Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH's RECOVER Initiative

Progress Update

December 15, 2022

RECOVER
Researching COVID to Enhance Recovery

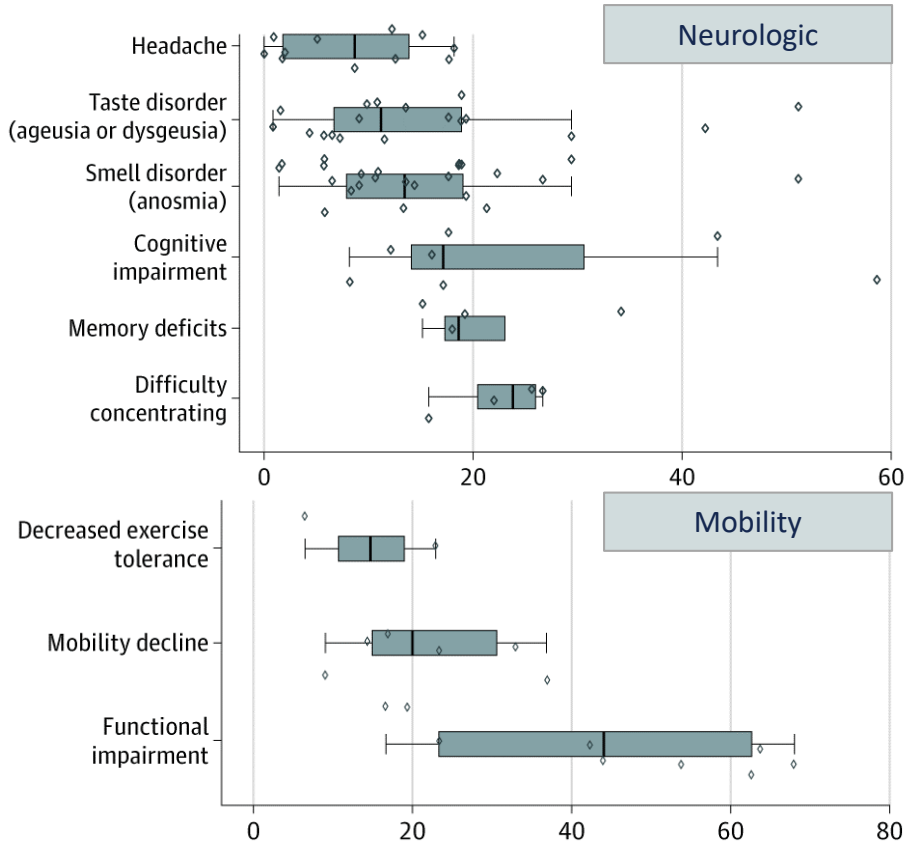
NIH National Institutes of Health
Researching COVID to Enhance Recovery

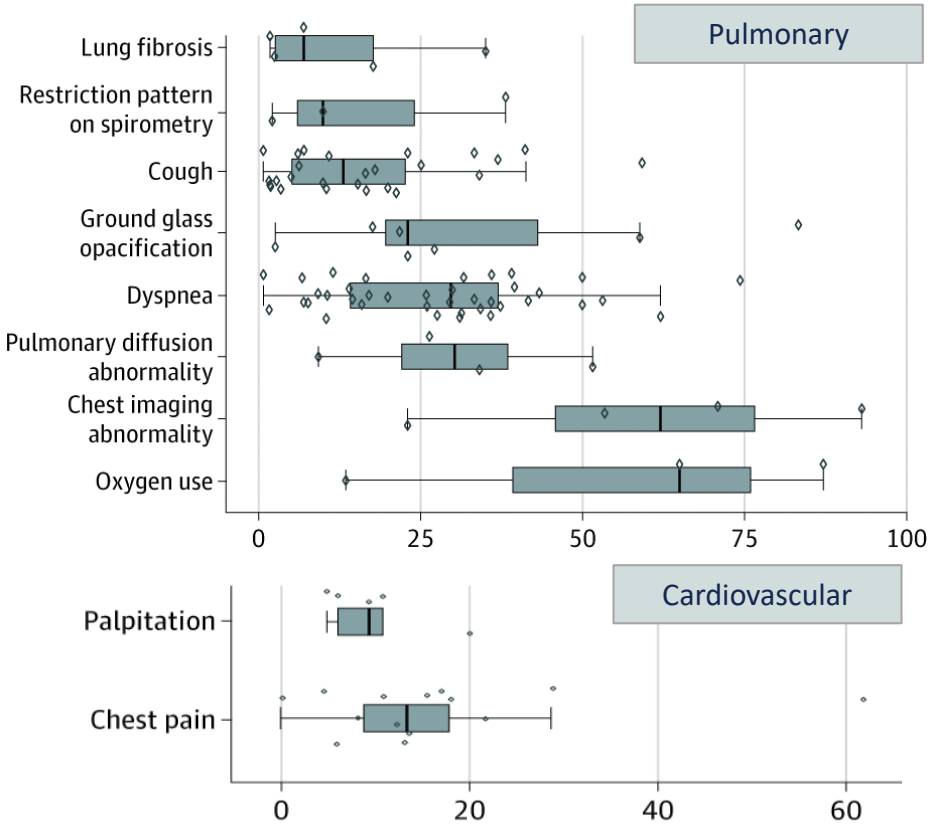
Short- and Long-term Rates of Post-acute Sequelae of SARS-CoV-2 Infection: A Systematic Review

(57 studies, Total n=250, 351 COVID-19 survivors, 79% hospitalized)

At six month time point 55% were judged to have at least one sequelae of COVID-19 infection.

- **Frequency of PASC varies widely depending on time from infection and severity of illness (e.g., 5-80%).**
- **Heterogeneous symptom set.**





PASC Frequency (%)

Groff et al., *JAMA Network Open*, October 2021

JAMA Network Open

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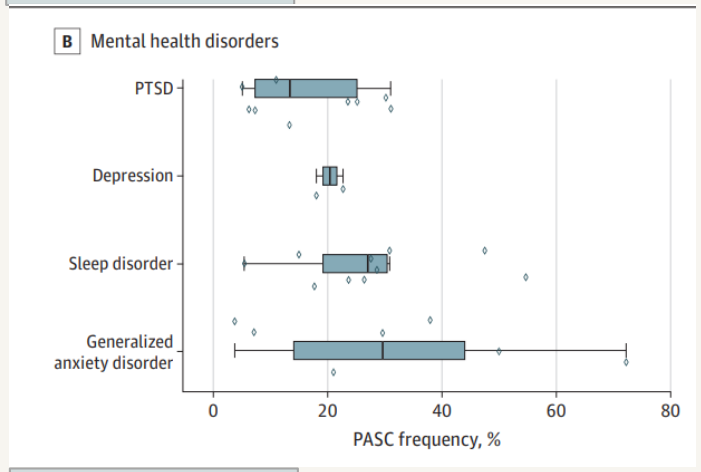
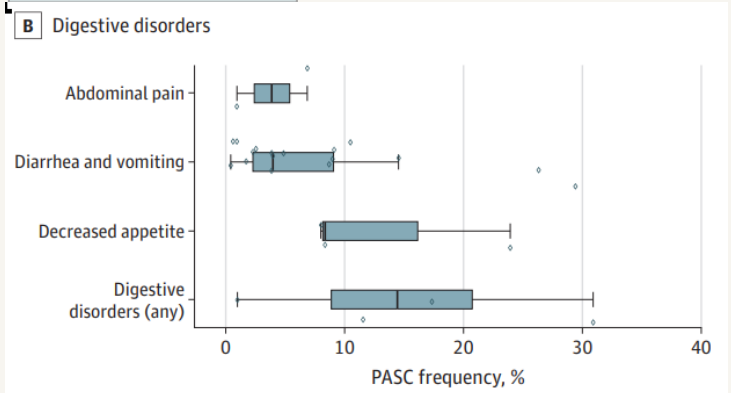
JAMA Network Open

