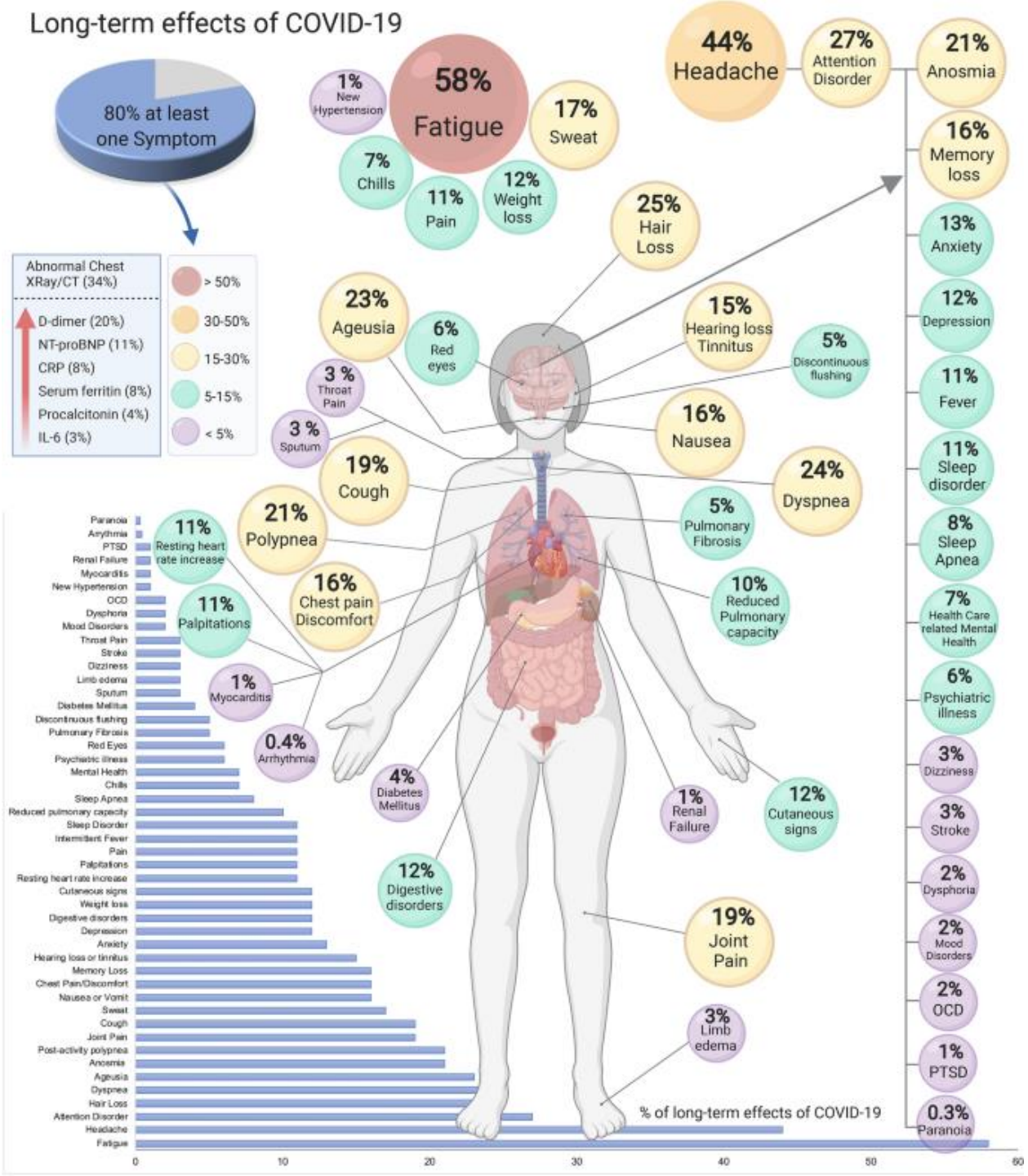
How does Long COVID manifest?

Myriad of Long COVID symptoms

How do we make sense of it all?



Lopez-Leon et al. *Sci Rep* (2021)

Most distinguishing LC symptoms

- **13,647 adults** prospectively followed in RECOVER cohort study (with and without SARS-CoV2 infection)
- Most distinguishing symptoms were **loss of smell/taste** & **post-exertional malaise**

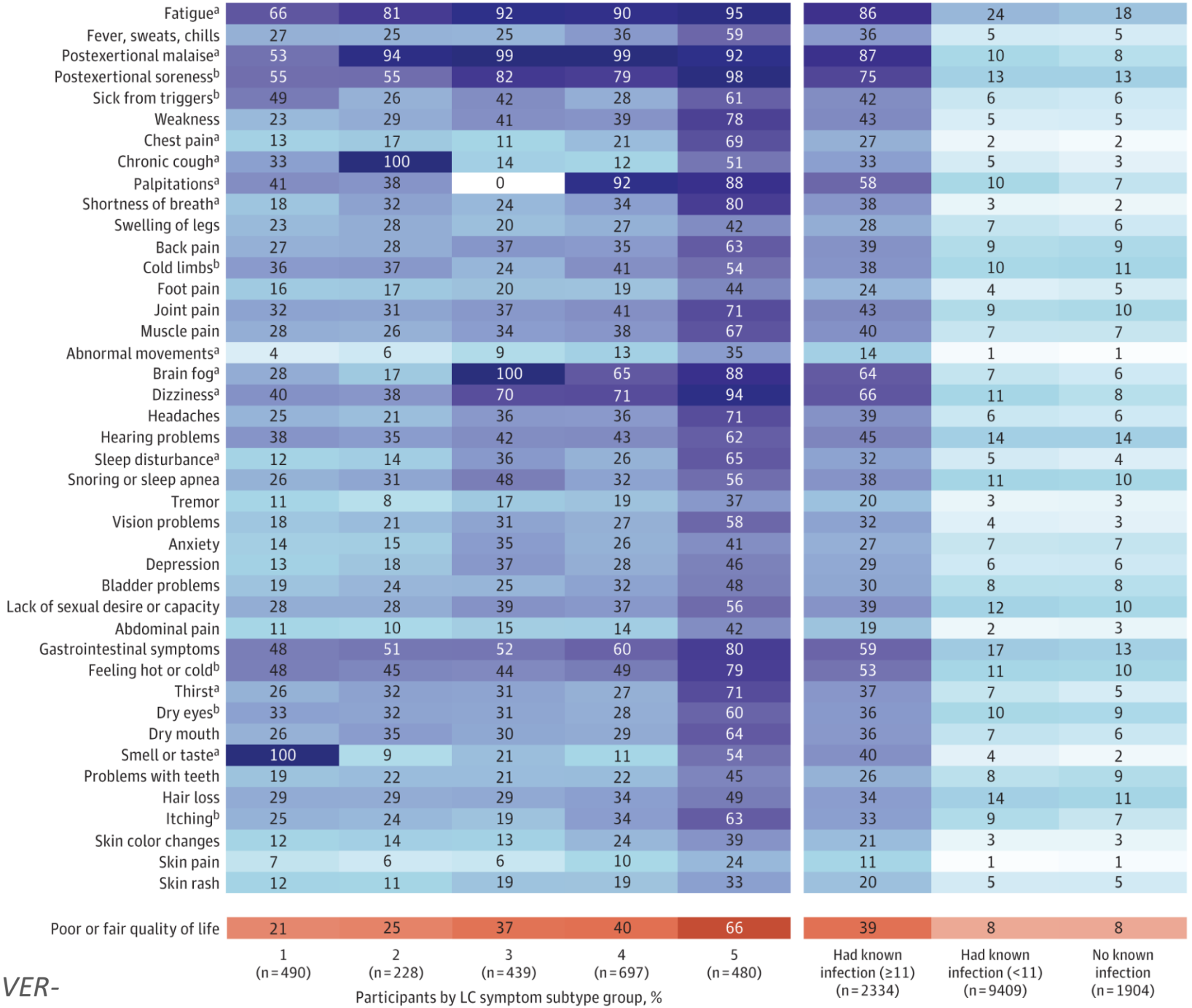
Table. Model-Selected Symptoms and Associated Points[a]

Symptom	2024 analysis[b]	
	Log odds ratio	Points[d]
Score contributors to the 2024 model		
Loss of smell or taste	0.734	7
Postexertional malaise	0.599	6
Chronic cough	0.436	4
Brain fog[e]	0.273	3
Thirst	0.062	1
Palpitations	0.234	2
Chest pain[e]	0.132	1
Fatigue[e]	0.138	1
Dizziness	0.168	2
Shortness of breath	0.182	2
Snoring or sleep apnea	0.060	1
Score contributors to the 2023 but not 2024 model		
Lack of sexual desire or capacity	0	0
Gastrointestinal symptoms	0	0
Abnormal movements	0.010	0
Hair loss	0	0
Sleep disturbance	0.038	0

Geng et al. *JAMA* (2024) *2024 Update of the RECOVER-Adult Long COVID Research Index*

Complex Phenotypes of Long COVID

- **Fatigue and Post-Exertional Malaise** are extremely common across all 5 clusters
- Quality of life and function worsens as symptom burden increases



