*Long COVID's Impact on Patients, Workers & Society*

*Webinar Nov. 1st, 2023*

*https://healthconference.org*

USA Health Watch

# The Effectiveness of Vaccines to Prevent Long COVID

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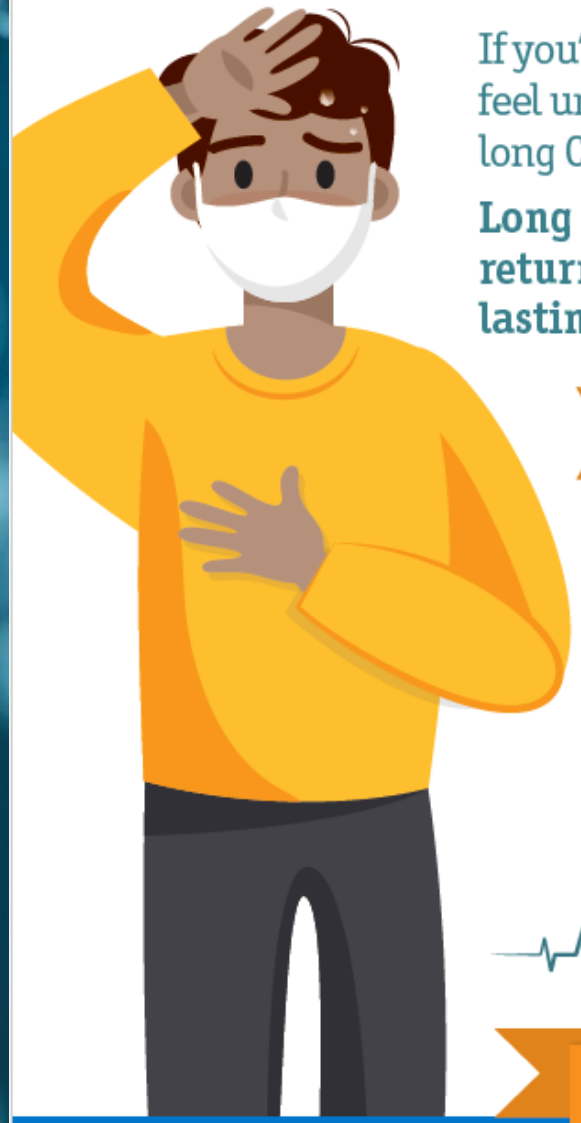
**Professor of Microbiology**
**University of Massachusetts Amherst**

# Disclosure

- I have no financial or intellectual property interests in any of the products or companies mentioned in this presentation.
- I have not personally worked on or supervised COVID-19 vaccine development.
- It is my goal to explain the science supporting vaccination but not necessarily to convince anyone to take any of the COVID-19 vaccines. That is a personal decision

# What's long COVID?

CardioSmart
AMERICAN COLLEGE of CARDIOLOGY



If you've recovered from COVID-19 but still feel unwell or have symptoms, you may have long COVID.

**Long COVID includes a wide range of new, returning or ongoing health problems lasting 4 or more weeks after COVID-19.**

Affects up to 1 in 3 people who've had COVID, including those with mild cases or no symptoms.

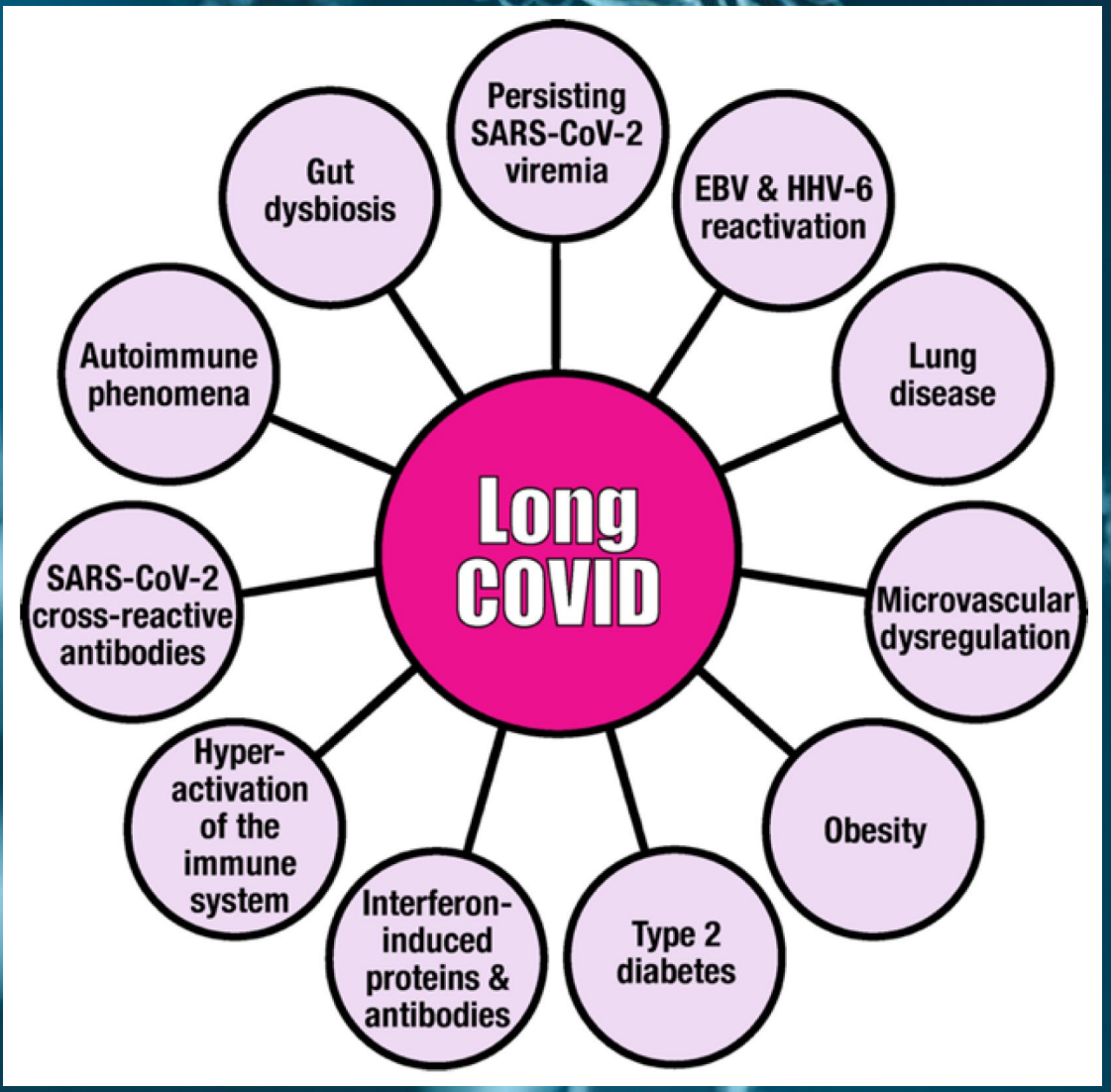
It can develop soon after COVID-19 or 3-6 months later and beyond.

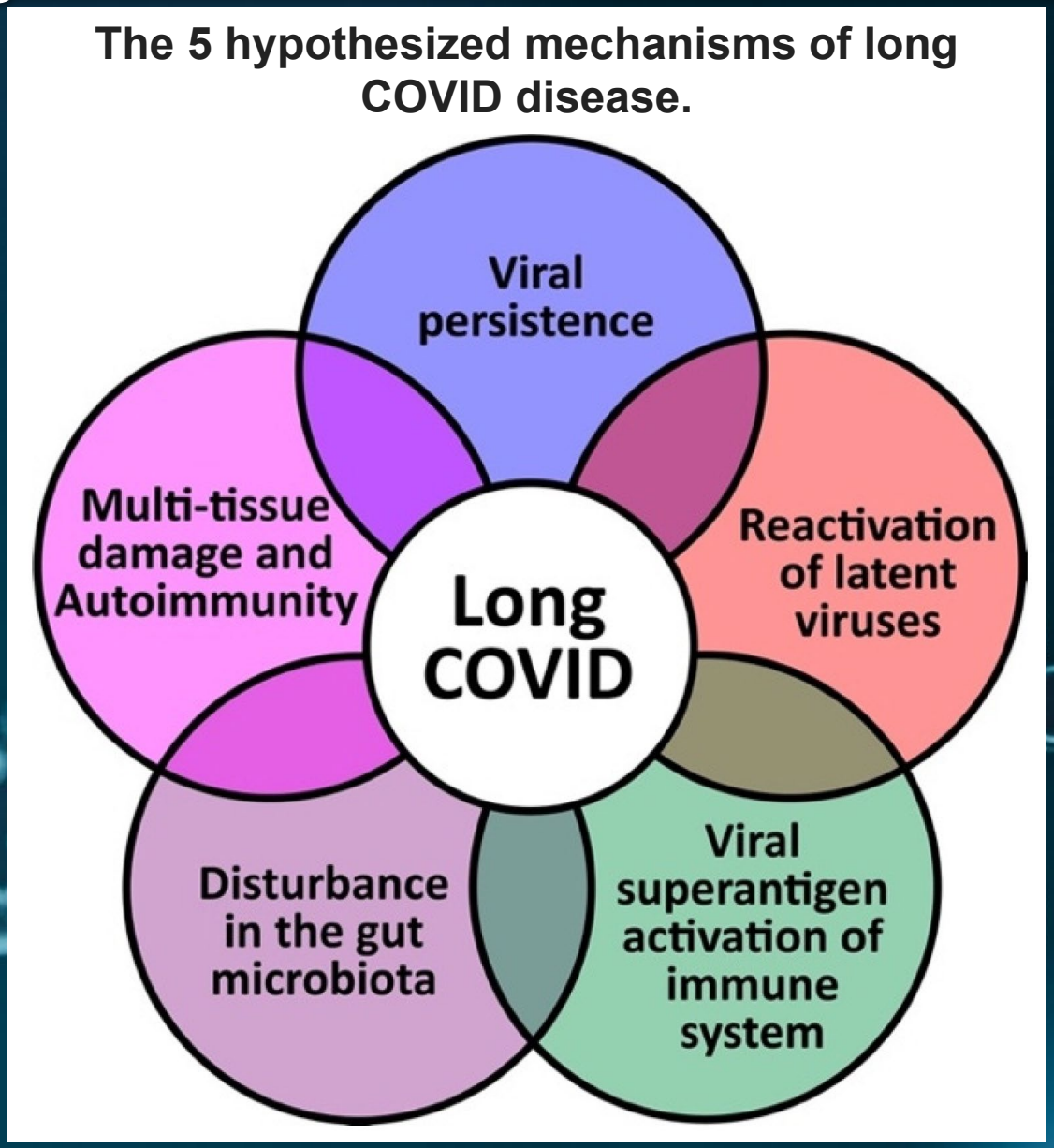
## COMMON SYMPTOMS

- Unusual tiredness
- Headaches or dizziness
- Shortness of breath
- "Brain fog" (difficulty thinking, focusing)
- Cough
- Chest pain
- Trouble sleeping
- Fast or pounding heartbeat
- Feeling worse with activity