recoverCOVID.org

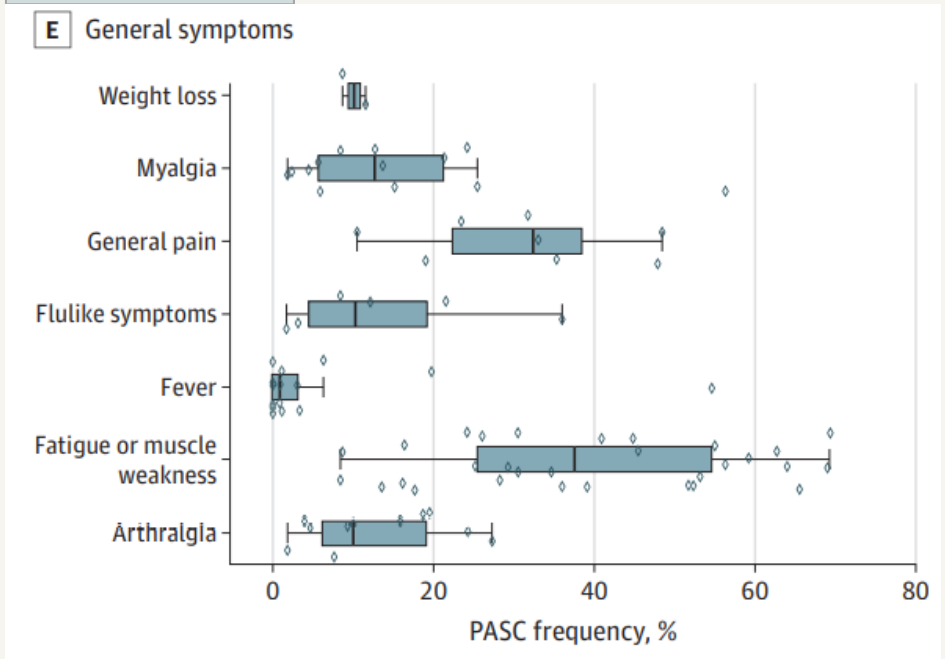
Mental Health



Digestive



General Symptoms



PASC Frequency (%) Groff et al., *JAMA Network Open*, October 2021

How prevalent is PASC?

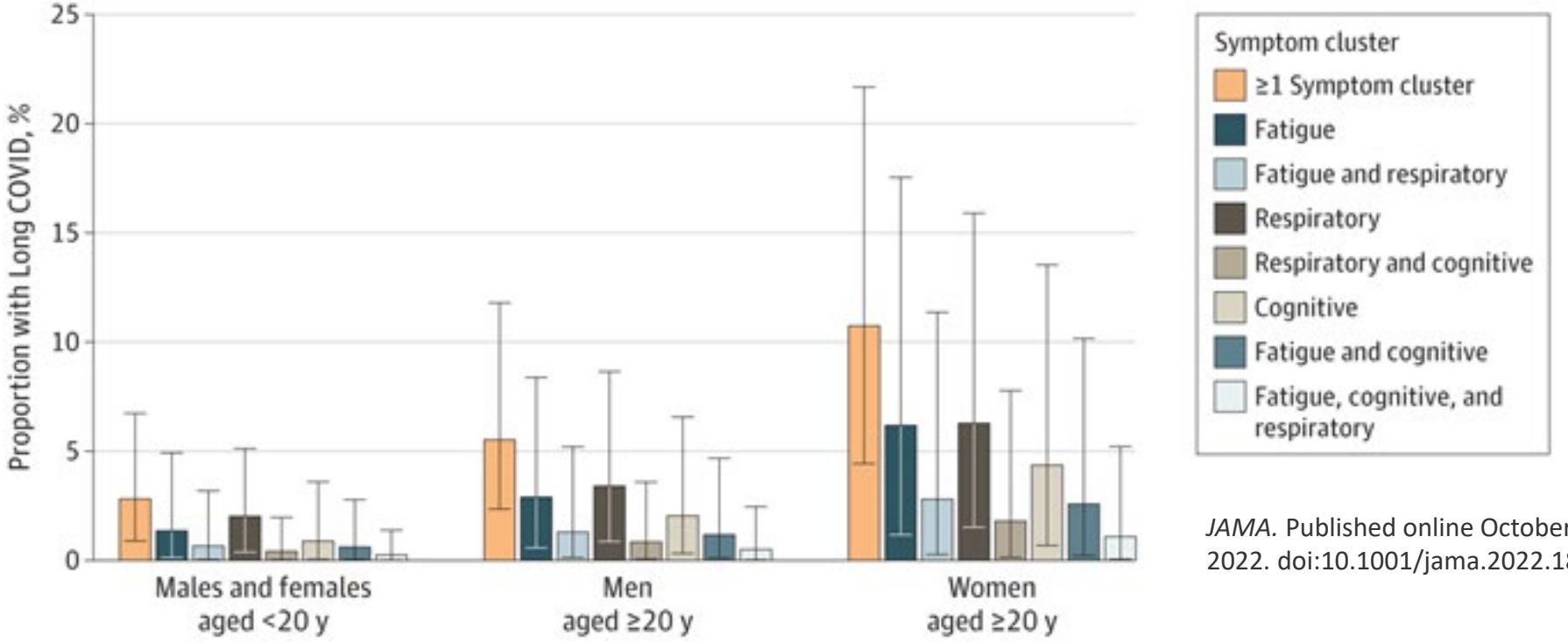
JAMA | Original Investigation

Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021

Global Burden of Disease Long COVID Collaborators

Metanalysis with data from 22 countries. Global Burden of Disease Long COVID Collaborators. *JAMA*, Published online October 2022

Proportion of Individuals Who Survived Symptomatic SARS-CoV-2 Infection and Who Experienced at Least 1 of the 3 Long COVID Symptom Clusters in 2020 and 2021



The estimated mean Long COVID symptom cluster duration was 9.0 months (95% UI, 7.0-12.0 months) among hospitalized individuals and 4.0 months (95% UI, 3.6-4.6 months) among nonhospitalized individuals