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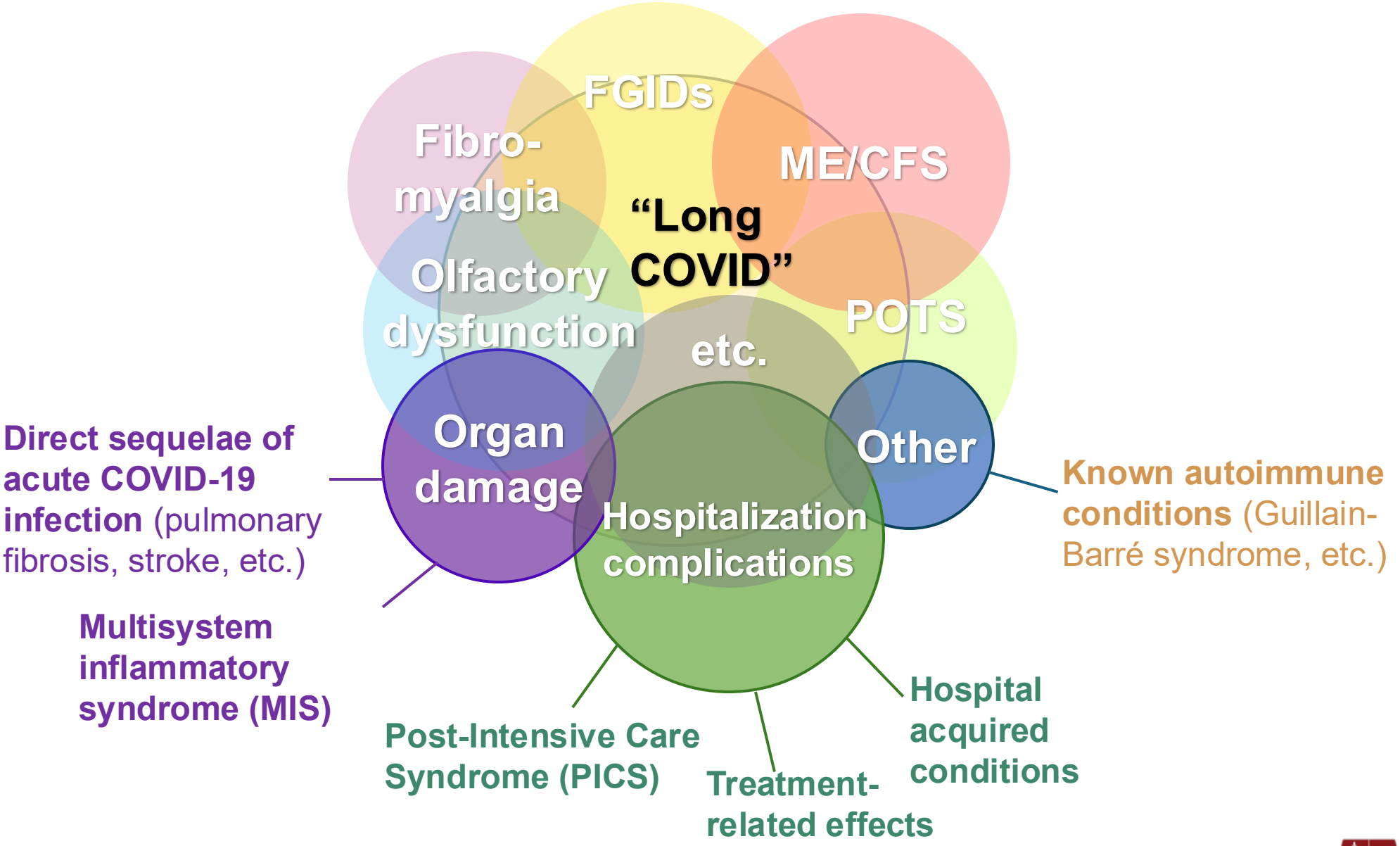
Long COVID: A Syndrome of Syndromes



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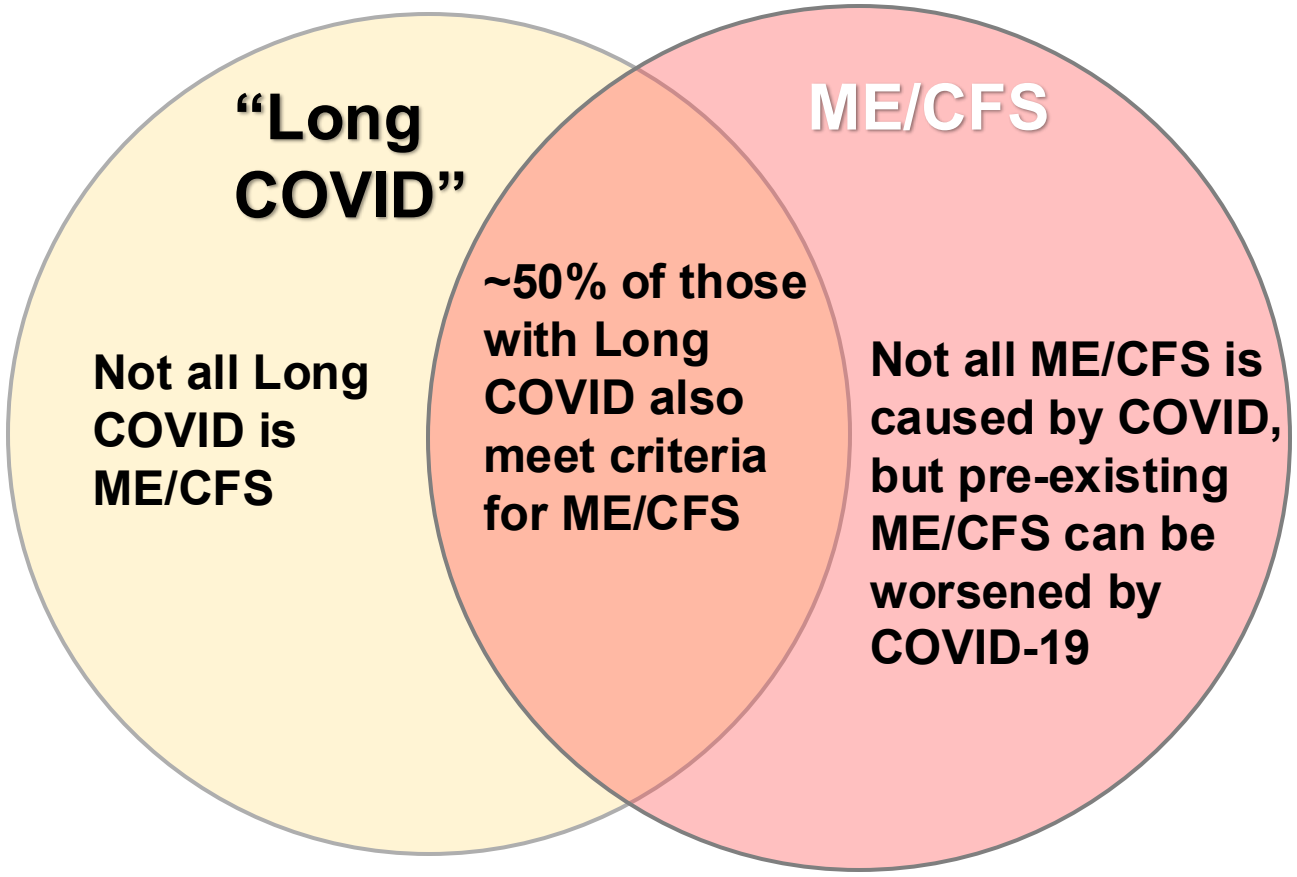
Long COVID: overlap with ME/CFS



2015 IOM Criteria for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS):

>6 months debilitating fatigue
Post-exertional malaise
Unrefreshing sleep
Brain fog or orthostatic intolerance

https://www.cdc.gov/me-cfs/hcp/diagnosis/iom-2015-diagnostic-criteria-1.html

1. Bonilla et al. *Front Neurol* (2023)
2. Komaroff & Dantzer. *Cell Rep Med* (2025)

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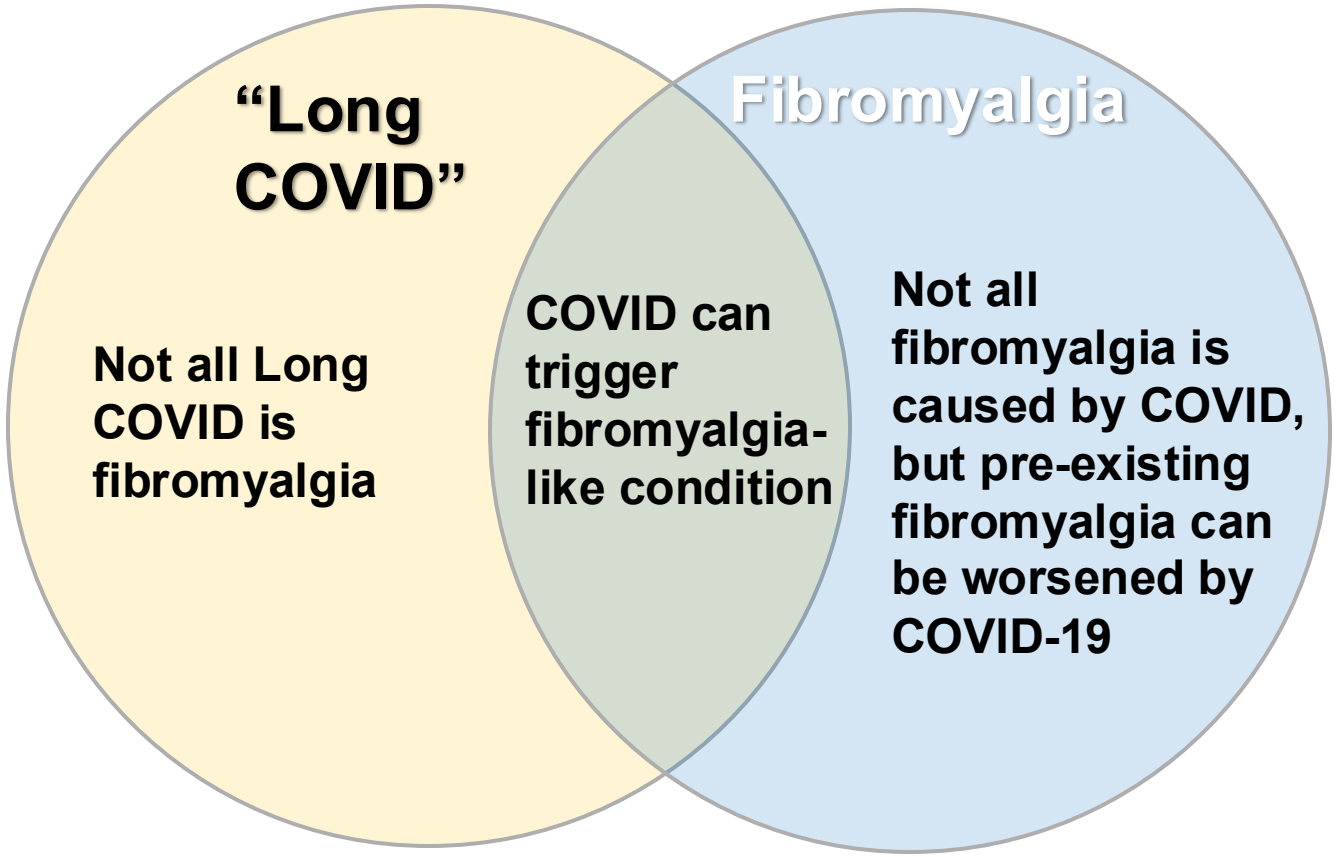
Long COVID: overlap with fibromyalgia