## TALK WITH YOUR HEALTH CARE TEAM

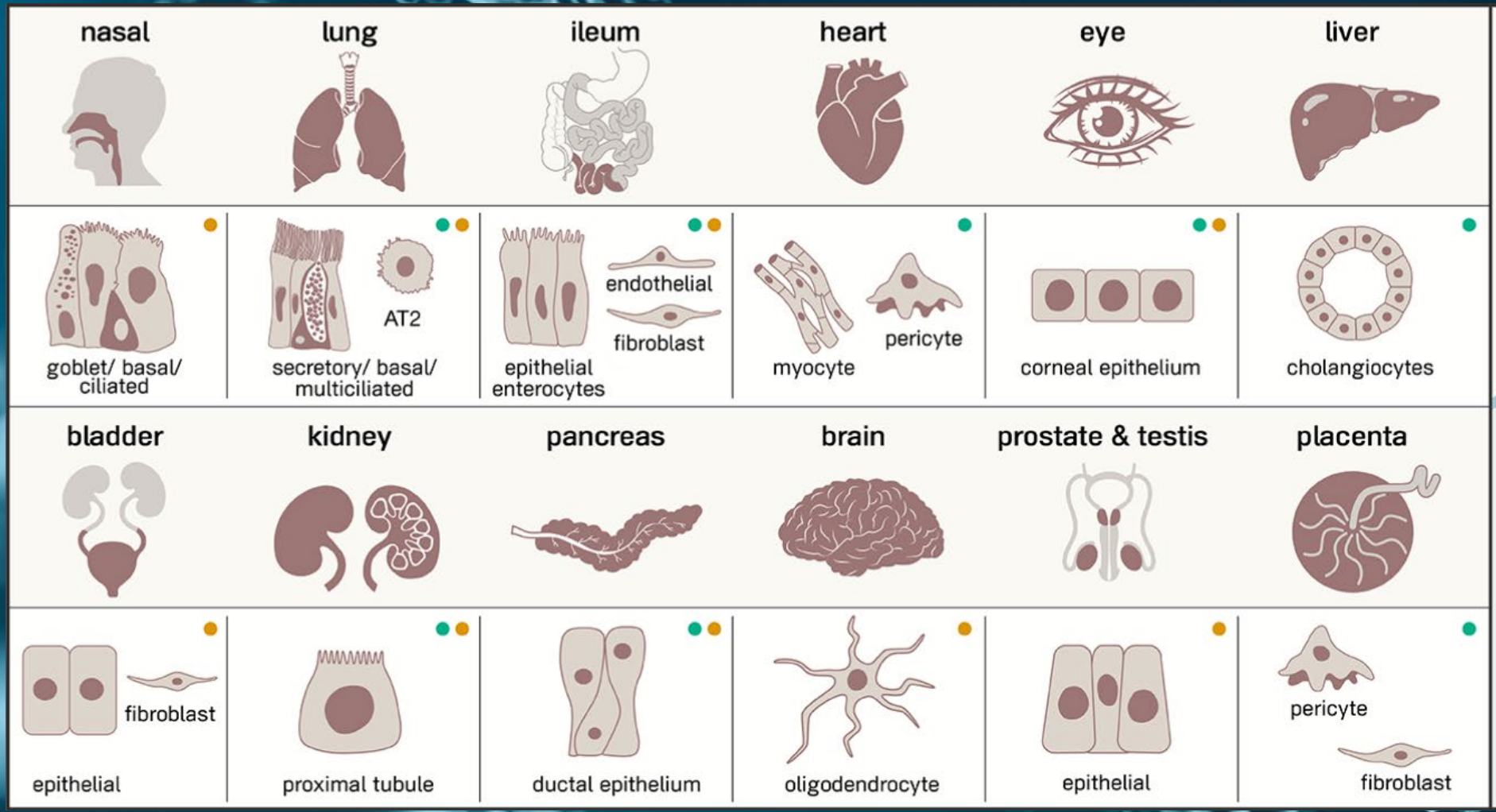
# Major Factors That May be Involved in The Pathophysiologic Mechanism of Long COVID Disease

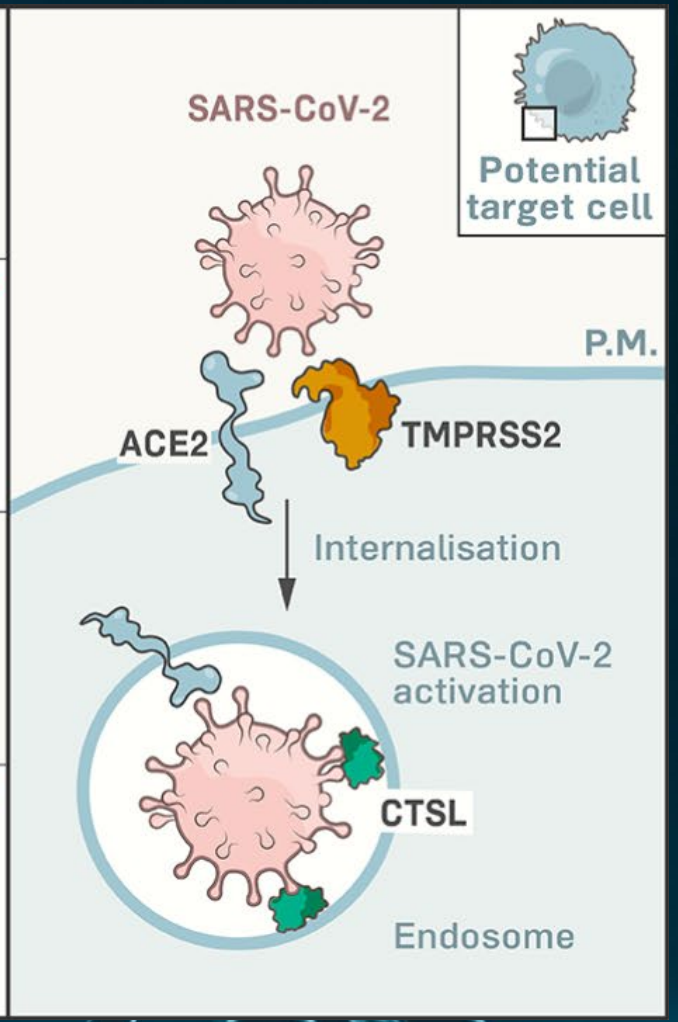



Vojdani A, Vojdani E, Saidara E, Maes M. Persistent SARS-CoV-2 Infection, EBV, HHV-6 and Other Factors May Contribute to Inflammation and Autoimmunity in Long COVID. *Viruses*. 2023; 15(2):400. https://doi.org/10.3390/v15020400

# Receptors for SARS-CoV-2 Present in Wide Variety of Human Cells




The Scientist **Chris Baraniuk** *Apr 29, 2020*

# Organ Systems Affected by Long COVID

## Mental Health
- Anxiety
- Depression
- Sleep problems
- Substance abuse

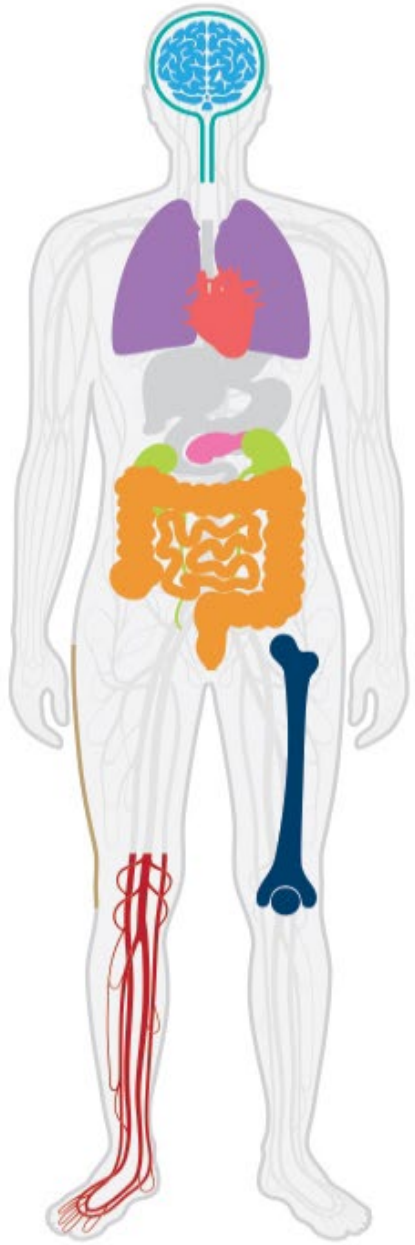
## Respiratory System
- Cough
- Low blood oxygen
- Shortness of breath