JAMA. Published online October 10, 2022. doi:10.1001/jama.2022.18931

UK Office for National Statistics:

Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021

- Persistent symptoms after 12 weeks of acute infection are **3.0% based on tracking specific symptoms, to 11.7% based on self-classification** of long COVID, using data to 1 August 2021.
- Among study participants **with COVID-19, 5.0% reported any of 12 common symptoms** 12 to 16 weeks after infection; however, **prevalence was 3.4% in a control** group of participants without a positive test for COVID-19, demonstrating the relative commonness of these symptoms in the population at any given time.
- Among study participants with COVID-19**, 3.0%** experienced any of 12 common symptoms for a **continuous period of at least 12 weeks** from infection, compared with **0.5% in the control** group.
- Prevalence of **self-reported long COVID is 11.7%** of study subjects experiencing long COVID (based on self-classification rather than reporting one of the 12 common symptoms) 12 weeks after infection, falling to 7.5% when considering long COVID that resulted in limitation to day-to-day activities; these percentages increased to 17.7% and 11.8% respectively when considering only participants who were symptomatic at the acute phase of infection.
- Prevalence was highest in **females, adults aged 50 to 69 years, people with a pre-existing** health condition, and those with **signs of high viral load at the time of infection.**

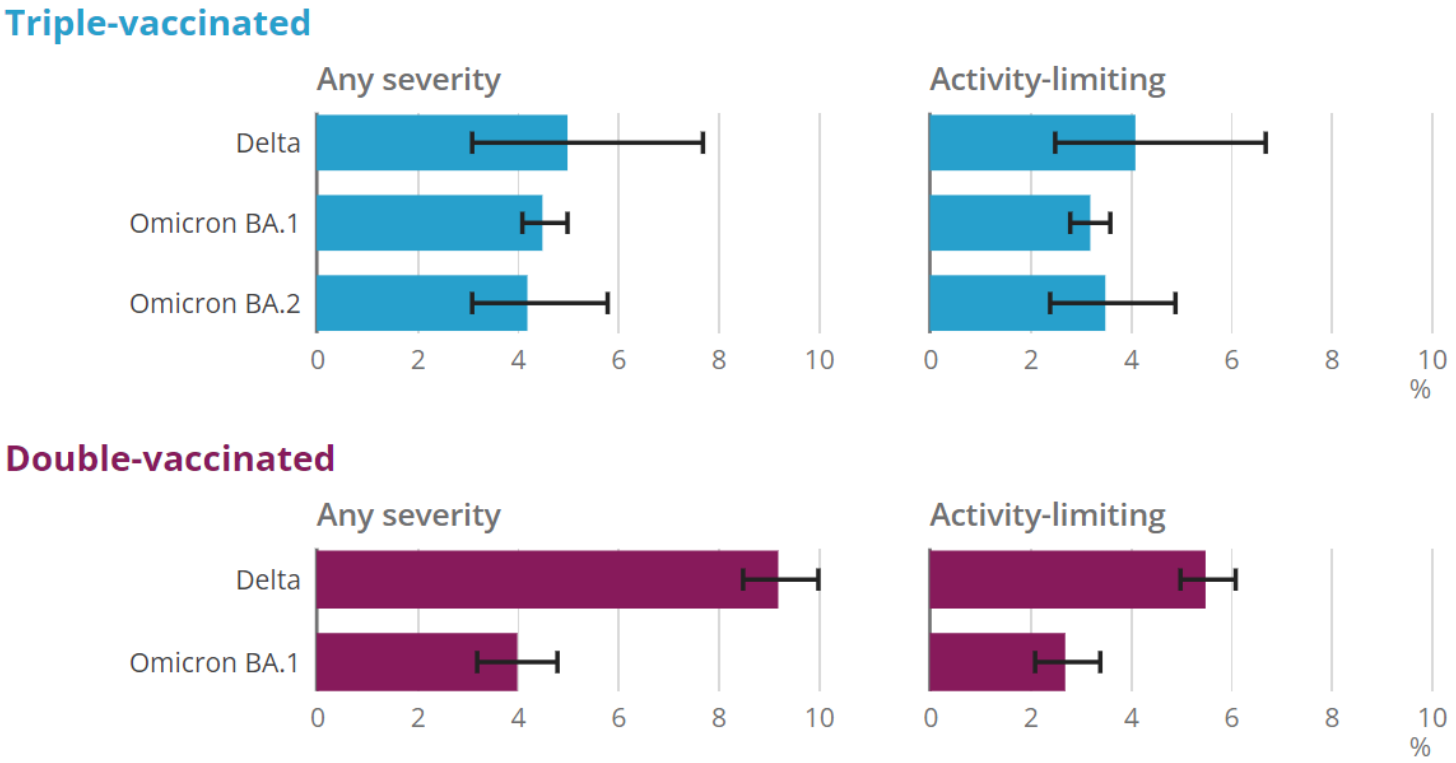
How does prevalence of PASC vary by variant?

Self-reported long COVID after infection with the Omicron variant in the UK

Self-reported long COVID after infection with the Omicron variant in the UK: 18 July 2022

The likelihood of self-reported long COVID after a first coronavirus (COVID-19) infection compatible with the Omicron BA.1 or BA.2 variants, compared with the Delta variant, using data from the COVID-19 Infection Survey.

Approximately 4% of triple-vaccinated adults reported experiencing long COVID 12 weeks after being infected with the Omicron BA.1 or BA.2 variants



UK Office for National Statistics - Coronavirus (COVID-19) Infection Survey. Released July 2022.

Post-COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020 – November 2021

Lara Bull-Otterson, PhD1; Sarah Baca1,2; Sharon Saydah, PhD1; Tegan K. Boehmer, PhD1; Stacey Adjei, MPH1; Simone Gray, PhD1; Aaron M. Harris, MD1