Fibromyalgia main features:

- Chronic widespread pain & tenderness
- Fatigue
- Sleep issues

https://www.niams.nih.gov/health-topics/fibromyalgia

1. Clauw & Calabrese. *Ann Rheum Dis* (2024)
2. Goldenberg. *Semin Arthritis Rheum* (2024)

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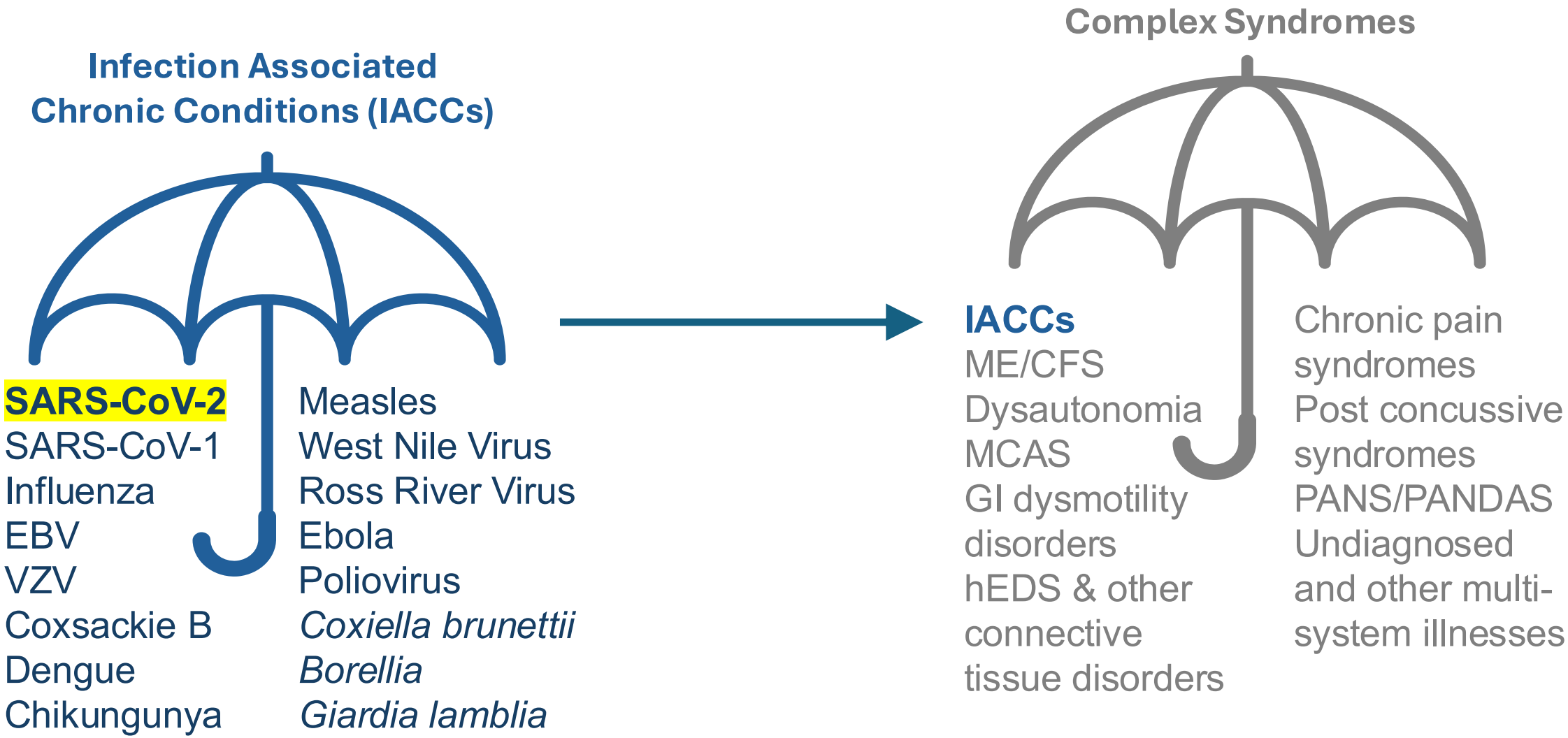
Beyond Long COVID: Umbrella and Overlap Syndromes



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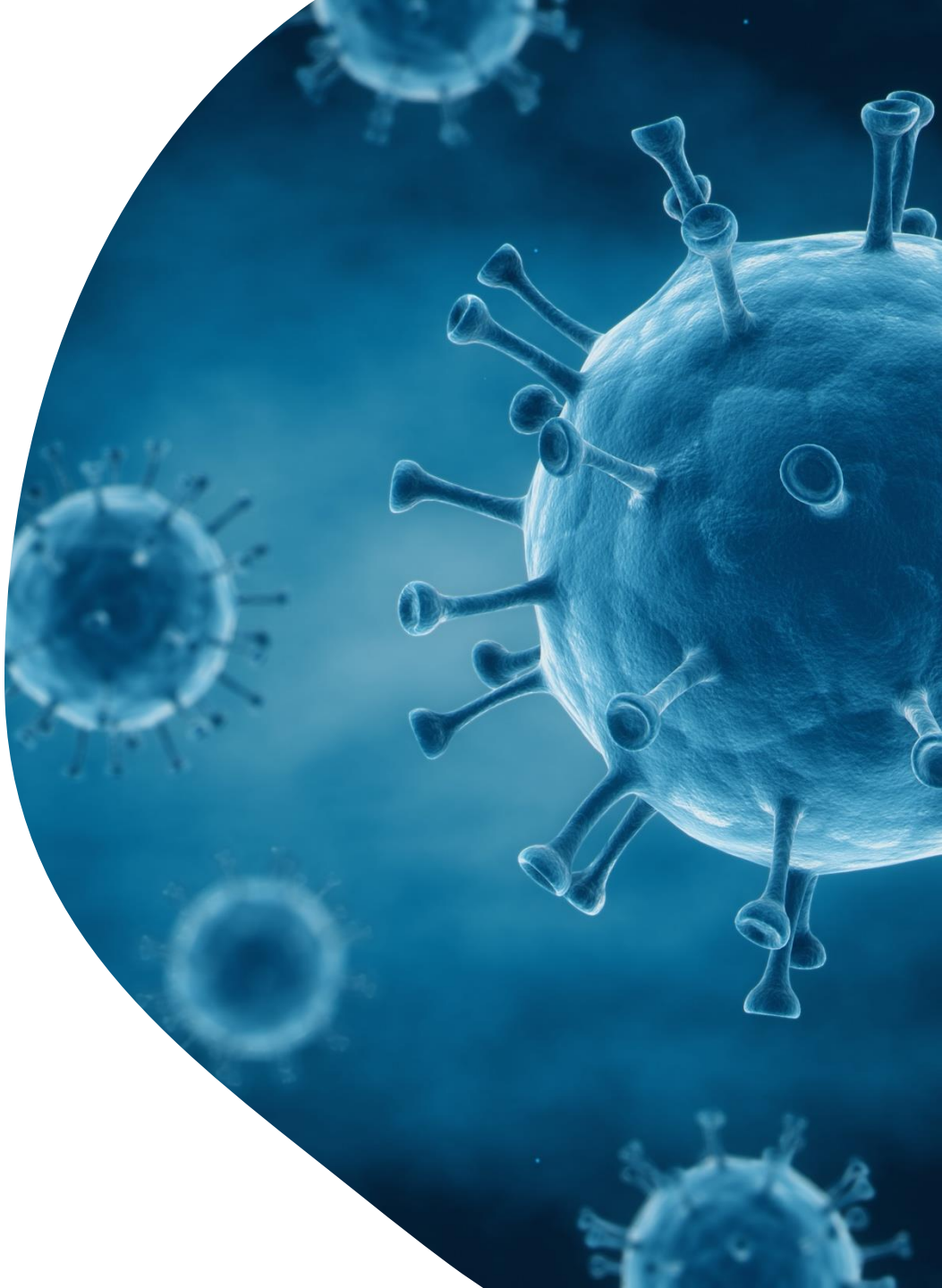
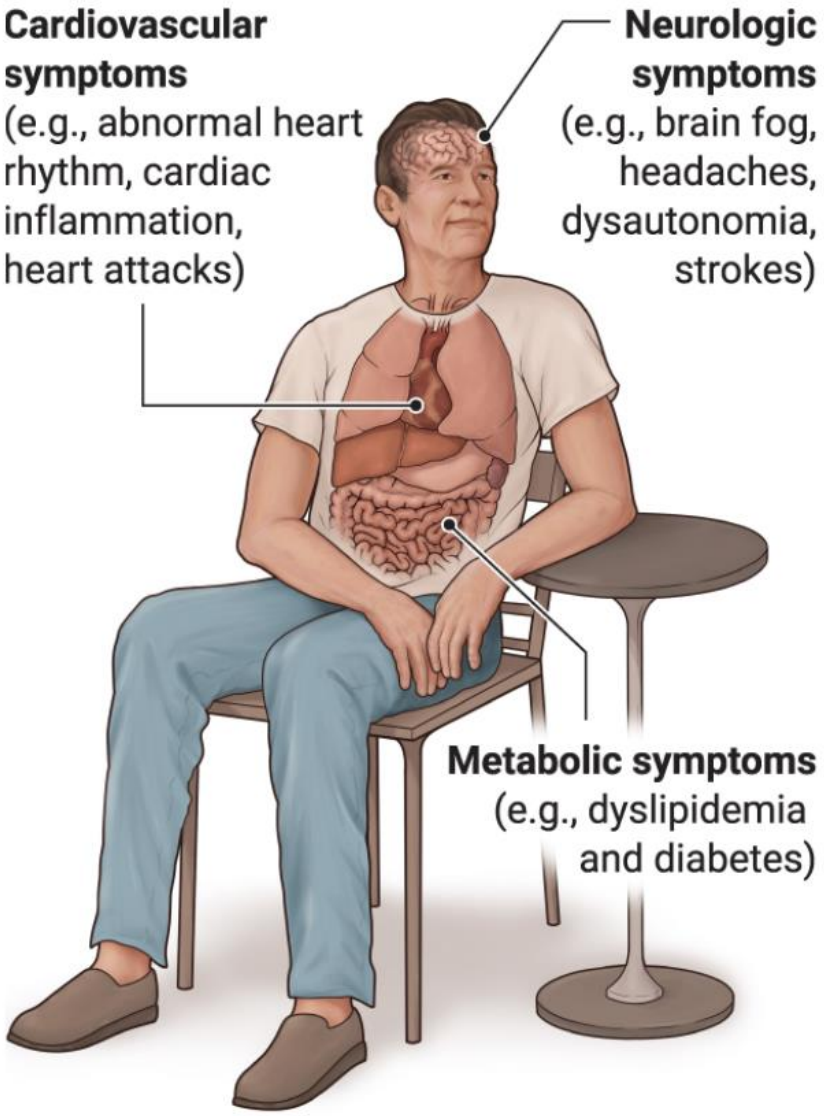
What **causes** Long COVID?