## Kidney
- Acute kidney injury
- Chronic kidney disease

## Gastrointestinal
- Diarrhea
- Acid reflux
- Constipation

## Skin Disorders
- Rash
- Hair loss

## Blood Disorders
- Anemia
- Blood clots



## Nervous System
- Stroke
- Headaches
- Memory problems
- Loss of smell and taste

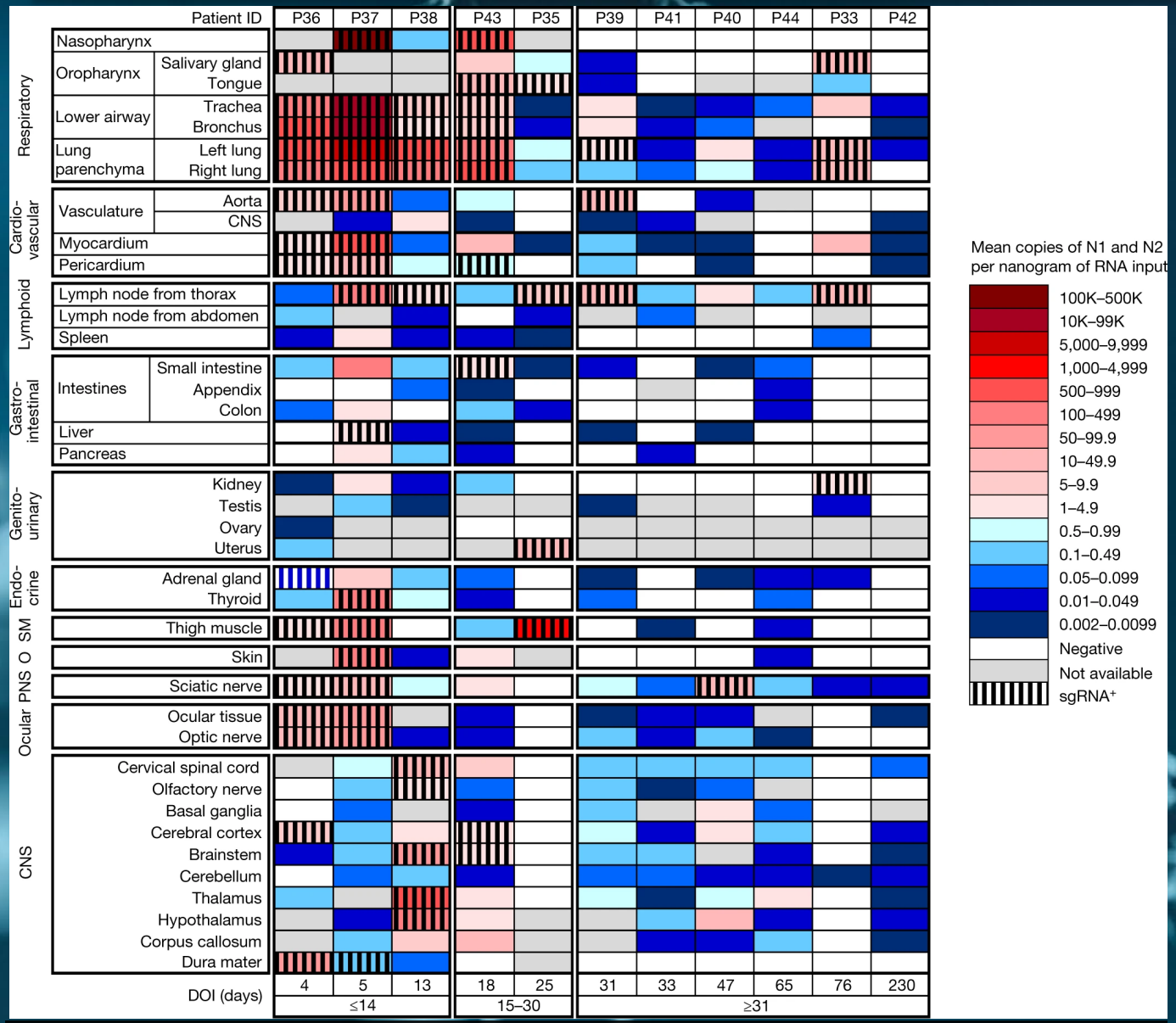
## Cardiovascular
- Arrhythmia
- Palpitations
- Heart failure
- Acute coronary disease

## Metabolic/Endocrine
- Obesity
- Diabetes
- High cholesterol

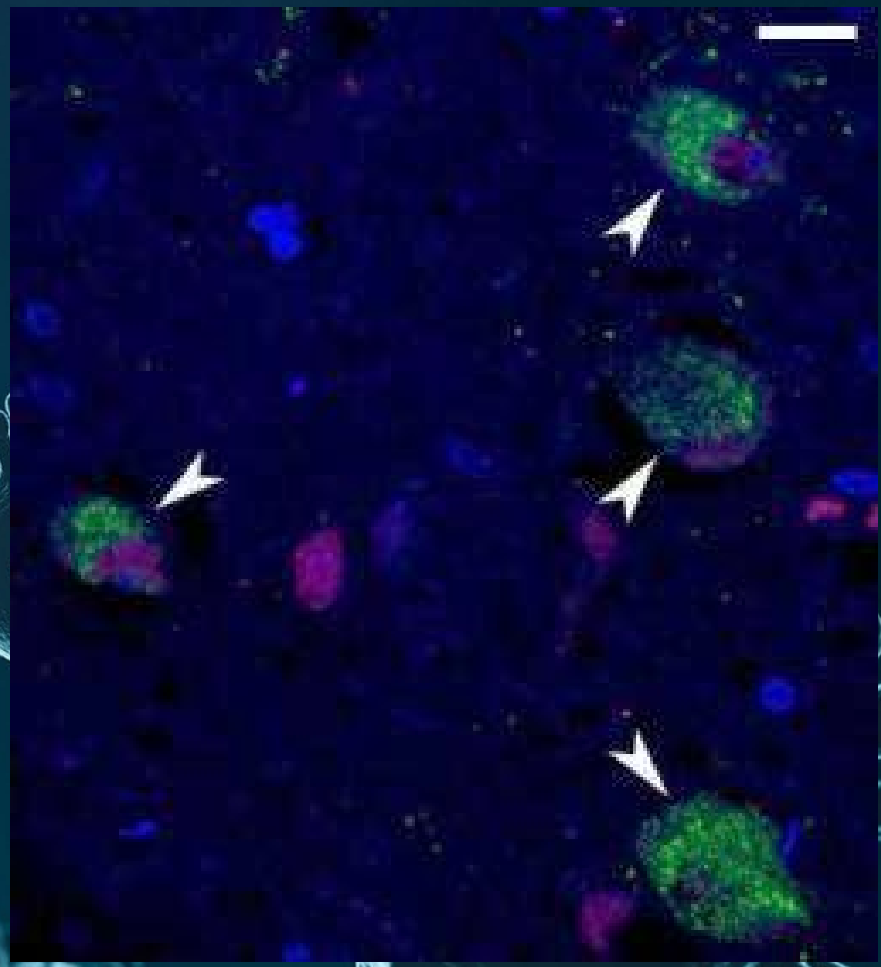
## Musculoskeletal
- Joint pain
- Muscle weakness

## General
- Fatigue
- Malaise
- Mitochondrial dysfunction

# SARS-CoV-2 Infection and Persistence in The Human Body



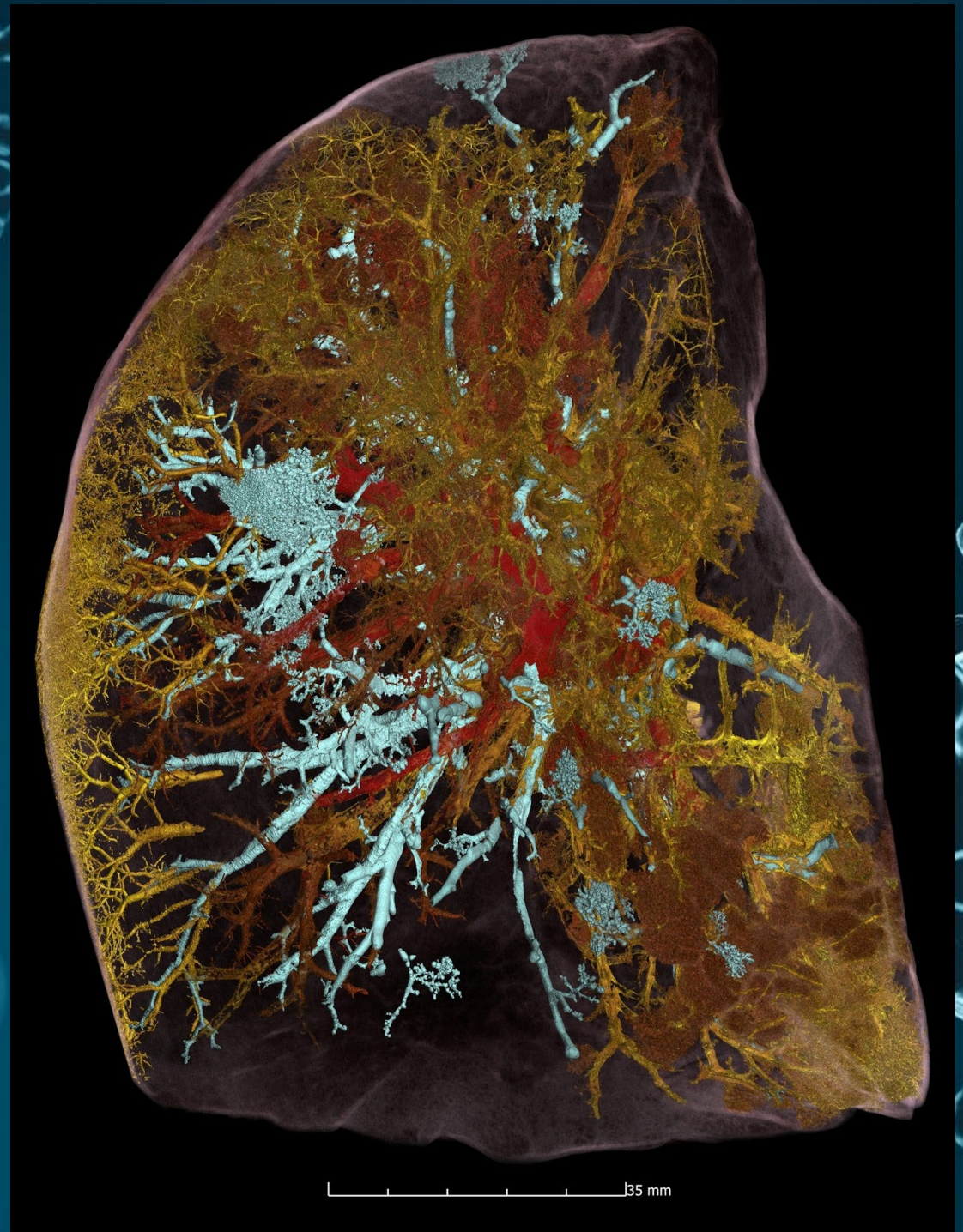

Stein, S.R., Ramelli, S.C., Grazioli, A. *et al.* SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* **612**, 758–763 (2022). https://doi.org/10.1038/s41586-022-05542-y



This immunofluorescent image shows SARS-CoV-2 components (green) specifically in neurons (magenta) in the hypothalamus of the brain of a person who died from COVID-19. Image captured and colorized at Rocky Mountain Laboratories in Hamilton, Montana. *Credit: NIAID*