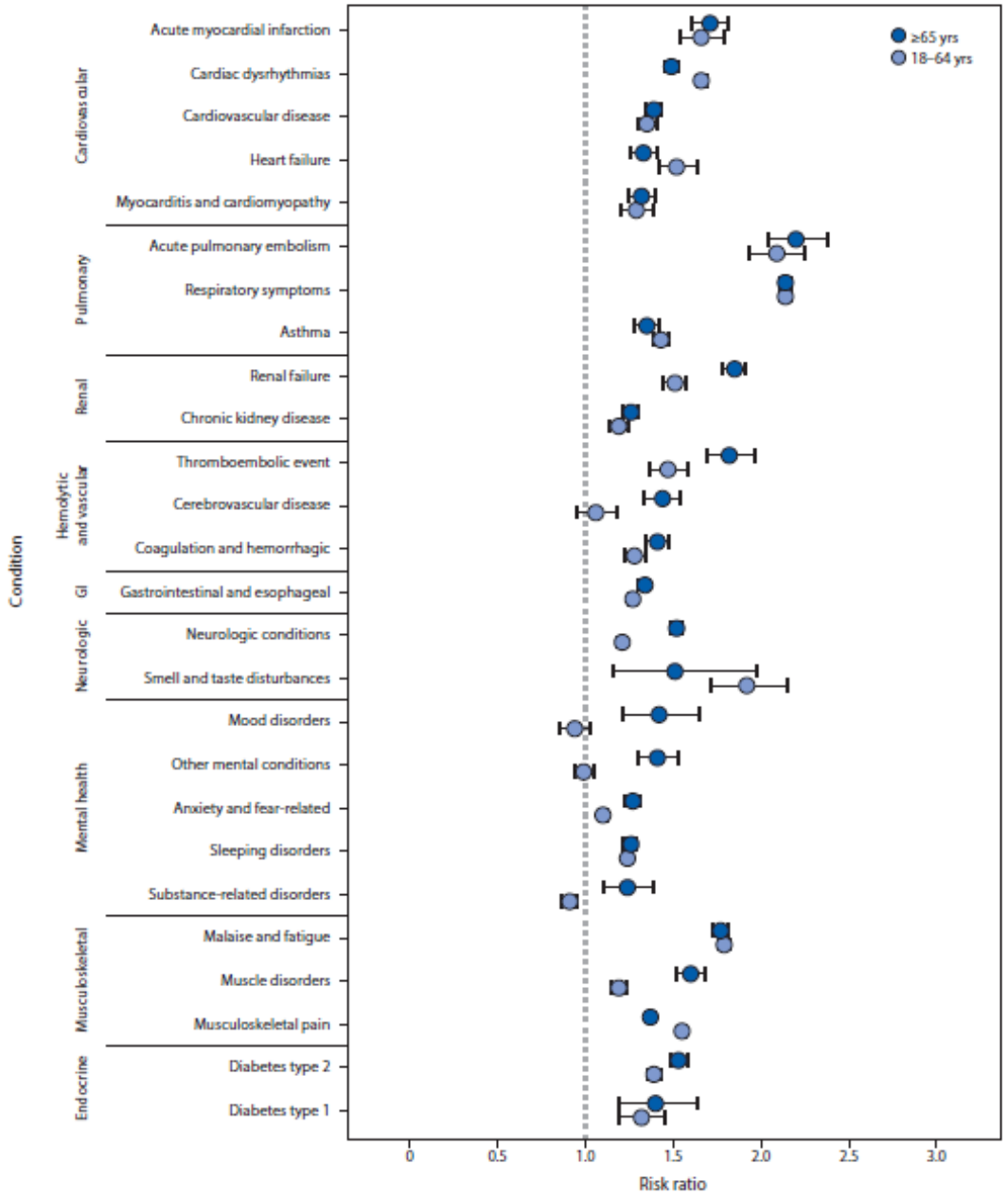
MMWR / May 27, 2022 / Vol. 71 / No. 21

Followed patients in Cerner Electronic Health Records for incident conditions occurring after 30 days of infection vs. control group without infection. Hospitalization status not defined.

- 38% of previously infected individuals developed an incident condition compared with 16% of controls.
- One in five COVID-19 survivors ≥ 18 years old experienced an incident condition that might be attributable to previous COVID-19.
- One in four survivors aged > 65 did so.

recoverCOVID.org

FIGURE. Risk ratios* for developing post-COVID conditions among adults aged 18–64 years and ≥65 years — United States, March 2020–November 2021



Abbreviation: GI = gastrointestinal.
* With CIs indicated by error bars; some error bars are not visible because of small CIs.

Hypothesized etiologies of PASC

- PASC is very likely a set of multiple conditions with varied underlying causes
- **Examples of hypothesized** causes:
  - **Persistence of SARS-CoV-2 virus or antigens and/or reactivation of other viruses** stimulating ongoing immune response
  - Viral infection and/or antigenic stimulation setting in motion a **dysregulated immune response** affecting various organs and tissues
  - Viral infection and/or inflammatory responses cause **damage to organs and tissues** that in turn results in dysfunction (e.g., neurologic, cardiac, pulmonary, renal, metabolic, GI)

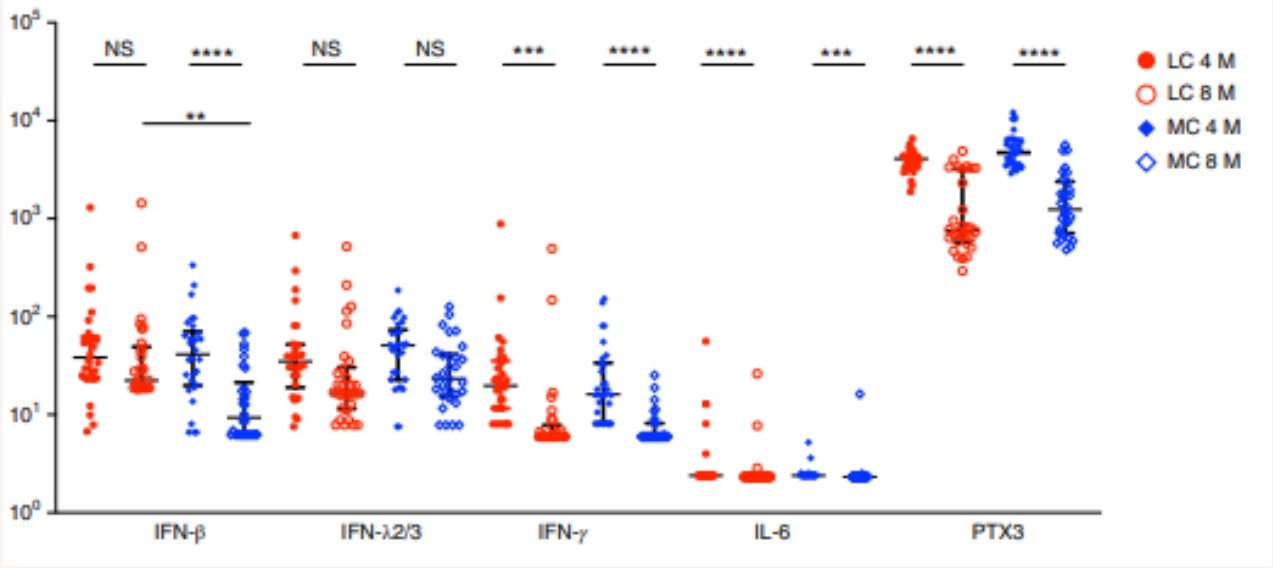
[1] https://assets.researchsquare.com/files/rs-1139035/v1_covered.pdf?c=1640020576
[2] https://www.nature.com/articles/s41590-021-01113-x
[3] https://www.nature.com/articles/s41586-021-03631-y.pdf
[4] https://www.biorxiv.org/content/10.1101/2022.01.07.475453v1

LETTERS
https://doi.org/10.1038/s41590-021-01113-x
nature immunology
Check for updates

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

Chansavath Phetsouphanh[1,7], David R. Darley[2,7], Daniel B. Wilson[3], Annett Howe[1], C. Mee Ling Munier[1], Sheila K. Patel[4], Jennifer A. Juno[5], Louise M. Burrell[4], Stephen J. Kent[5,6], Gregory J. Dore[1,2], Anthony D. Kelleher[1,2,7] and Gail V. Matthews[1,2,7]

- Patients with Long Covid 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.