Leading Models of Disease Pathogenesis



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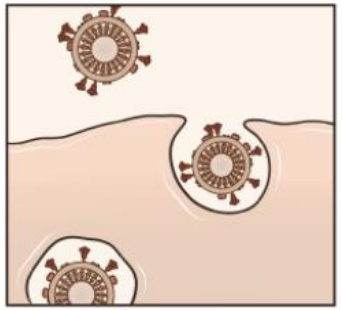

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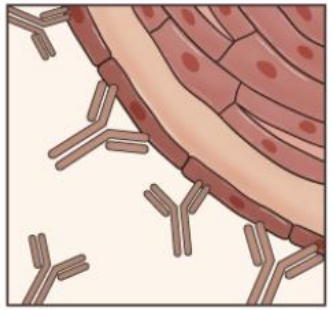
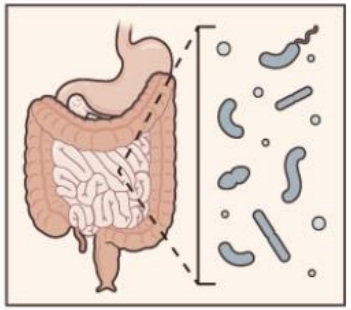


Immune dysregulation may increase immune reactivity.



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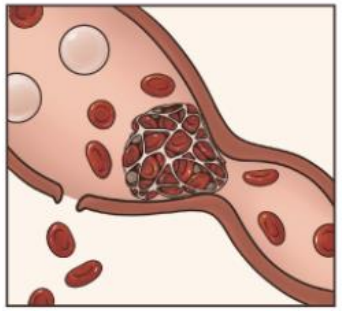

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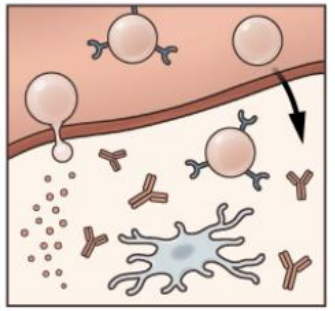

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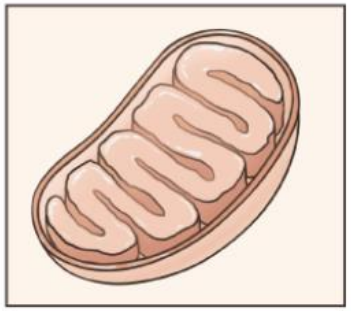


Mitochondrial dysfunction may impair metabolism and lead to fatigue and metabolic symptoms.

Al-Aly, Topol. *Science*. 2024

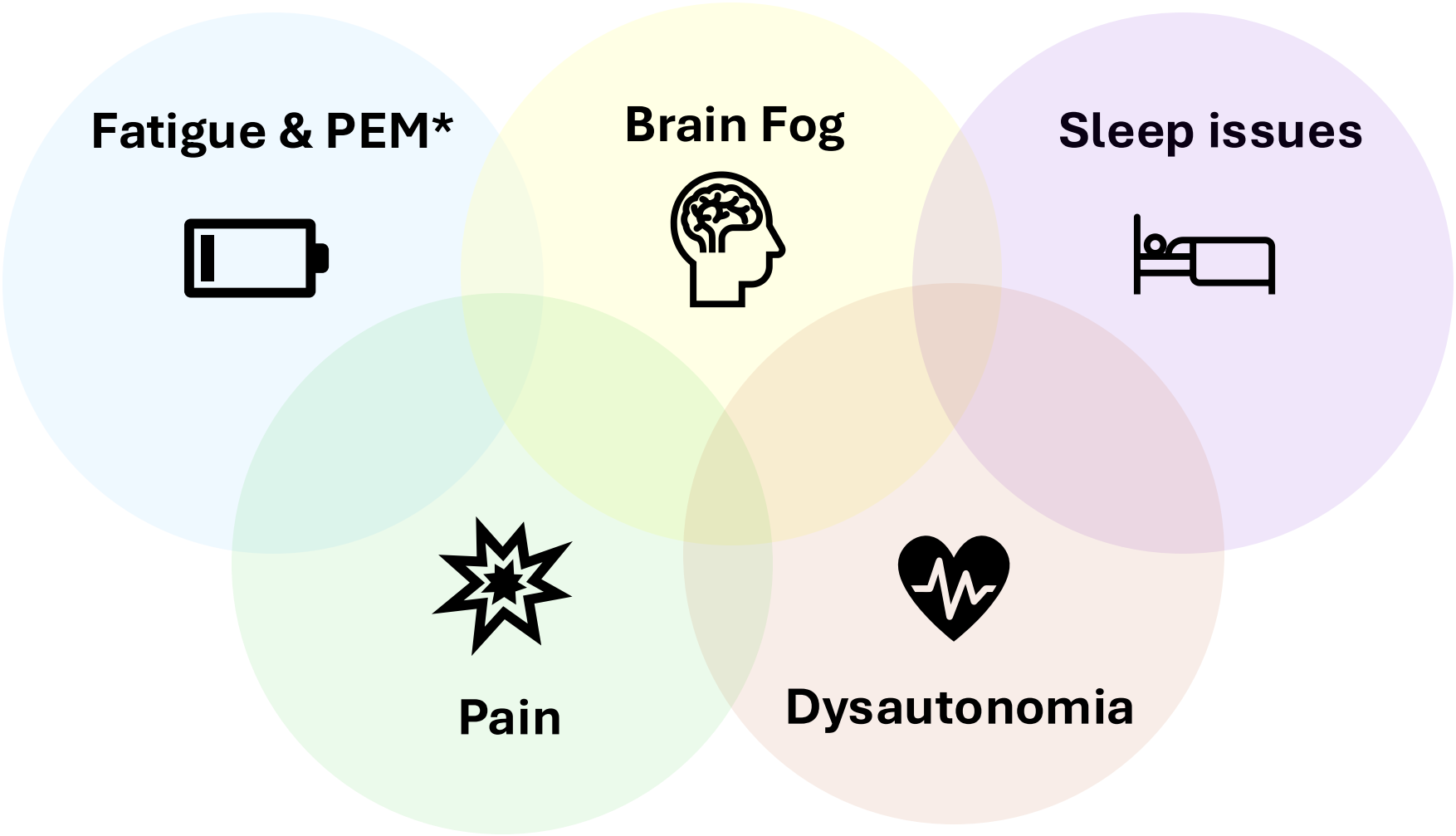
Preventing Long COVID

- **Preventing acute COVID** is the only guarantee (infection prevention measures).
- People with acute COVID-19 infection should ensure they **rest**.
- **Vaccination** (meta-analysis)
  - 620 221 participants, two doses of vaccine reduces LC by 36.9% and three doses by 68.7%
  - Decreased risks of cardiovascular especially after third dose
- **Antivirals and other agents** may reduce the risk of LC.
  - Nirmatrelvir
  - Molnupiravir
  - Ensitrelvir
  - Metformin

Marra et al. Antimicrob Steward Healthc Epidemiol. 2023
Xu Y et al. Eur Heart J. 2025
Jiang et al. J Infect. 2024
Xie et al, JAMA Intern Med. 2023
Yotsuyanagi et al. Antiviral Res. 2024

Recognizing Long COVID

Big 5 Common Manifestations



*PEM: post-exertional malaise

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Diagnosing Long COVID is based on Clinical Evaluation