# Hierarchical Phase-Contrast Tomography (HiP-CT) of COVID Lung

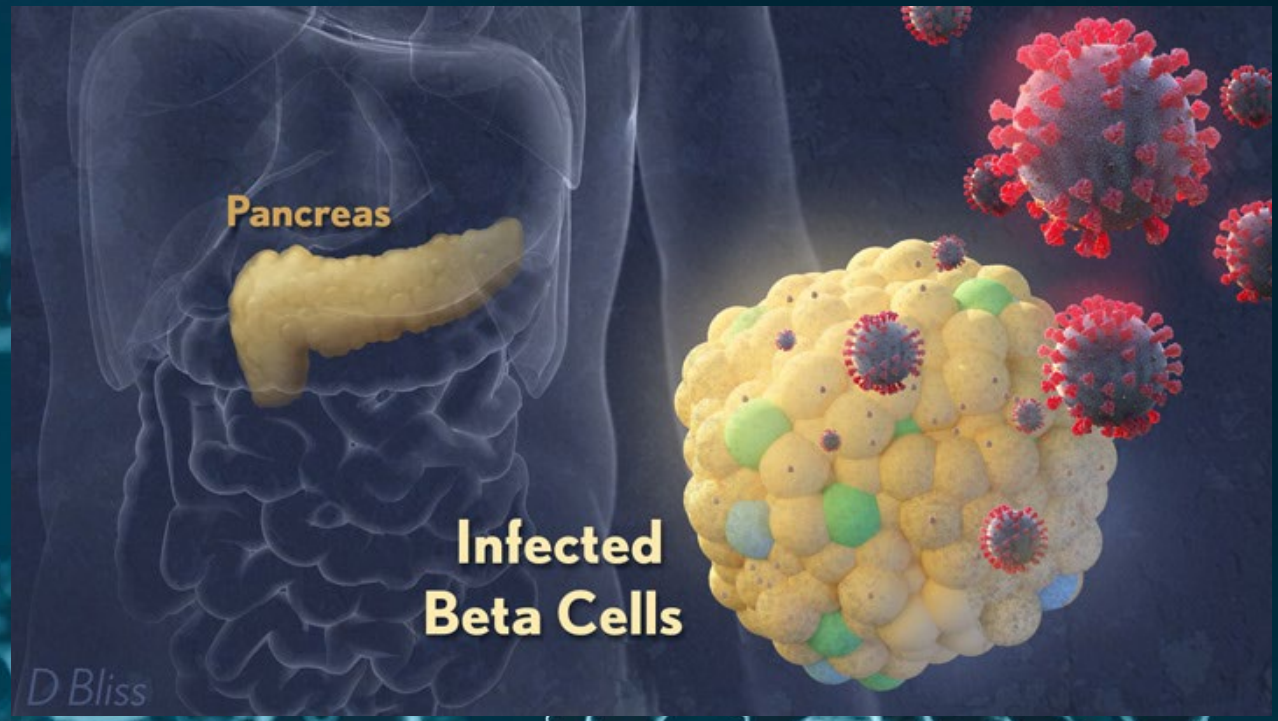
BY MICHAEL GRESHKO
PHOTOGRAPHS BY LUCA LOCATELLI AND ESRF, HUMAN ORGAN ATLAS




This HiP-CT scan reveals the vasculature within a lung lobe from a 54-year-old male who died of COVID-19. HiP-CT scans show that in severe COVID-19 cases, the lungs' blood vessels are severely damaged: Here, airspaces are colored with cyan, open blood vessels are colored in red, and **blocked, damaged blood vessels are colored in yellow**.

# Post-COVID Diabetes

**Patients in the study were about 40% more likely than the control groups to develop mainly type 2 diabetes.**




SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Müller JA, Groß R, Conzelmann C, Münch J, Heller S, Kleger A, et al. Nat Metab. 2021 Feb;3(2):149-165.

Posted on June 8th, 2021 by Dr. Francis Collins, NIH

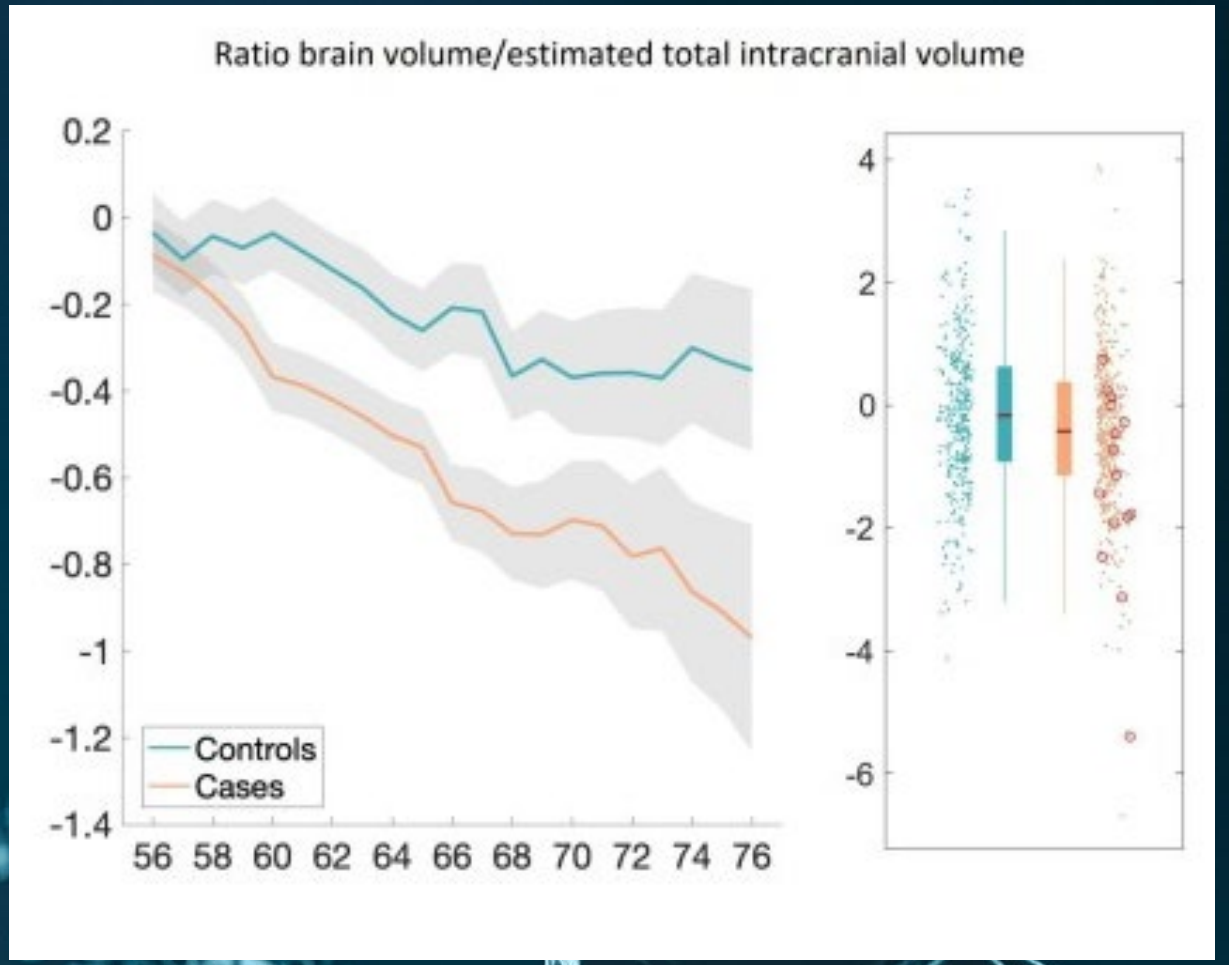
# Study Verifies COVID-19 Infection Increases Diabetes Risk | Cedars-Sinai

# Even Mild COVID is Linked to Brain Damage

## Even a mild case of COVID can shrink your brain the same as aging 10 years

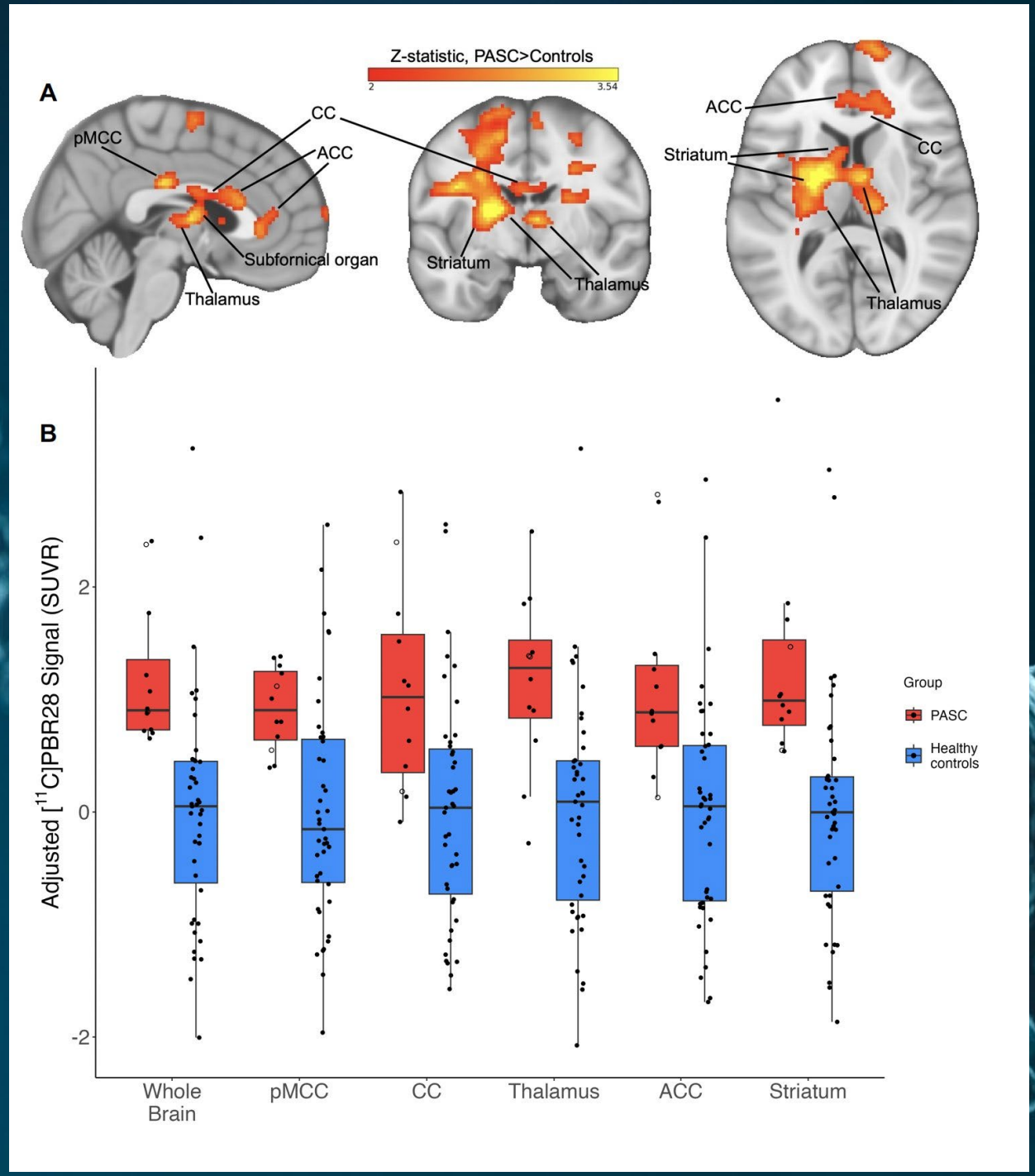
Hierarchical Phase-Contrast Tomography or 'HiP-CT' of Human Brain. Performed at the ESRF-EBS 4th generation synchrotron in Grenoble