Potential role for autoimmunity in PASC.

- **Auto antibodies to multiple self antigens are observed during acute COVID-19 infection.**
  - **Diverse functional autoantibodies in patients with COVID-19 (Nature) 10.1038/s41586-021-03631-y ;**
  - **New-onset IgG autoantibodies in hospitalized patients with COVID-19 (Nat Commun) 10.1038/s41467-021-25509-3;**

A number of small studies suggesting autoimmunity in some persons with PASC.

- **Dysregulated autoantibodies targeting vaso- and immunoregulatory receptors in Post COVID Syndrome correlate with symptom severity.** DOI: 10.3389/fimmu.2022.981532
- **Autoimmune Effect of Antibodies against the SARS-CoV-2 Nucleoprotein** DOI: 10.3390/v14061141
- **Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases** DOI: 10.3389/fimmu.2020.617089
- **Autoimmunity is a hallmark of post-COVID syndrome** doi: 10.1186/s12967-022-03328-4
- **Persistent Autoimmune Activation and Proinflammatory State in Post-Coronavirus Disease 2019 Syndrome** DOI: 10.1093/infdis/jiac017
- **Persistent IgG anticardiolipin autoantibodies are associated with post-COVID syndrome** DOI: 10.1016/j.ijid.2021.09.079

Elevated vascular transformation blood biomarkers in Long-COVID indicate angiogenesis as a key pathophysiological mechanism

Patel et al. Molecular Medicine (2022) 28:122
https://doi.org/10.1186/s10020-022-00548-8

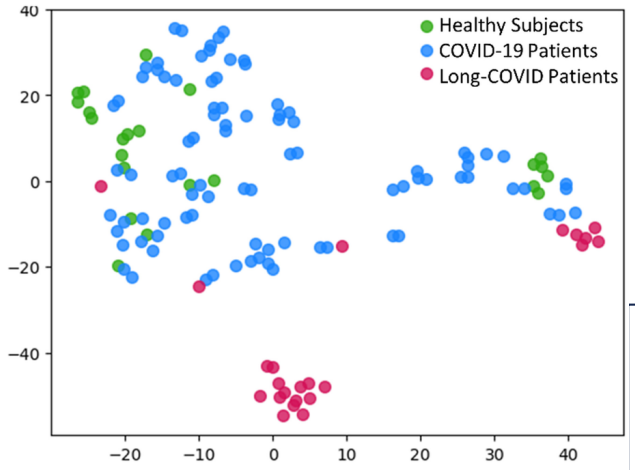
Molecular Medicine

A

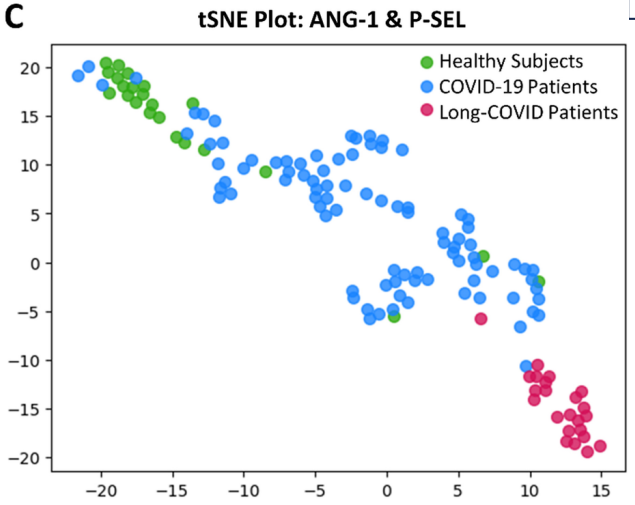
Feature Ranking

	Analyte	% Importance
1	ANG-1	21.7
2	P-SEL	15.4
3	MMP-1	12.5
4	VE-Cad	9.3
5	Syn-1	7.8
6	Endoglin	6.0
7	PECAM-1	5.4
8	VEGF-A	5.4
9	ICAM-1	5.3
10	VLA-4	3.3
11	E-SEL	3.1
12	Thrombomodulin	1.8
13	VEGF-R2	1.7
14	VEGF-R3	1.5

B



C



RESEARCH ARTICLE Open Access

Elevated vascular transformation blood biomarkers in Long-COVID indicate angiogenesis as a key pathophysiological mechanism

Maitray A. Patel[1], Michael J. Knauer[2], Michael Nicholson[3], Mark Daley[1,4], Logan R. Van Nynatten[3], Claudio Martin[3,5], Eric K. Patterson[5], Gediminas Cepinskas[5,6], Shannon L. Seney[5], Verena Dobretzberger[7], Markus Miholits[7], Brian Webb[8] and Douglas D. Fraser[5,9,10,11,12*]

dimensionality reduction of all fourteen significant biomarkers, shows separation cluster of Long-COVID outpatients with some mixing with acutely ill COVID-19 inpatients and healthy control subjects

dimensionality reduction of two selected biomarkers, ANG-1 and P-SEL, showed distinct separation and clustering of Long-COVID outpatients from acutely ill COVID-19 inpatients and healthy control subjects

Cell

Article

Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation

Authors

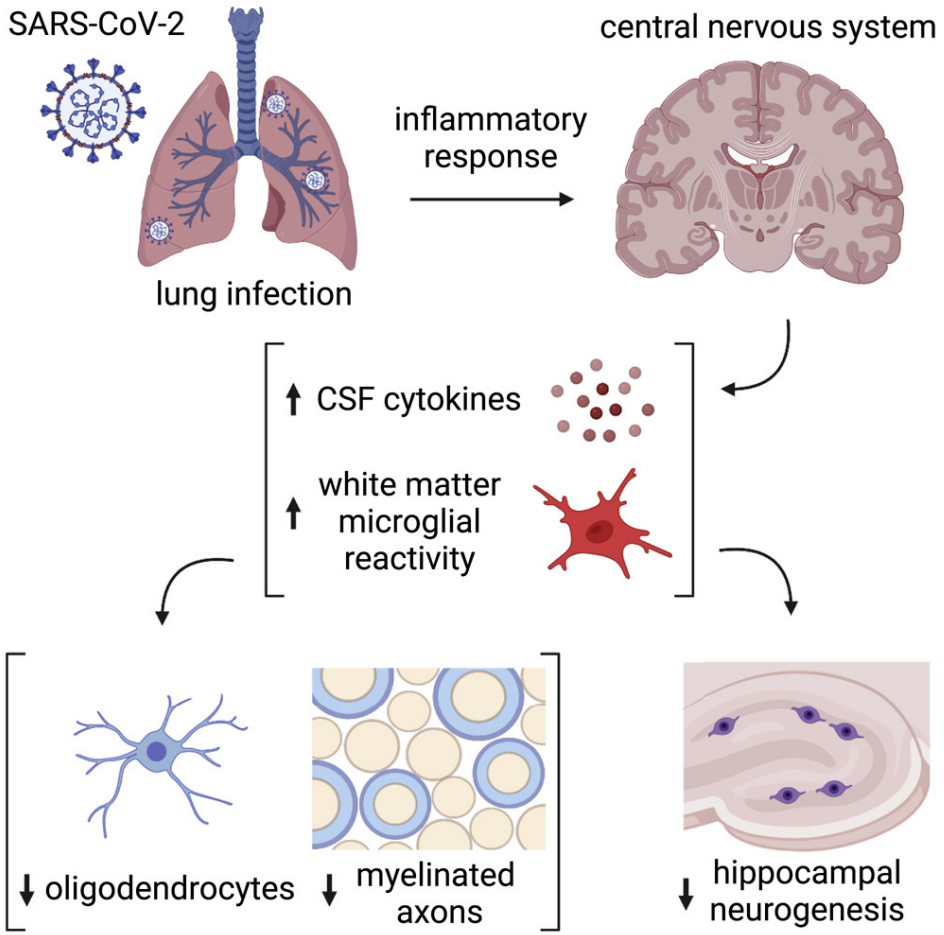
Anthony Fernández-Castañeda, Peiwen Lu, Anna C. Geraghty, ..., Avindra Nath, Akiko Iwasaki, Michelle Monje