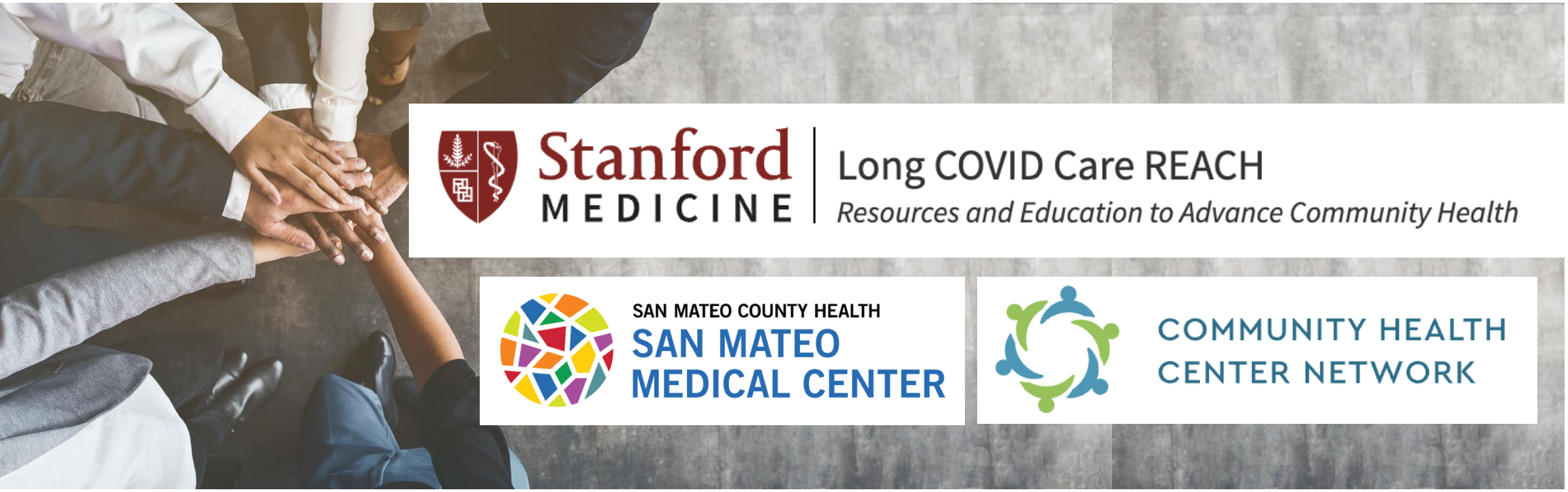
- Full clinical history and patient's pre-morbid conditions

- Relevant laboratory studies to evaluate for co-existing conditions (thyroid, blood count, metabolic panel, vitamins, etc.)

  Routine laboratory studies have NOT been shown to be specific for Long COVID

- Long COVID clinical diagnosis (ICD U09.9 code) guided by broad NASEM definition (3+ months of symptoms)

Erlandson et al. *Ann Intern Med*. (2024)
Ely et al. *NEJM* (2024)



Stanford MEDICINE | Long COVID Care REACH

Resources and Education to Advance Community Health

SAN MATEO COUNTY HEALTH
SAN MATEO MEDICAL CENTER

COMMUNITY HEALTH CENTER NETWORK

https://goto.stanford.edu/REACH

Stanford MEDICINE | Department of Medicine

Team Science

AHRQ Agency for Healthcare Research and Quality

UNRAVELING LONG COVID: Advances in Clinical Practice

Prior CME Webinar recordings from Aug, 2024 (Session 1):
https://stanford.cloud-cme.com/course/courseoverview?P=5&EID=52228

Recent CME Webinar recordings from May, 2025 (Session 2):
https://stanford.cloud-cme.com/course/courseoverview?P=5&EID=52660

Equity
ME/CFS
Autonomic
Cardiac
Pulmonary
Vaccines
Sleep
Smell/Taste
Headaches
Gastrointestinal
Coagulation/Hematologic
Behavioral health
Speech Therapy
Physical Therapy
Integrative Medicine

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Consensus Guidance Statements

https://www.aapmr.org/advocacy/current-priorities/long-covid-pasc

aapm&r

View our Mental Health Guidance Statement

View our Neurological Symptoms Guidance Statement

View our Autonomic Dysfunction Guidance Statement

View our Pediatrics Guidance Statement

View our Cardiovascular Complications Guidance Statement

View our Cognitive Symptoms Guidance Statement

View our Breathing Discomfort Guidance Statement

View our Fatigue Guidance Statement

Long COVID Compendium

Long COVID Treatment/Management

- Individually-tailored and patient-centered
  - targeting symptoms/syndromes and pathobiology models
- Multi/inter-disciplinary care often needed
- Rehabilitation strategies (especially within first 6 months)
  - Pacing strategies (avoiding post-exertional crashes)
  - Tailored physical therapy (including breathing exercises)
  - Cognitive and speech rehabilitation
- Potential off-label medications (currently no FDA-approved drugs)
- Enrollment in clinical trials if appropriate
- Wraparound services:
  - psychosocial support
  - disability navigation, etc.

Targeted treatments for Long COVID?

- Urgent need for rigorous clinical trials
- Unlikely to be one-size-fits-all

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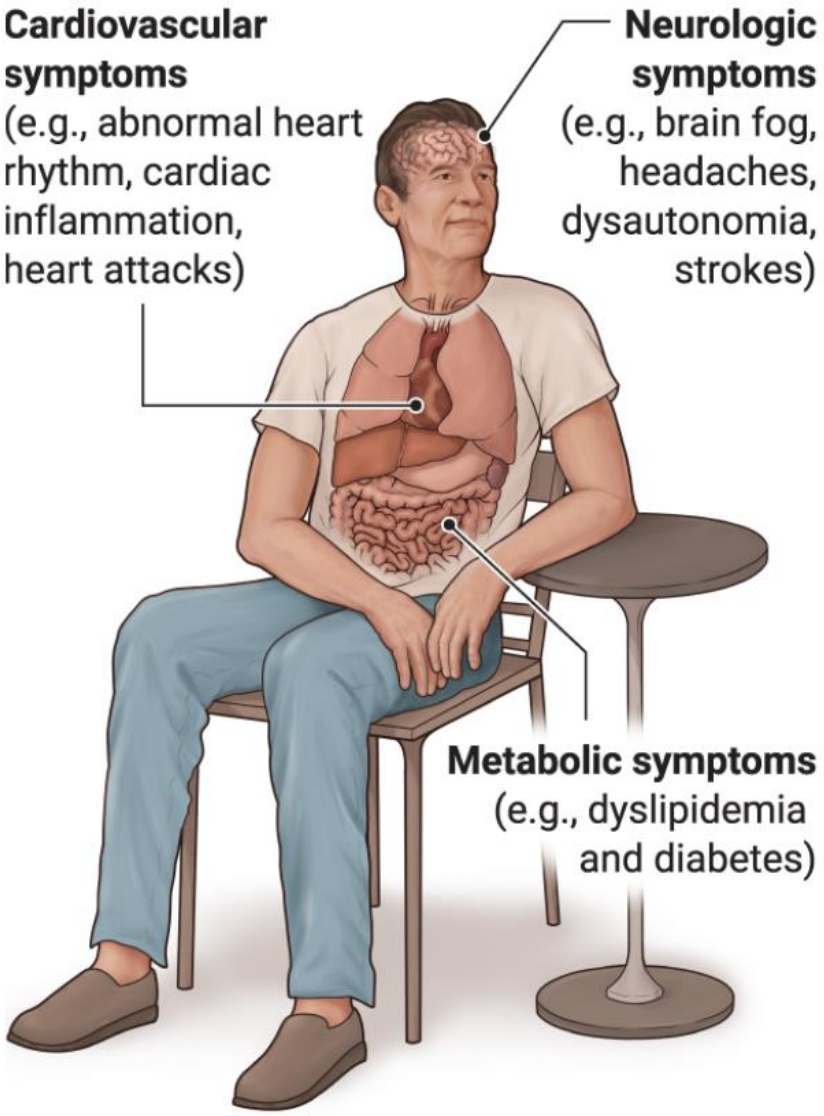
Leading Models of Disease Pathogenesis



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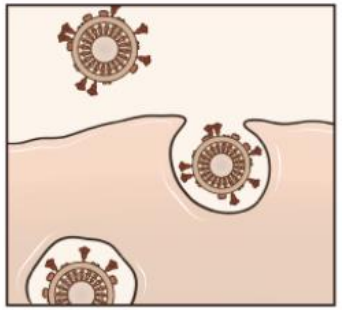

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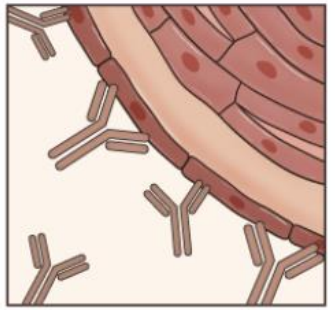

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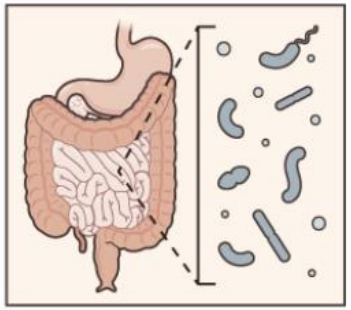

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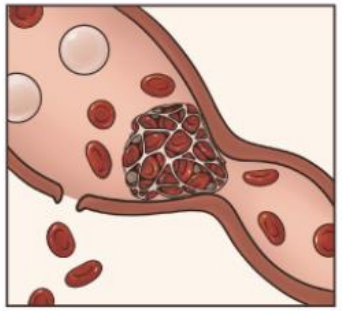

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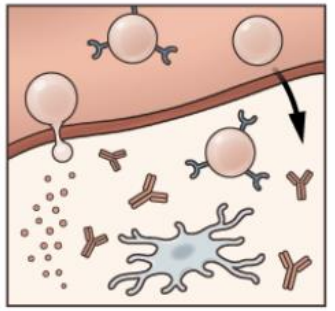

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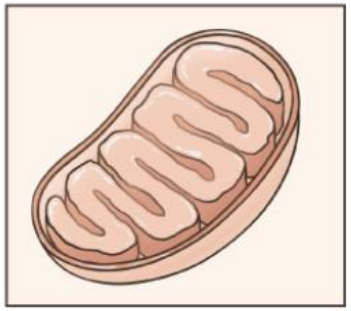