## COVID-19 Kills Blood Vessels in The Brain of Infected Individuals!




The graph shows changes in the size of the brain between Covid patients (orange) and those who did not catch the virus (blue). It shows in both cases those who had Covid saw a faster decline while they aged (Credits: Douaud, G., Lee, S., Alfaro-Almagro, F. *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 604, 697–707 (2022). https://doi.org/10.1038/s41586-022-04569-5)

# Neuroinflammation in post-acute sequelae of COVID-19 (PASC) as assessed by [$^{11}$C]PBR28 PET correlates with vascular disease measures




**pMCC = posterior midcingulate cortex; CC = corpus callosum; ACC = anterior cingulate cortex**

M.B. VanElzakker, M. G. H. Martinos and Hannah F. Bues

bioRxiv preprint doi: https://doi.org/10.1101/2023.10.19.563117 ; this version posted October 20, 2023

# COVID-19 Increases The Risk of Cardiovascular Disease 12 Months Later!

Hierarchical Phase-Contrast Tomography or ‘HiP-CT’. Performed at the ESRF-EBS 4th generation synchrotron in Grenoble

Xie, Y., Xu, E., Bowe, B. *et al.* Long-term cardiovascular outcomes of COVID-19. ***Nat Med*** (2022). https://doi.org/10.1038/s41591-022-01689-3

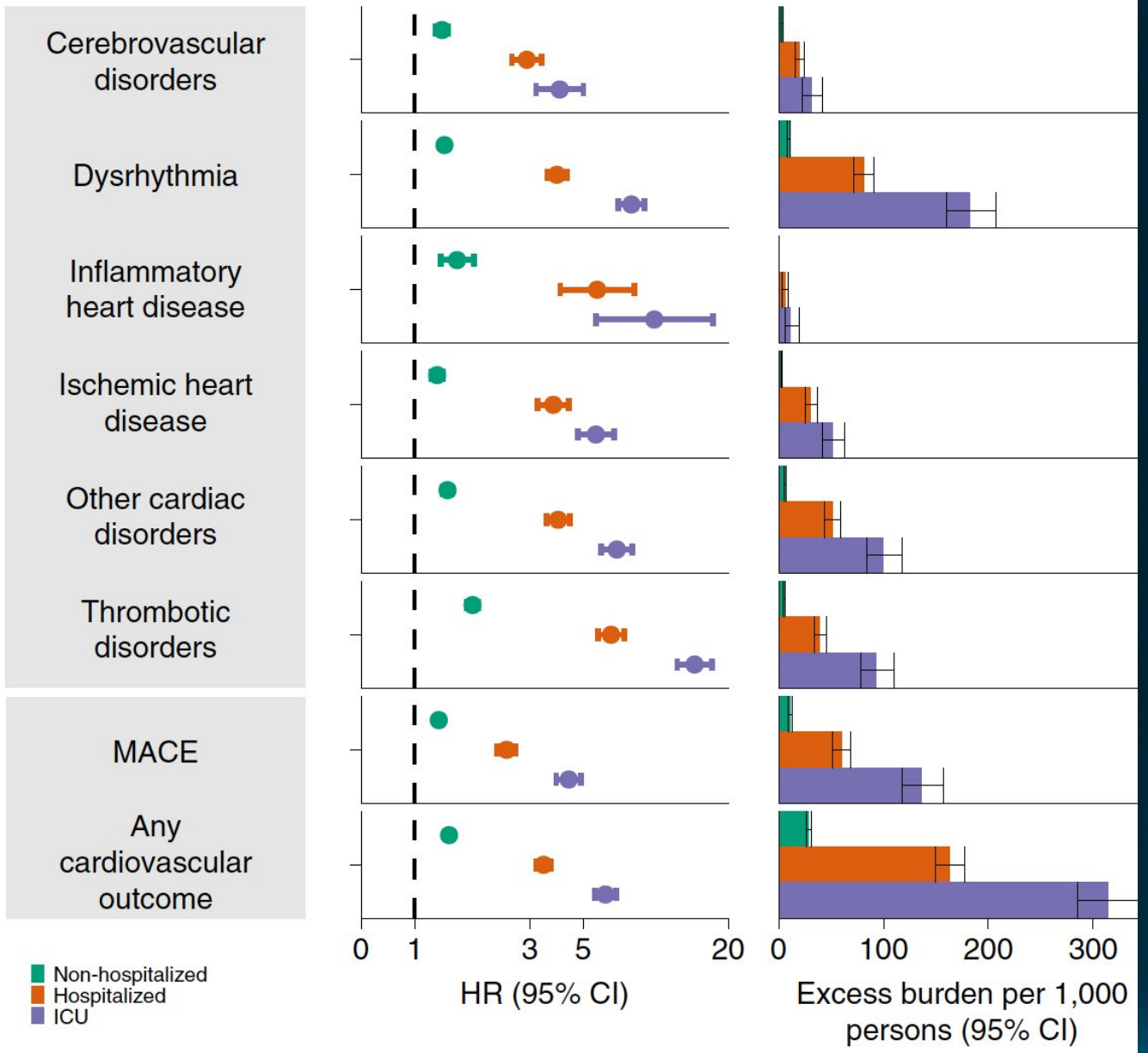
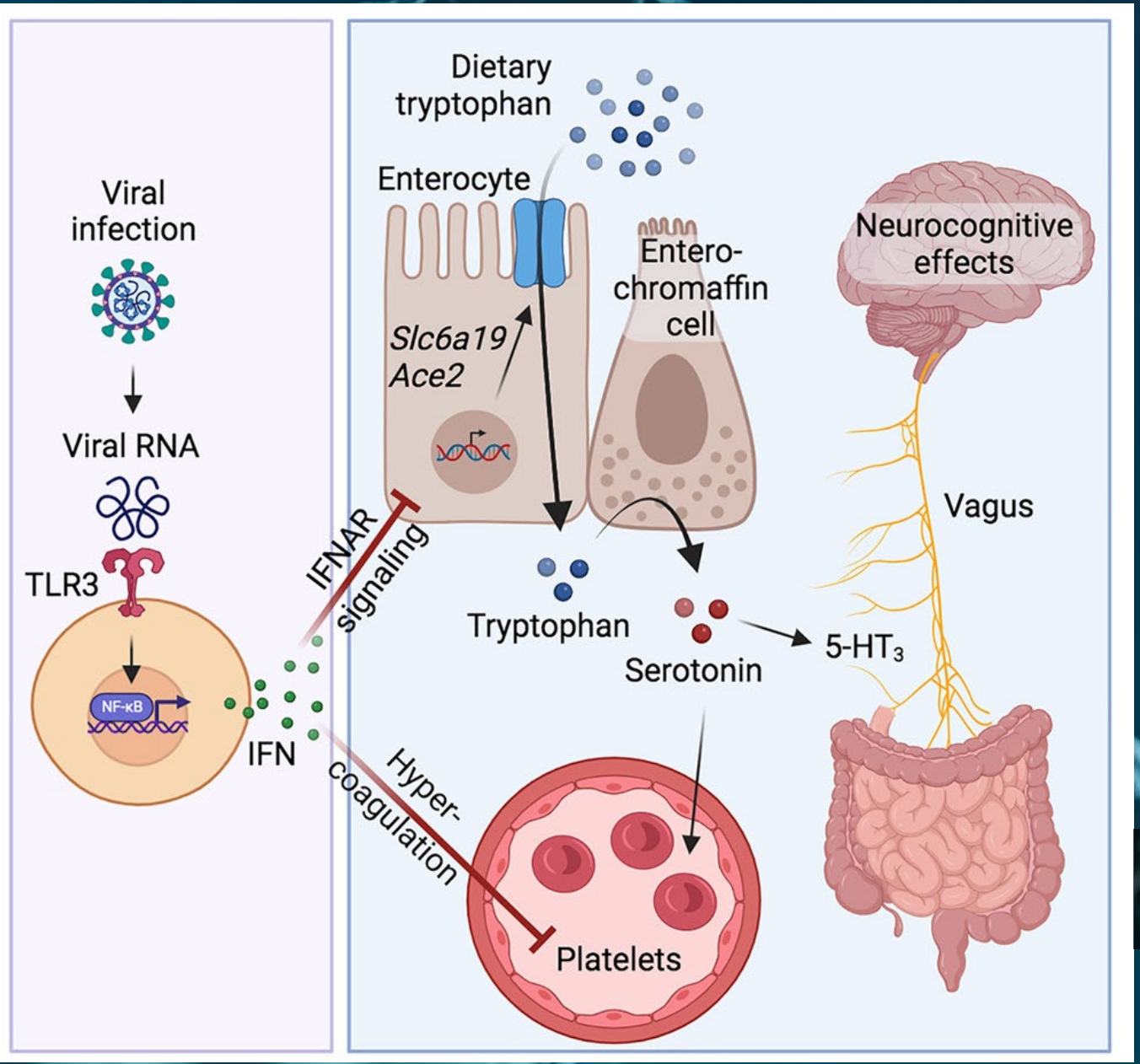