Correspondence

akiko.iwasaki@yale.edu (A.I.), mmonje@stanford.edu (M.M.)

In brief

Mild respiratory COVID causes neuroinflammation and multi-lineage cellular dysregulation in the central nervous system, a phenomenon mirroring cancer-therapy-related cognitive impairment.



Is there persistence of viral material?

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

SARS-CoV-2 infection and persistence throughout the human body and brain

Daniel Chertow (chertowd@cc.nih.gov)
National Institutes of Health https://orcid.org/0000-0002-1675-1728

Chertow et al.
Research Square
(preprint), Posted
December 2021

Autopsies on 44 COVID-19 patients from acute infection through over 7 months following symptom onset.

- SARS-CoV-2 is widely distributed even in patients who died with asymptomatic or mild infection
- Virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection
- RNA in multiple anatomic sites, including brain, for up to 230 days after symptom onset.
- Paucity of inflammation or viral cytopathology outside the lung

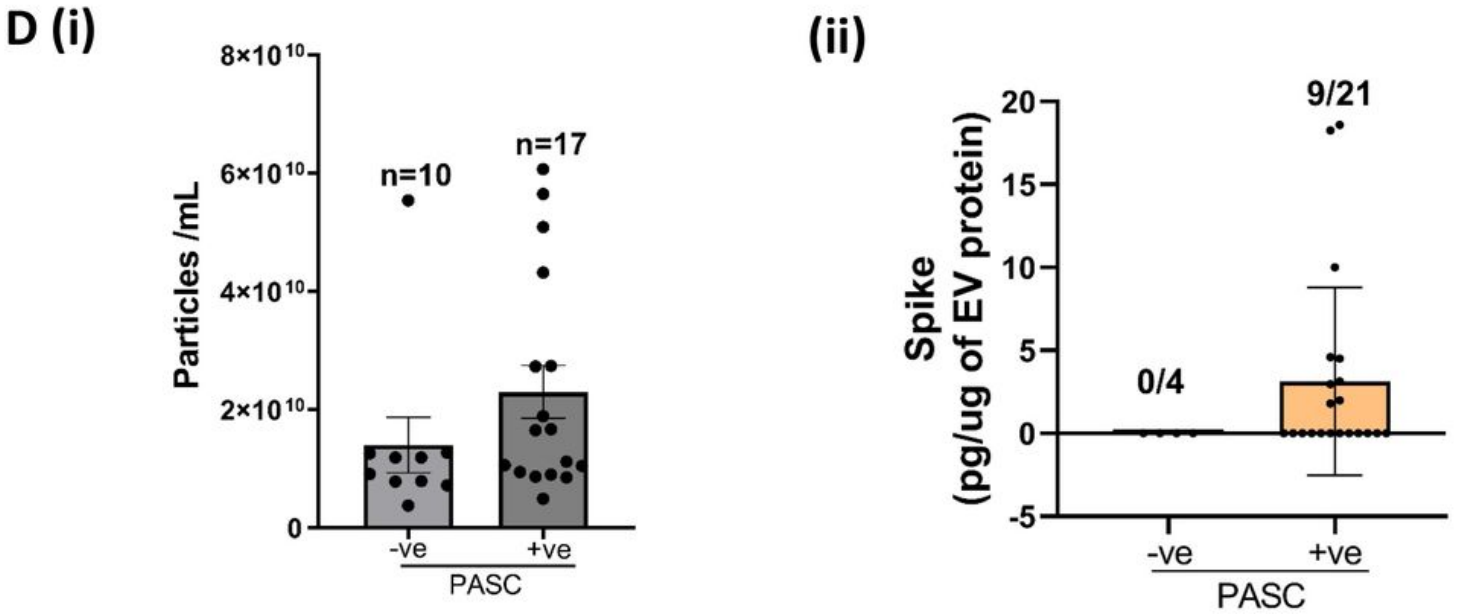
NIH

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES
CSH Cold Spring Harbor Laboratory
BMJ Yale

Persistent Presence of Spike protein and Viral RNA in the Circulation of Individuals with Post-Acute Sequelae of COVID-19

Vaughn Craddock, Aatish Mahajan, Balaji Krishnamachary, Leslie Spikes, Prabhakar Chalise, Navneet K. Dhillon
doi: https://doi.org/10.1101/2022.08.07.22278520

Exocytic Vesicle (EV) numbers (i) and EV-linked Spike protein (ii) in the plasma from individuals with and without PASC as measured by Nanoparticle Tracking Analysis and ELISA, respectively.