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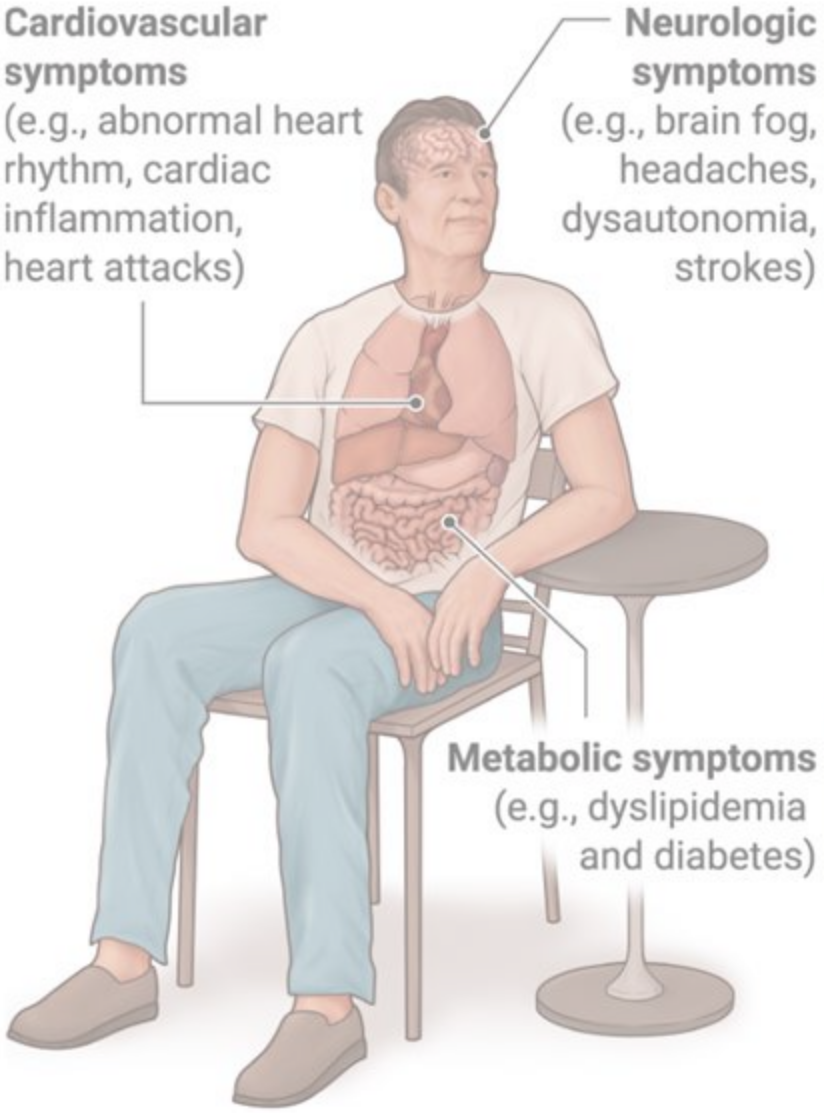
Al-Aly, Topol. *Science*. 2024

Therapeutic Candidates Targeting Mechanistic Pathways

Nirmatrelvir



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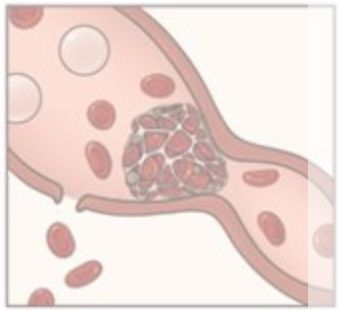

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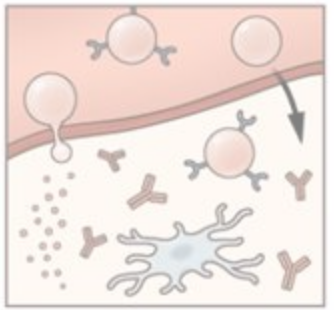

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Al-Aly, Topol. (2024*) Science*. doi: 10.1126/science.adl0867

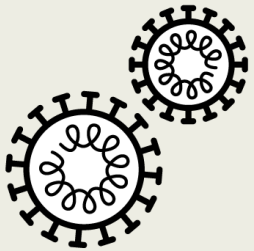
Clinical Trials: Paxlovid 15 days (no benefit)

JAMA Internal Medicine

RCT: Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection

POPULATION

63 Men, 92 Women



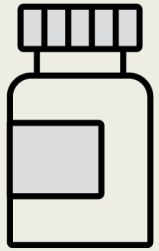
Adults with at least 3 mo of moderate to severe postacute sequelae of SARS-CoV-2 infection (PASC) symptoms

Median (IQR) age, 43 (34-54) y

INTERVENTION

155 Participants randomized

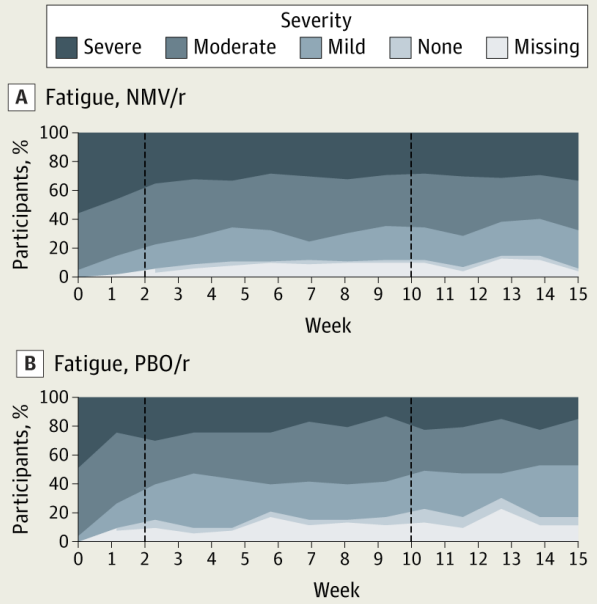
102 Nirmatrelvir-ritonavir (NMV/r)
Oral NMV/r, 300 mg/100 mg, twice daily for 15 d



53 Placebo-ritonavir (PBO/r)
Oral PBO/r twice daily for 15 d

FINDINGS

At 10 wk, no statistically significant difference was found in the model-derived severity outcome pooled across 6 core symptoms (eg, fatigue) between the NMV/r and PBO/r groups



SETTINGS / LOCATIONS

1 US medical center

PRIMARY OUTCOME

Severity of 6 PASC symptoms (fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, and cardiovascular symptoms) based on Likert score (0, none; 1, mild; 2, moderate; 3, severe) at 10 wk

Geng LN, Bonilla H, Hedlin H, et al. Nirmatrelvir-ritonavir and symptoms in adults with postacute sequelae of SARS-CoV-2 infection: the STOP-PASC randomized clinical trial. *JAMA Intern Med*. Published online June 7, 2024. doi:10.1001/jamainternmed.2024.2007

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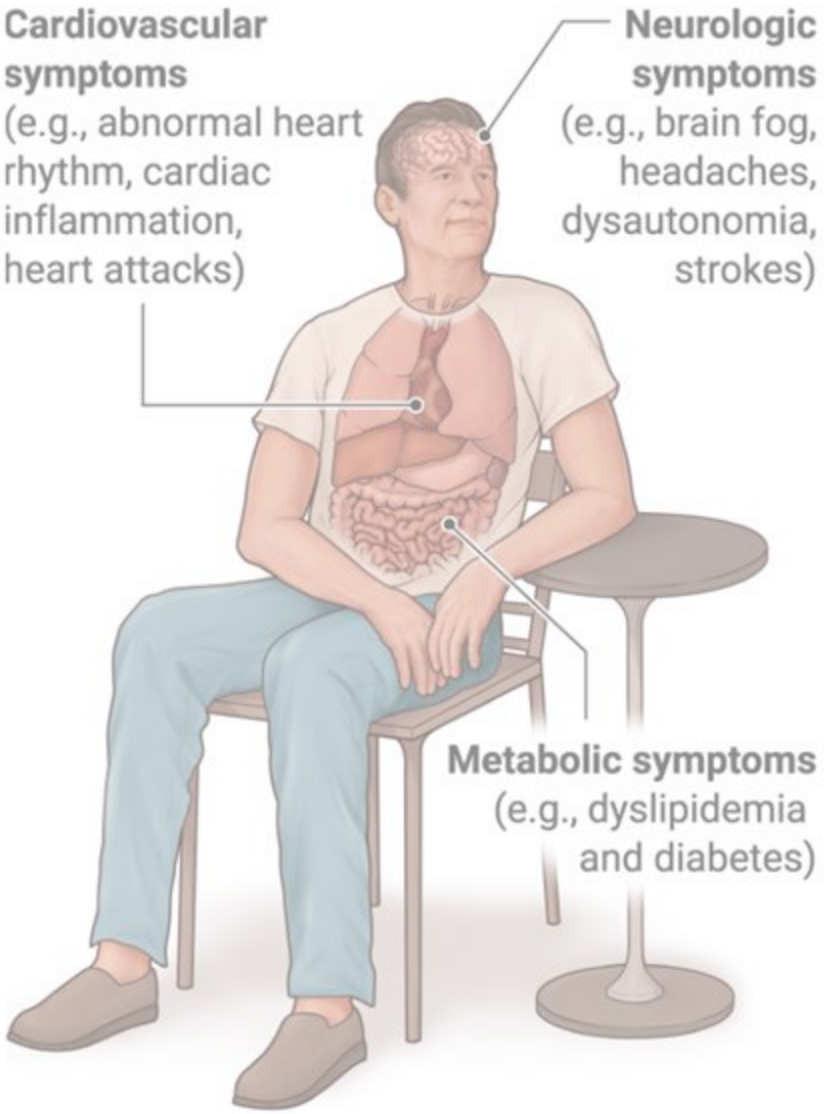
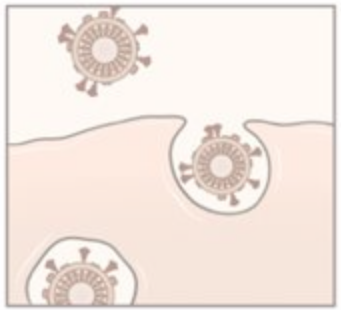
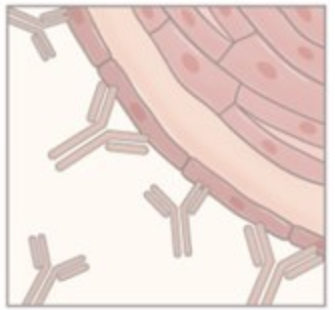
Therapeutic Candidates Targeting Mechanistic Pathways



GRAPHIC: A. MASTIN/*SCIENCE*

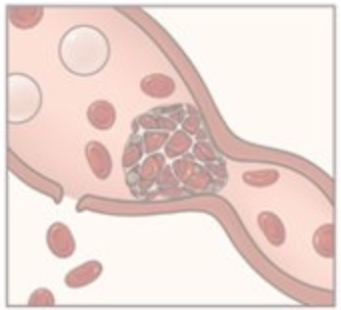


Viral persistence may cause inflammation and reactivate dormant viruses.