**Fig. 6 | Risks and 12-month burdens of incident post-acute COVID-19**

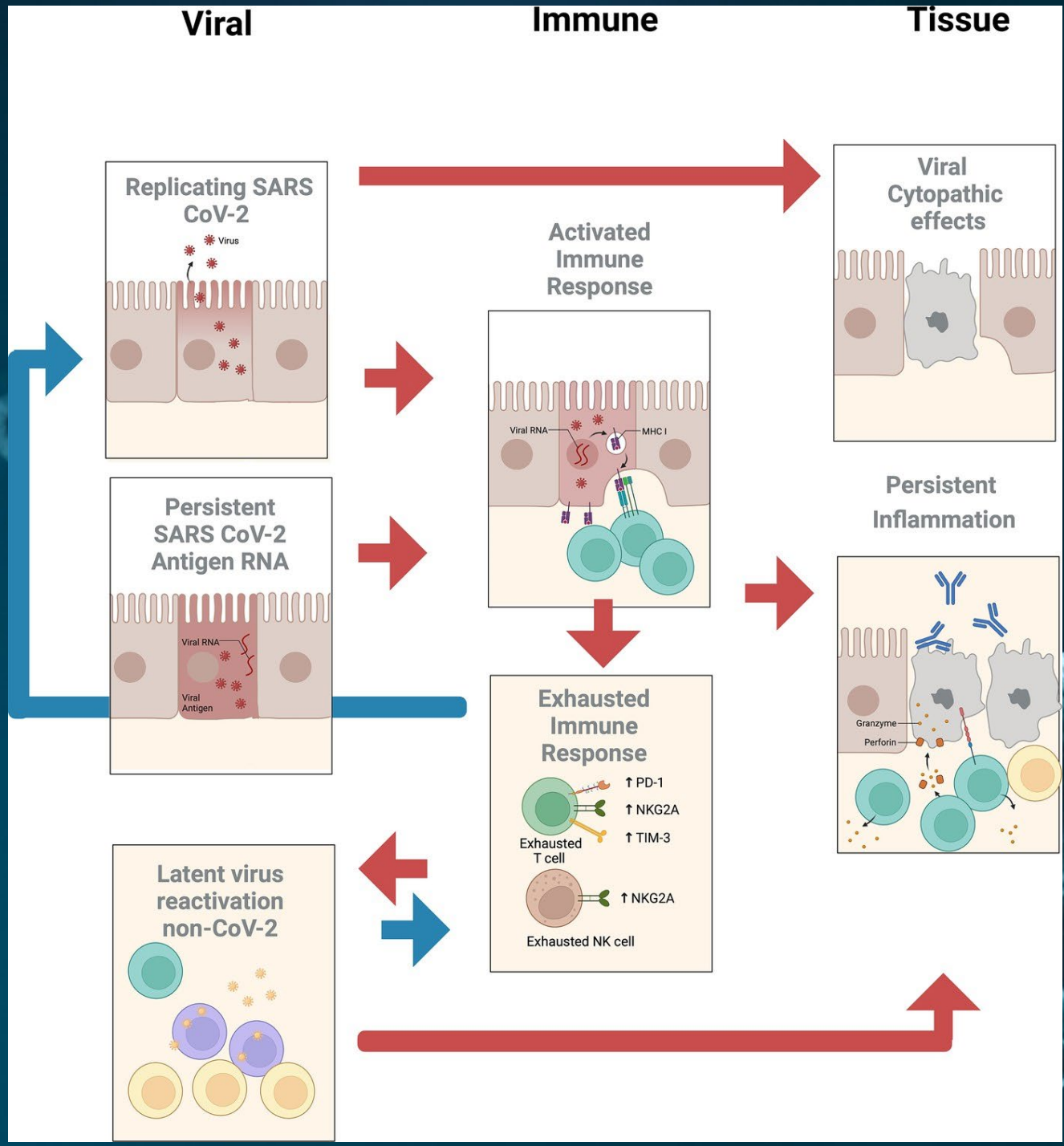
# Serotonin Reduction in Long COVID Drives Brain Fog




- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

**Wong et al. Cell, 2023.**
https://doi.org/10.1016/j.cell.2023.09.013

# Summary of Potential Viral, Immune, and Tissue Roles in Post-acute Sequelae of SARS CoV-2 Infection (PASC).




Chen, et al. RECOVER Mechanistic Pathways Task Force (2023) **Viral persistence, reactivation, and mechanisms of long COVID** *eLife* **12**:e86015. https://doi.org/10.7554/eLife.86015

# Latent Viruses Activated Following SARS-CoV-2 Infection

### Cytomegalovirus (CMV)

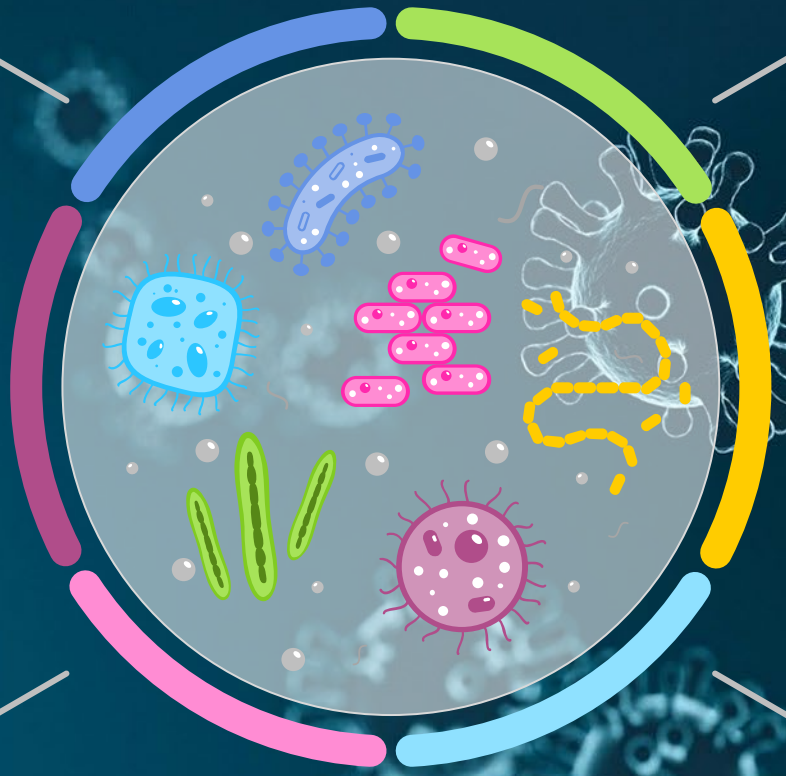
In Babies: brain, liver, spleen, lung, and growth problems.

### Human Herpesvirus Family

Herpes simplex virus (HSV) 1 & 2; Kaposi Epstein-Barr Virus (EBV); Sarcoma-associated Herpesvirus; Varicella-Zoster Virus (VZV)

### Parvovirus B19

'slapped face rash', sore throat, headache, cough



### Human Endogenous Retrovirus K (HERV-K)

Associated with malignant tumors of the testes; has multiple copies in the human genome

### Adenovirus

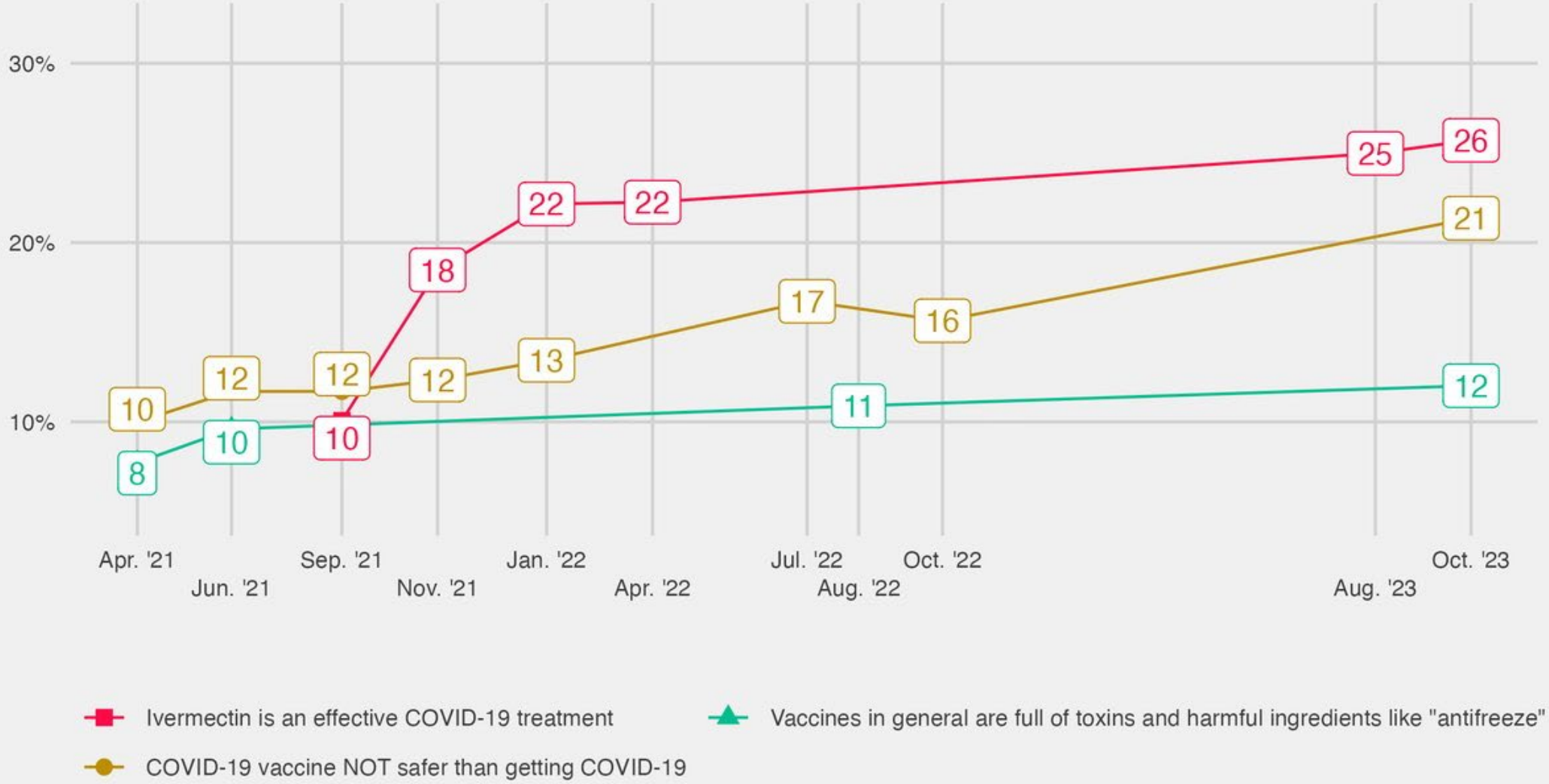
Typically cause mild cold- or flu-like illness.