NIH

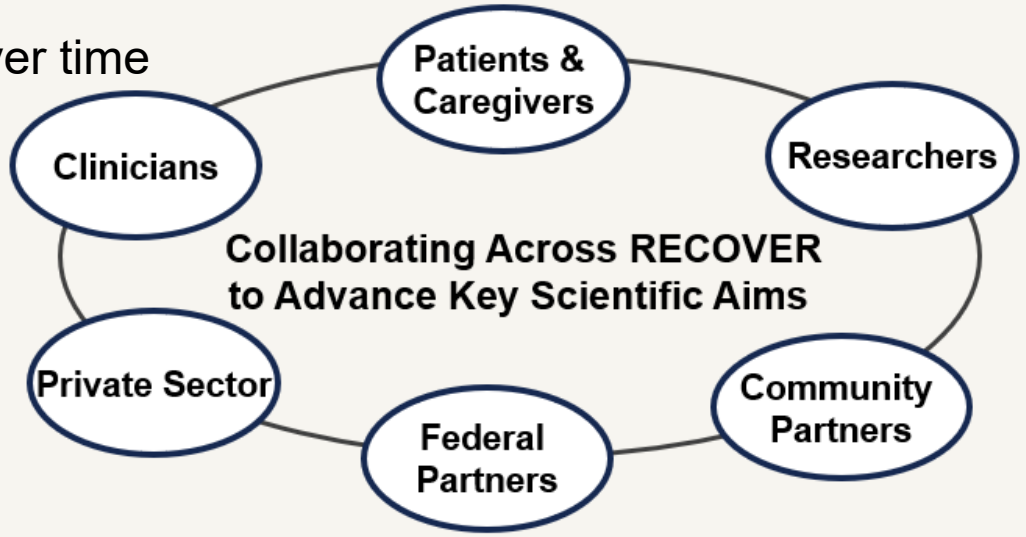
NIH RECOVER Initiative

Goal

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

Key Scientific Aims

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC



Guiding Principles

Patient-centered, participants as partners

National Scale with Inclusive, diverse participation & community engagement

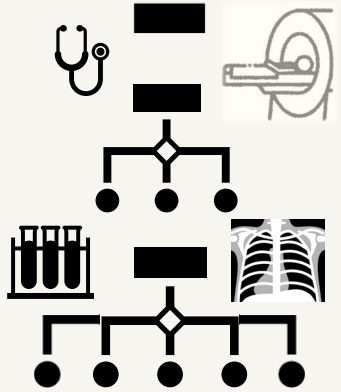
Platform protocols, standardized methodologies, and common data elements

Adaptive approaches based on emerging science

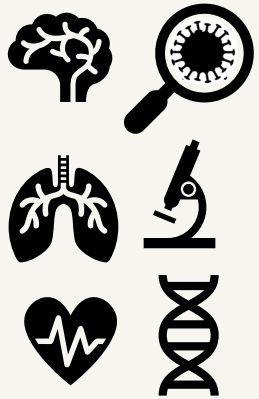
recoverCOVID.org

Key Progress in 2022 *(as of September)*

~10,000 adult patients enrolled in past 9 months



8 longitudinal clinical cohort studies and related sub-studies



42+ pathobiology studies

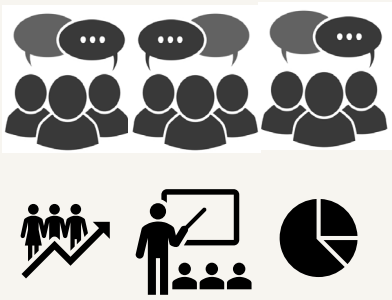
5 master protocol-driven platform clinical trials under development

EHR study results: ~40 reports (17 draft, 9 submitted, 11 preprint, 3 published)

Data repositories and shared analytic workbench; initial RECOVER data release to consortium in process

Study of potential PASC biomarker

Launched mobile health platform; designed patient registry



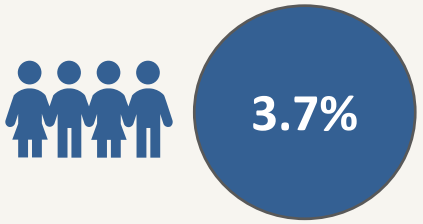
Collaborative patient community engagement and research seminar series

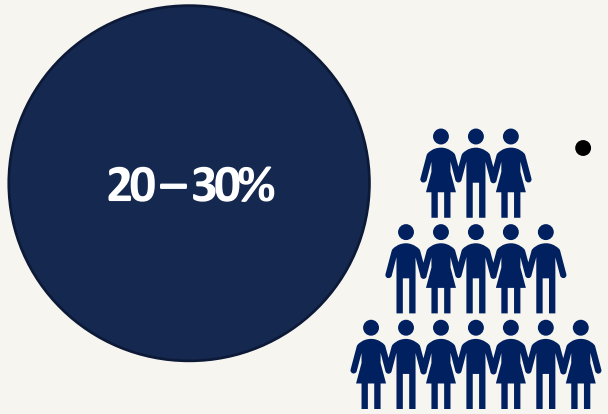
RECOVER-All of Us precision medicine collaboration

RECOVER Study: Preliminary Findings

Proportion of RECOVER participants developing PASC symptoms of varying severity

- ***EHR Studies*:**
  - **Hospitalization for COVID-19 and PASC incidence**
    - Incidence of PASC over time higher among people who were hospitalized for COVID-19 (8-20%) than non-hospitalized (4-8%)
  - **PASC incidence in children**
    - 3.7% SARS-CoV-2 infected children go on to develop PASC (Link, *JAMA Pediatrics)*





- ***Cohort Study*:** Significant % of adult participants enrolled during acute infection report persistent and/or new onset symptoms months after acute infection compared to uninfected individuals
  - Among participants recruited during acute infection, 20-30% report symptoms at 3 months, whereas 5-15% of uninfected participants develop these symptoms

RECOVER Study: Preliminary Findings

What are the impacts of different variants and vaccination?

EHR Studies:

- **Higher peaks of PASC early in the pandemic** (a period with more severe acute illness) and with Delta variant (Link: *In preparation*)
- **Vaccination *decreases* a patient's predicted probability of PASC** (Link: *The Lancet and Link: Long COVID Risk and Pre-COVID Vaccination: An EHR-Based Cohort Study from the RECOVER Program*)
- **Vaccination protects against cardiac complications of SARS-CO-V-2 infections in male teens and young adults:** Teen boys (12-17) and young men (18-29) had 2-6x and 7-8x respective higher risk of heart complications after COVID-19 infection compared to after vaccination (Link: *Morbidity and Mortality Weekly Report*)

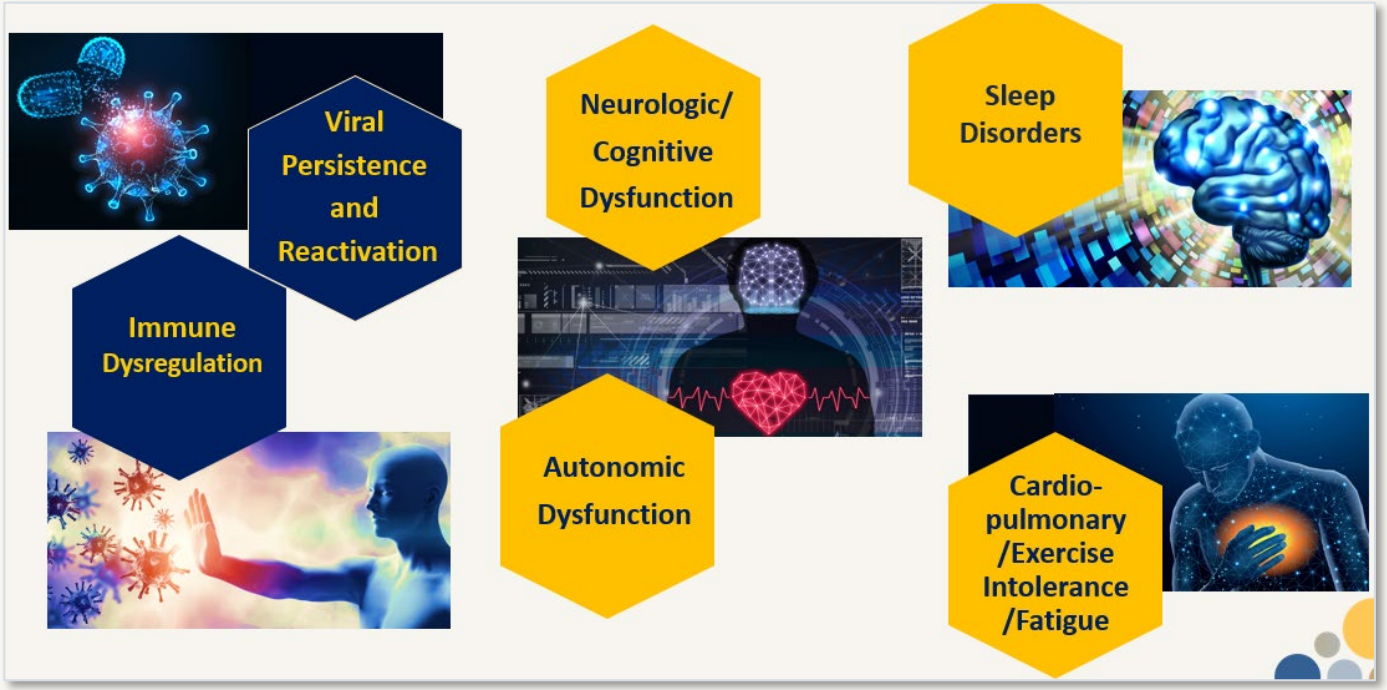
Cohort Studies:

- Predominant symptoms are fairly consistent across infection waves
- Lower overall rates of symptoms observed in participants infected in later years
- Vaccinated individuals infected with Omicron variant continue to be at risk for PASC, though the chance of PASC is lower than individuals infected pre-Omicron

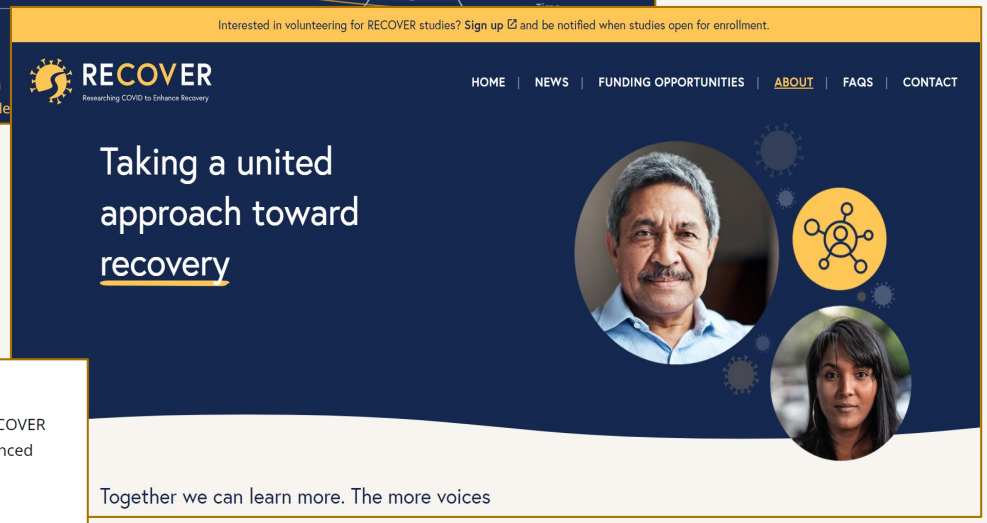
PASC Master Protocol-Driven Platform Clinical Trials Span Range of Dominant Symptom Clusters and Proposed Etiologic Pathways

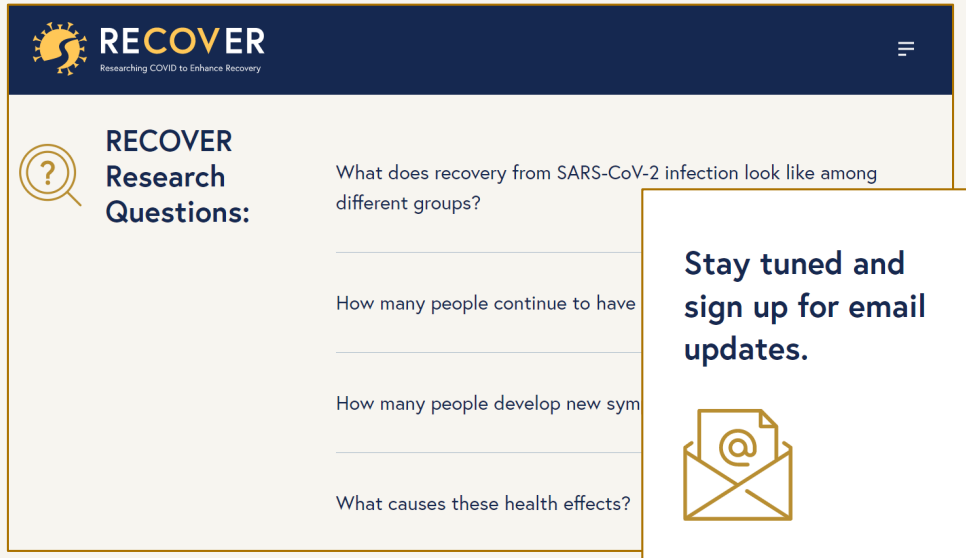
- Solicited clinical trial concepts from clinical research community
- Analyzed data from RECOVER clinical cohorts to identify major symptom clusters and inform trial endpoint selection
- Engaged key stakeholders and agencies in development process: patients, clinicians, FDA, CMS, PCORI and others as appropriate, including industry
- 5 platform protocols under development and, as appropriate, regulatory review and spanning major PASC symptom clusters and proposed etiologic pathways

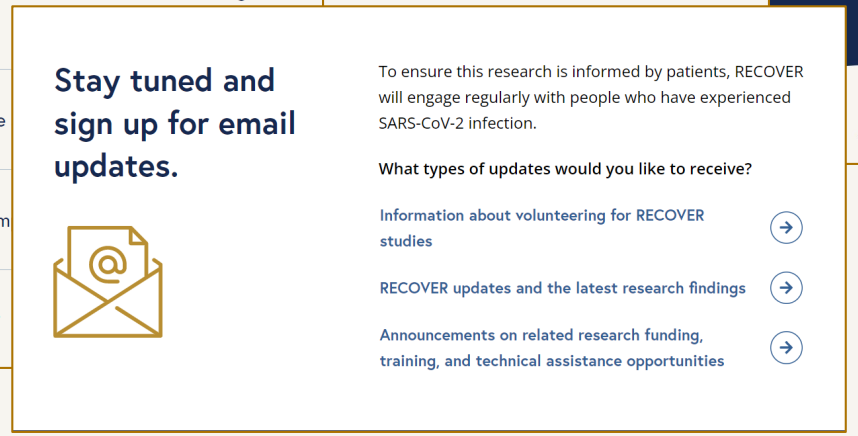
RECOVER Clinical Trial Platforms Portfolio



Staged roll-out starting end of 2022 and early 2023







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