Immune dysregulation may increase immune reactivity.

Microbiome dysbiosis may impair gut-brain signaling and metabolic regulation.



Endothelial inflammation may activate coagulation cascades and elicit microthrombosis.

LDN

Neuronal inflammation may result from activated microglia and immune cells.

Mitochondrial dysfunction may impair metabolism and lead to fatigue and metabolic symptoms.

Al-Aly, Topol. (2024*) Science*. doi: 10.1126/science.adl0867

Clinical trials

RECOVER
Researching COVID to Enhance Recovery

HOME | ABOUT THE PROGRAM | CLINICAL TRIALS | FAQS

Ivabradine
IVIG

Autonomic Dysfunction

Dizziness, fast heart rate, shortness of breath, upset stomach, or other changes in body functions that happen automatically

BrainHQ
tDCS (device)
Rehabilitation

Cognitive Dysfunction

Brain fog, trouble thinking clearly, memory changes, slowed attention, and other symptoms related to brain function

Cardiopulmonary rehabilitation

Exercise Intolerance and Fatigue

Exhaustion or low energy that interferes with daily activities

Modafinil/Solriamfetol
Melatonin/Light therapy

Sleep Disturbances

Changes in sleep patterns or ability to sleep

Paxlovid up to 25 days

Viral Persistence

When the virus that causes COVID-19 stays in the body and causes damage to organs or the immune system to not function properly

Learn more → about why we are studying these focus areas

https://trials.recovercovid.org/

Rehabilitation (168)

- Exercise (51)
- General rehabilitation including telerehabilation (46)
- Respiratory muscle training (17)
- Cognitive rehabilitation (7)
- Virtual reality rehabilitation (7)
- Breathing and chest mobilization exercises (6)
- Olfactory training (6)
- Yoga rehabilitation (6)
- Heart rate variability biofeedback (2)
- Vocal-based respiratory training (2)
- Activity tracker and a bespoke mobile phone application
- Akili Interactive digital treatment 'AKL-T01'
- Benson's relaxation technique
- BREATHE program for long COVID
- Counterweight-Plus/DiRECT diet weight management program
- Long COVID optimal health program
- Lymphatic drainage massage
- Manual therapy (hand operated technique and breathing exercises)
- Neurofeedback therapy
- NexJ Connected Wellness
- Online singing, breathing and wellbeing program (ENO Breathe)
- PowerBreathe® and Therosold PEP® tools
- Proprioceptive training
- Rehabilitation robot (Luna by EGZOTech ©)
- REMM-HIIT
- Slow-paced breathing
- Sniffin' sticks Duftquartett
- Whole body vibration training

Psychotherapy (12)

- Cognitive behavioral therapy (3)
- Adhera® Digital Health Intervention
- Amygdala and insula retraining program
- HUS internet therapy for bodily stress syndromes
- LISTEN intervention
- Mind body syndrome therapy
- Mindful self-compassion training
- PACS coping and recovery intervention
- Telemedicine mindfulness-based protocol
- Wearable brain sensing wellness device (Muse™-S)

Education (4)

- Cognitive psychoeducation
- Education and strategies intervention
- Medical psychoeducational talks
- Pain and self-management education

Pharmacotherapy (77)

- Clochicine (5)
- Nintedanib (4)
- Pirfenidone (4)
- Ivermectin (2)
- Methylprednisolone (2)
- Mometasone (2)
- Montelukast (2)
- Prednisolone (2)
- Treamid (bisamide derivative of dicarboxylic acid) (2)
- Anhydrous enol-oxaloacetate
- Apixaban
- Atorvastatin
- AXA1125
- Bioarginina C
- Budesonide
- Caffeine
- Cerebrolysin
- Donepezil
- Echinochrome A
- Erythropoietin
- Famotidine
- Fampridine (sustained release)
- Fibrotac
- Gabapentin
- Immulina™ (spirulina)
- ImmunoSEB + ProbioSEB CSC3 (probiotic complex)
- Intranasal Insulin
- Ibudilast
- Ivabradine
- Lactoferrin
- Leronlimab

Pharmacotherapy Cont.

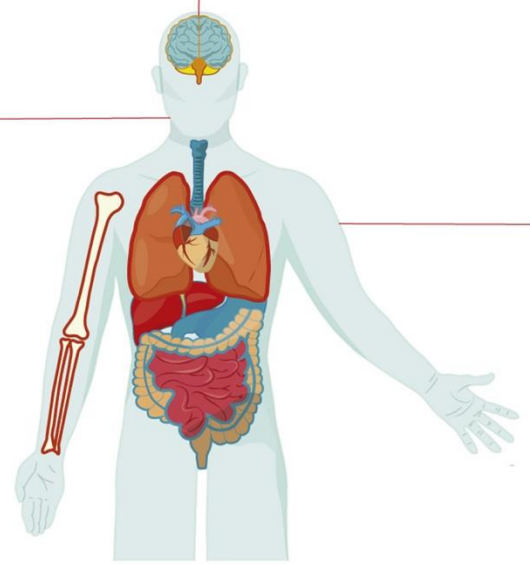
- Loratadine
- LYT-100 (deupirfenidone)
- Metoprolol succinate
- Mycophenolate mofetil
- MYMD1® (Isomyosmine)
- Naltrexone
- Niagen (vitamin B3)
- Omni-Biotic® Pro-Vi 5
- Pentoxifyinlline
- Pimozide
- Prednisone
- Prospekta
- Remdesivir
- Rivaroxaban
- Rosuvastatin
- RSLV-132
- Ruconest
- S-1226 (8%)
- Sacubitril / Valsarta
- Sodium pyruvate nasal spray
- Somatropin
- Sulodexide
- Taxifolin Aqua
- Temelimab (formerly GNbAC1)
- Theophylline
- TNX-102
- Vitamin D3
- Vortioxetine
- Xltran Plus™ or Xltran™
- Zofin™ (formerly Organicell Flow)

Complementary and Alternative Medcine (64)

- TCM (25)
- Ayurveda (24)
- Homeopathic medications (4)
- ADAPT-232 (Chisan®)
- Coenzyme Q10
- Cracie bojungikgi-tang extract
- Curcumin/boswellia serrata/ascorbic acid mixture
- Gyeongbang gyeongok-go
- Hanpoong Soonsimhwan
- IMMUNODAAT™ botanical ingredient
- Nutraceuticals
- Omega-3 (Eicosapentaenoic acid + docosahexaenoic acid)
- Targeted wellness formula C™
- 5-aminolevulinic acid phosphate

Others (43)

- Transcranial current direct stimulation (9)
- Photobiomodulation (4)
- Transcutaneous auricular vagus nerve stimulation (4)
- Electrical stimulation (2)
- Hyperbaric oxygen (2)
- Allogeneic culture-expanded adipose-derived mesenchymal stem cells
- Allogenic marrow stromal cells
- Bone marrow mesenchymal stem cell derived extracellular vesicles
- CIMAvax-EGF®
- Cold knee casts
- Cranial electrotherapy stimulation
- High tone power therapy
- Hope Biosciences adipose-derived mesenchymal stem cells – allogeneic (HB-adMSCs)
- Human immunoglobulin G
- Hydrogen-oxygen generator with nebulizer
- Inogen One® G4 (portable oxygen concentrator)
- Intraoperative use of PEEP - Fixed and individualized
- Lactobacillus plantarum 299v in fermented oat drink
- Microcannula harvest adipose derived tissue stromal vascular fraction (tSVF)
- MON002 (autologous monocytes)
- Personalized multidisciplinary day-hospital intervention
- Plasma exchange
- Platelet rich plasma
- Pulsed ultrasound
- Resistive capacitive monopolar radio frequency at 448 kHz (INDIBA®)
- Stellate ganglion block
- Whole-body cryotherapy



Symbols next to each intervention represent the targeted system:

Pulmonary system:
Cardiovascular system:
Non-system specific:
Mental health:
Musculoskeletal system:
Nervous system:
Gastrointestinal system:

Vast array of registered trials for Long COVID (Sept, 2022)

Fawzy et al. *Clin Microbiol Infect.* (2023)

What is the prognosis?

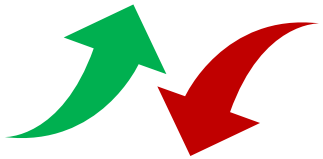
What are the long-term outcomes?