**Others**:
**HIV, John Cunningham (JC) virus; BK virus (**Human polyomavirus 1)

Post-acute sequelae of SARS-CoV-2 infection (PASC) associated with latent virus activation

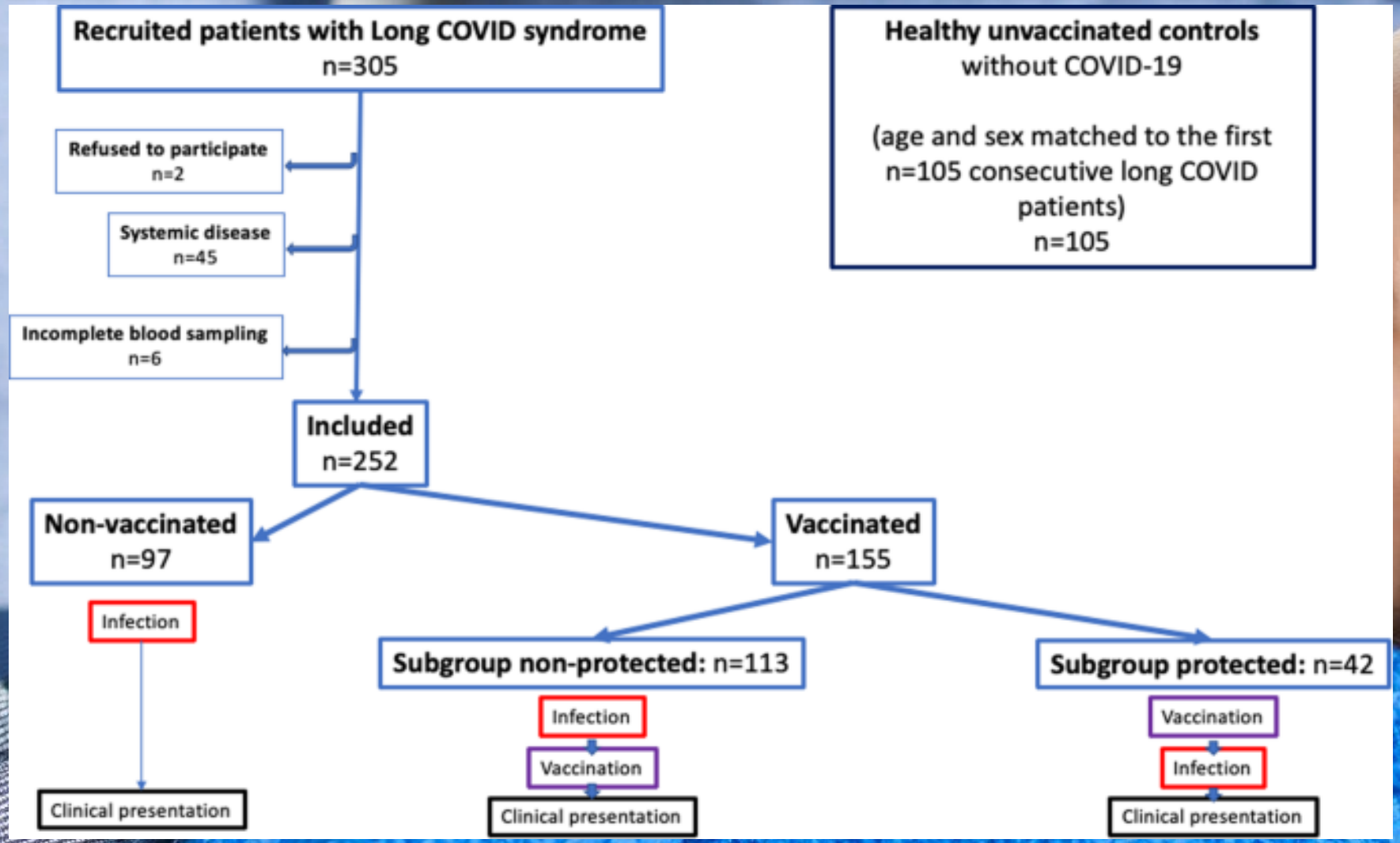
# Increasing Belief in Vaccine Misinformation

(% of respondents holding science-inconsistent views)




Source: ASAPH Survey, April 2021 - October 2023
Note: Combined subcategories may not add to totals in topline and text due to rounding.

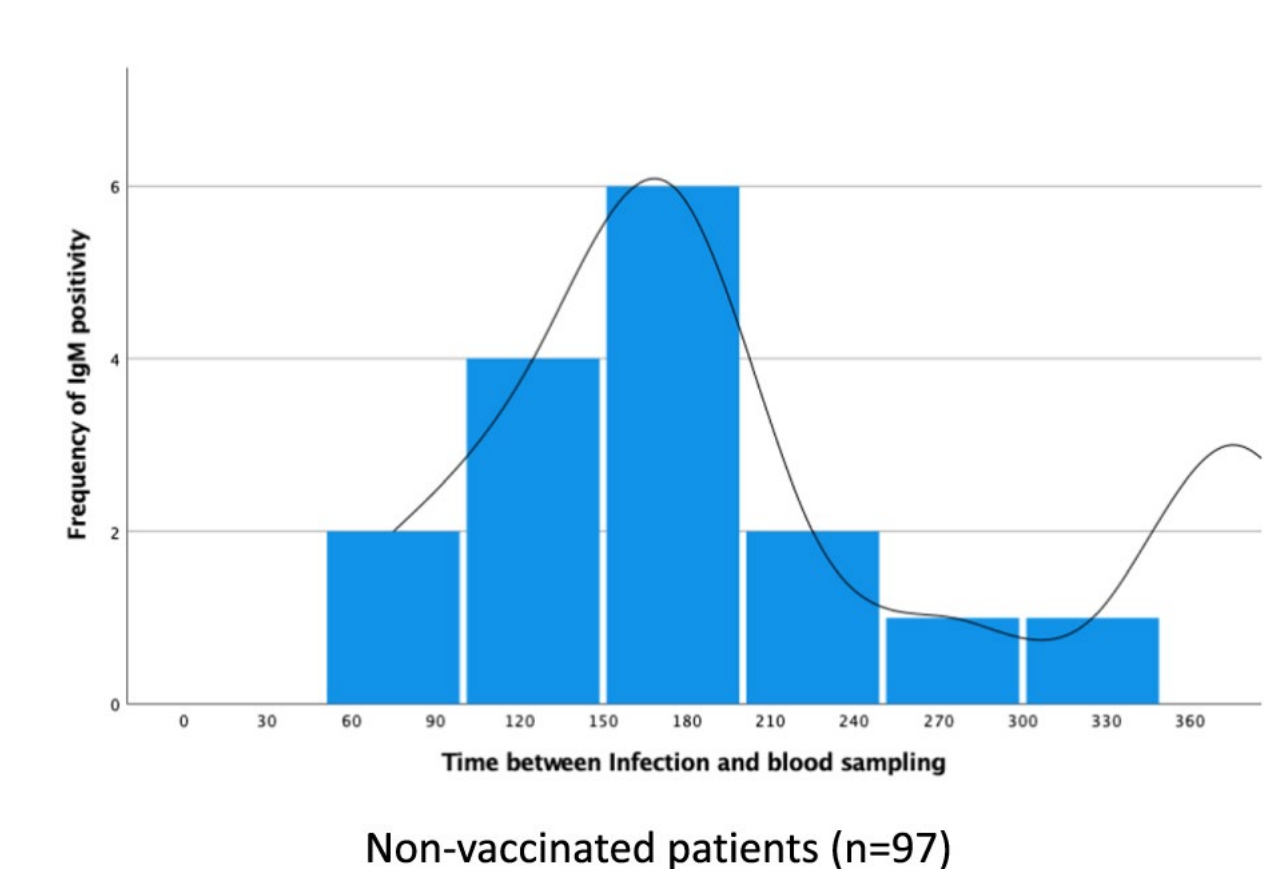
# Anti-SARS-CoV-2 Vaccination May Interrupt Viral Cross-talk in Patients with Long-COVID Syndrome