Prognosis and Trajectory

Overall limited longitudinal data beyond 2 years, but general patterns are observed:

- **Rapid improvement** – symptoms generally resolve within 3 months
  Not considered Long COVID

- **Gradual improvement** – symptoms gradually improve over 3-12 months
  Sometimes plateau but generally improved enough to function



- **Relapse-remitting** – periods of improvement may alternate with periods of symptom recurrence/worsening
  Sometimes plateau but generally improved enough to function

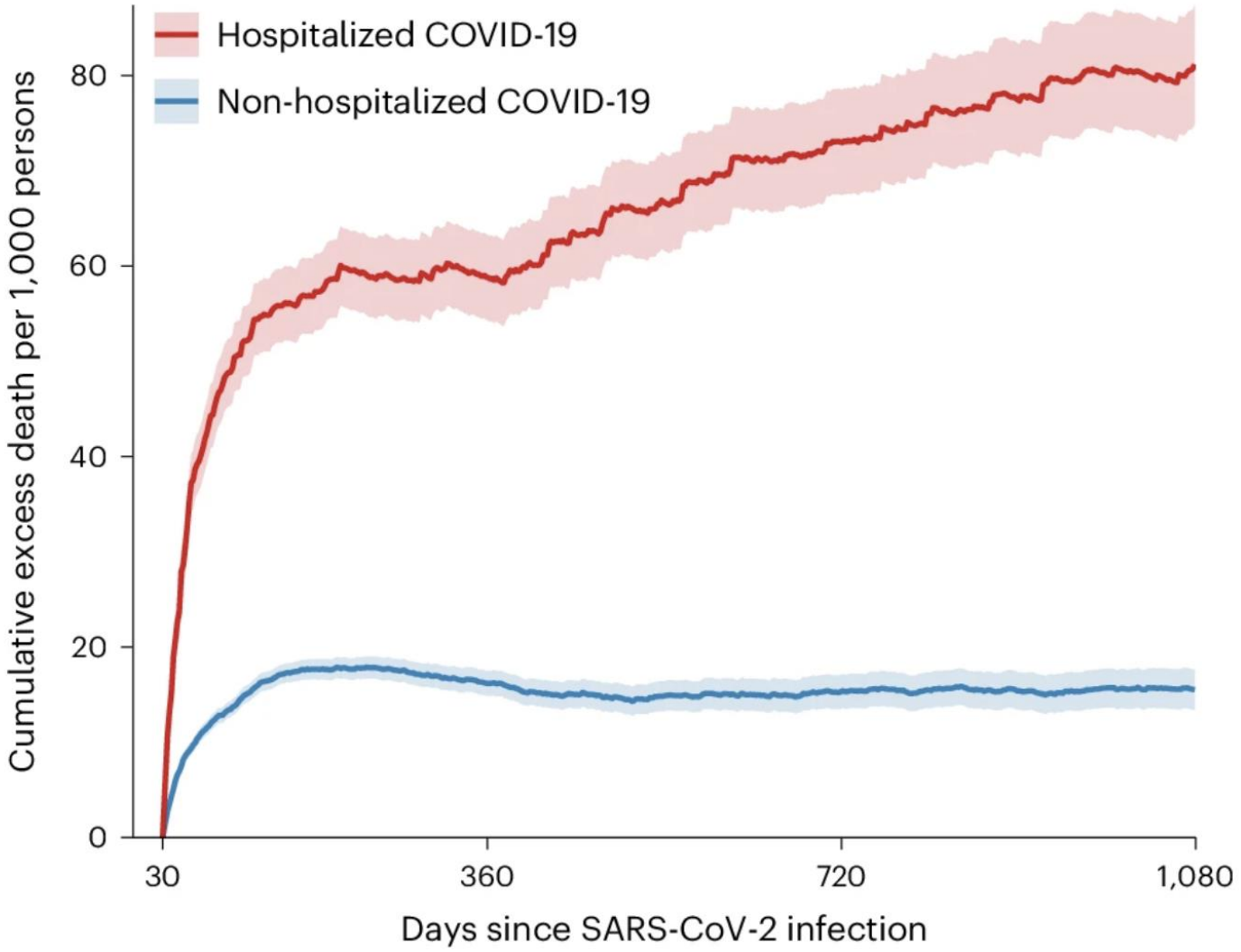
- **Persistent/progressive** – ongoing/worsening symptoms and/or organ dysfunction ≥1 year
  Typically the most debilitated group

NASEM Report (2024) *A long COVID definition: a chronic, systemic disease state with profound consequences*.
NASEM Report (2024) *Long-Term Health Effects of COVID-19: Disability and Function Following SARS-CoV-2 Infection.*

Long Term Outcomes Post-COVID

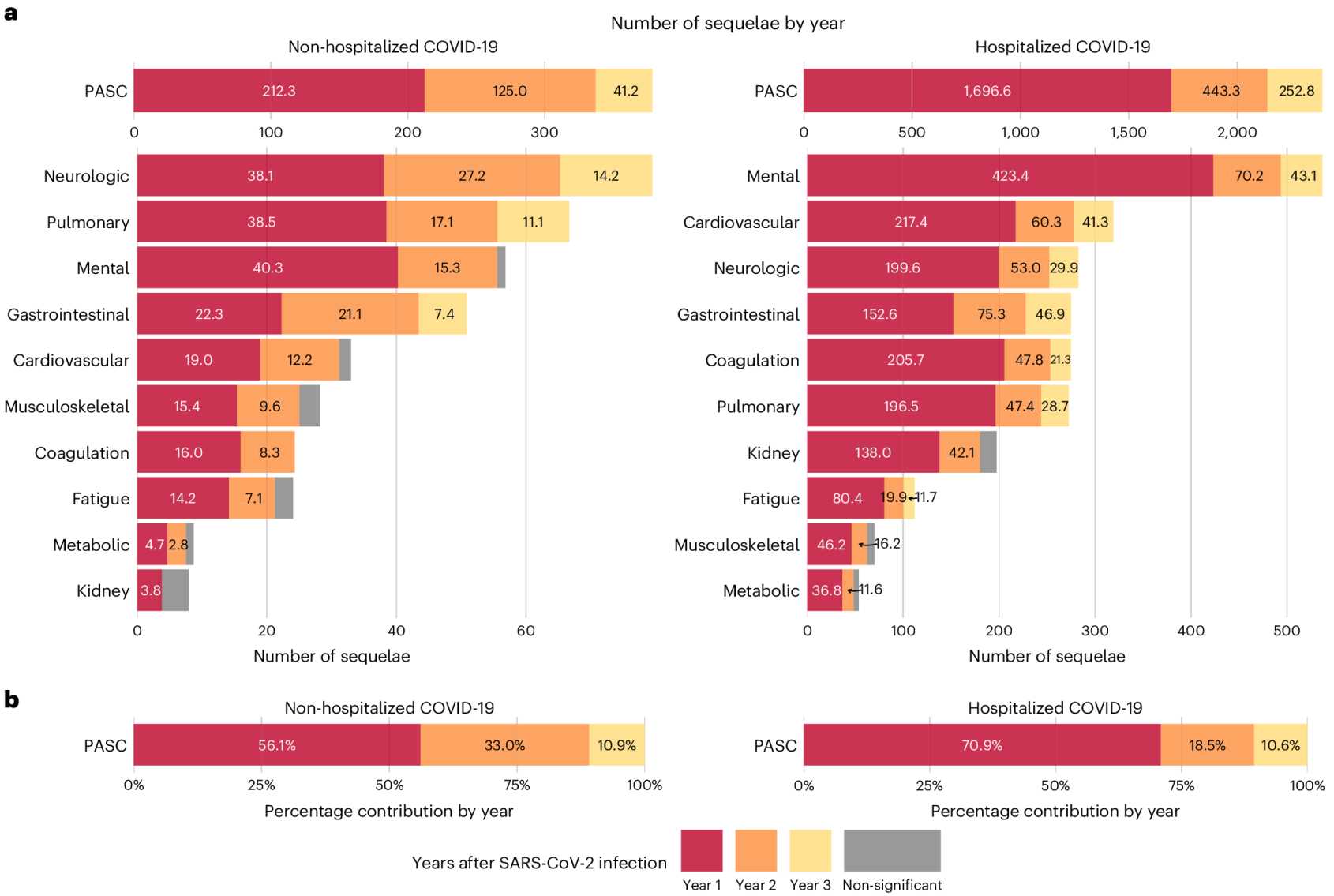
U.S. Veterans Affairs national EHR study of 135,161 people with SARS-CoV-2 infection and 5,206,835 controls without infection followed for 3 years:

- Among hospitalized patients, risk of death declined over time but was still elevated 3 years after infection (**29% increased risk of death**)
- Among non-hospitalized individuals, the increased risk of death was no longer present after the first year of infection



Cai et al. *Nat Med.* (2024) Three-year outcomes of post-acute sequelae of COVID-19

Long Term Outcomes Post-COVID



- Both <u>non-hospitalized</u> *and* <u>hospitalized groups</u> still experienced **increased multi-system health problems 3 years post-infection** compared to uninfected controls.

- 3-year cumulative burden of disability-adjusted life years **DALYs due to PASC was high** among the non-hospitalized group (**91.2 DALYs**), and even higher among the hospitalized group (**766.2 DALYs**)

Cai et al. *Nat Med.* (2024) Three-year outcomes of post-acute sequelae of COVID-19

Future Directions

- **Clinical trials are a priority** – we need to find effective therapies
- **Pathobiology studies** – we need biomarker(s) and better mechanistic understanding of LC subtypes & overlaps with other related conditions
- **Many questions remain** – impact of reinfections, new variants, updated vaccines, etc.? long-term prognosis beyond 5 years?
- **Improving clinical care** –
  - Diagnostic guidelines
  - Evidence-based and patient-centered
  - Access and care models

Acknowledgements

- PACS Multidisciplinary Clinical Team & Staff
- STOP-PASC Study Team
- RECOVER Study and Trials Teams
- REACH Study team
- Research Students and Staff
- Collaborators and Community Partners
- Department of Medicine Team Science
- OUR PATIENTS

https://goto.stanford.edu/REACH

STOP-PASC study is funded by and conducted in research collaboration with Pfizer, Inc.

RECOVER Initiative:

NIH National Institutes of Health
Researching COVID to Enhance Recovery

REACH Study:

AHRQ Agency for Healthcare Research and Quality

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