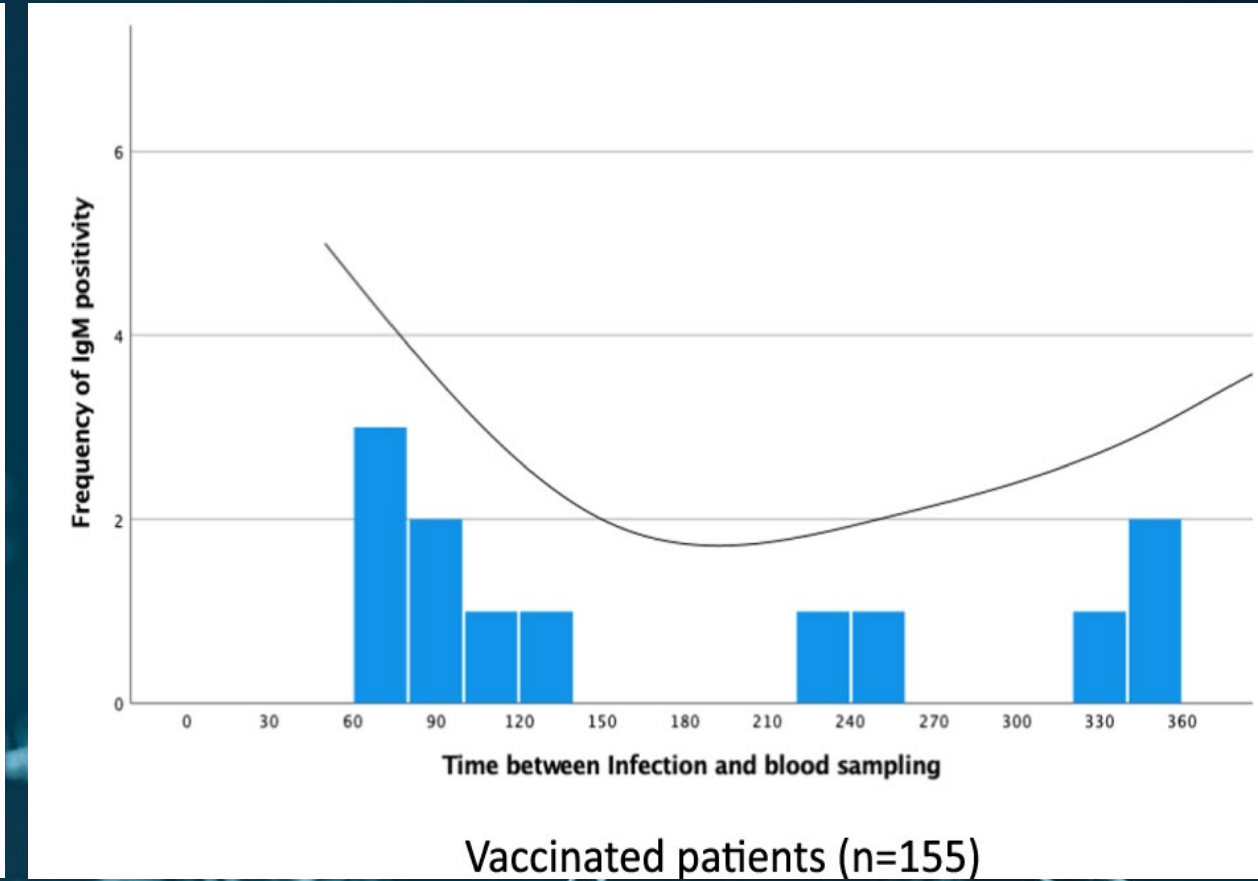

Gyöngyösi, M., Lukovic, D., Mester-Tonczar, J. *et al.* **Effect of monovalent COVID-19 vaccines on viral interference between SARS-CoV-2 and several DNA viruses in patients with long-COVID syndrome**. *npj Vaccines* **8**, 145 (2023). https://doi.org/10.1038/s41541-023-00739-2

Cardiology Long-COVID Unit of the Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria: ClinicalTrials.gov Identifier: NCT05398952

# Cumulative IgM positivity, for Herpes Simplex virus (HSV), Varicella-zoster virus (VZV), Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and Parvovirus-B19




Non-vaccinated patients (n=97)

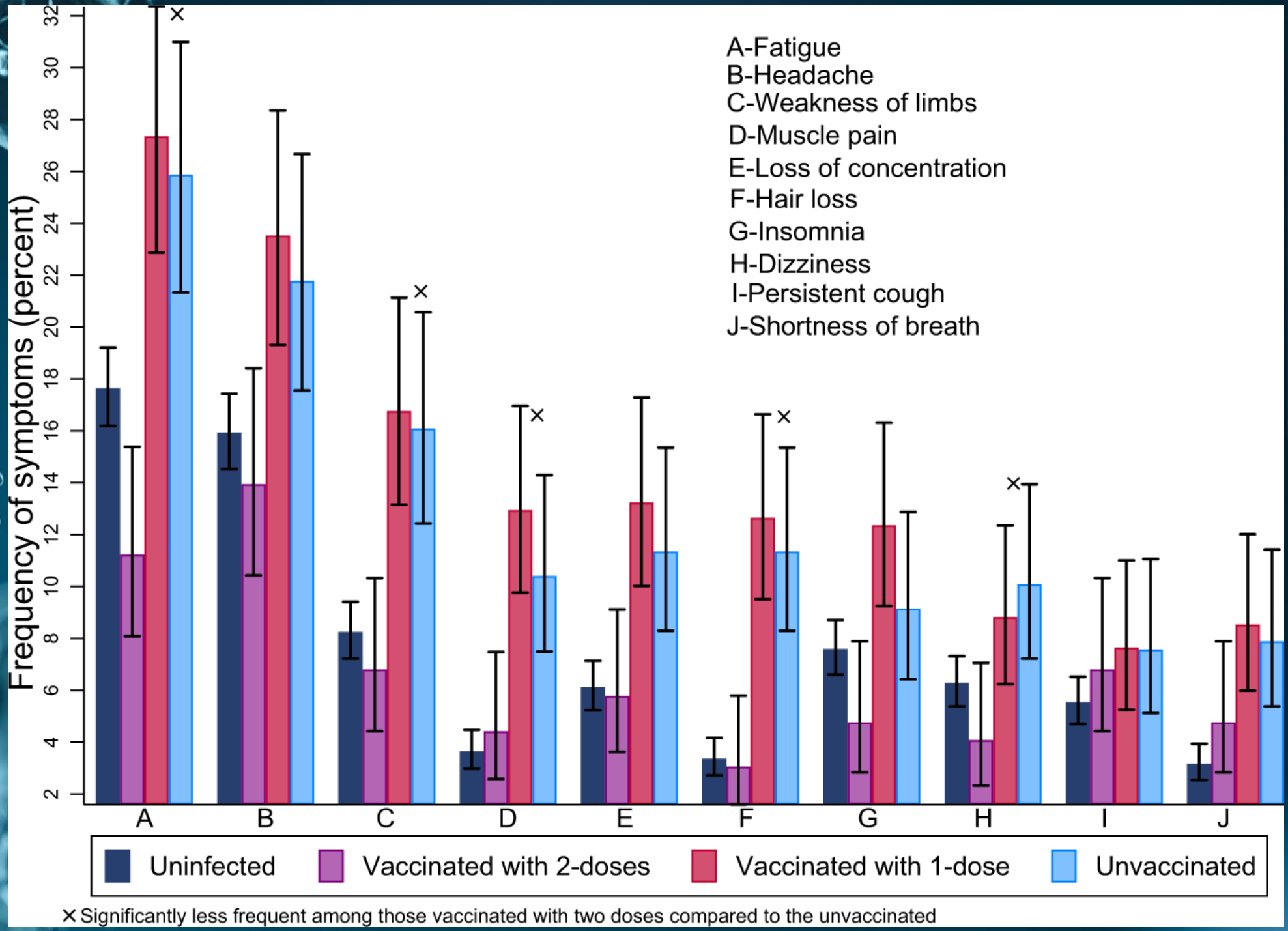



Vaccinated patients (n=155)

Gyöngyösi, M., Lukovic, D., Mester-Tonczar, J. *et al.* Effect of monovalent COVID-19 vaccines on viral interference between SARS-CoV-2 and several DNA viruses in patients with long-COVID syndrome. *npj Vaccines* **8**, 145 (2023). https://doi.org/10.1038/s41541-023-00739-2

# Association between BNT162b2 vaccination and reported incidence of post-COVID-19 symptoms: cross-sectional study 2020-21, Israel

Kuodi, P., Gorelik, Y., Zayyad, H. *et al.* Association between BNT162b2 vaccination and reported incidence of post-COVID-19 symptoms: cross-sectional study 2020-21, Israel. *npj Vaccines* **7**, 101 (2022). https://doi.org/10.1038/s41541-022-00526-5



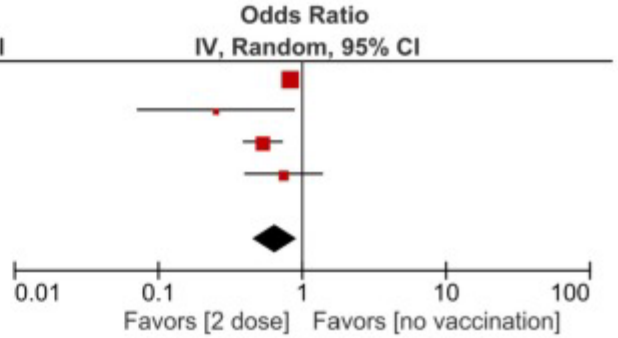
Watanabe A, Iwagami M, Yasuhara J, Takagi H, Kuno T. **Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis.** Vaccine. 2023 Mar 10;41(11):1783-1790. doi: 10.1016/j.vaccine.2023.02.008. Epub 2023 Feb 8. PMID: 36774332; PMCID: PMC9905096.

Study involved six observational studies involving 536,291 unvaccinated and 84,603 vaccinated (before SARS-CoV-2 infection) patients (mean age, 41.2–66.6; female, 9.0–67.3%) and **six** observational studies involving 8,199 **long COVID patients** (mean age, 40.0 to 53.5; female, 22.2–85.9%) who received vaccination after SARS-CoV-2 infection were included.

a) two-dose vaccination vs. no vaccination

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Al-Aly [16] | -0.1936 | 0.0134 | 42.0% | 0.82 [0.80, 0.85] |
| Azzolini [17] | -1.3863 | 0.6363 | 7.0% | 0.25 [0.07, 0.87] |
| Emecen [23] | -0.6349 | 0.1563 | 32.2% | 0.53 [0.39, 0.72] |
| Meza-Torres [22] | -0.3011 | 0.3142 | 18.8% | 0.74 [0.40, 1.37] |
| **Total (95% CI)** | | | **100.0%** | **0.64 [0.45, 0.92]** |

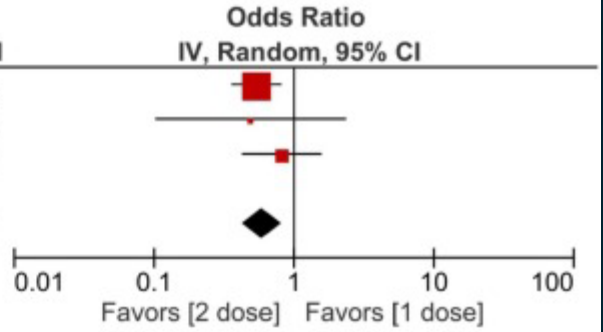
Heterogeneity: Tau² = 0.08; Chi² = 11.52, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 2.39 (P = 0.02)




b) two-dose vaccination vs. one-dose vaccination

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Antonelli [25] | -0.6162 | 0.2005 | 69.2% | 0.54 [0.36, 0.80] |
| Azzolini [17] | -0.7133 | 0.7933 | 4.4% | 0.49 [0.10, 2.32] |
| Meza-Torres [22] | -0.1985 | 0.3249 | 26.4% | 0.82 [0.43, 1.55] |
| **Total (95% CI)** | | | **100.0%** | **0.60 [0.43, 0.83]** |

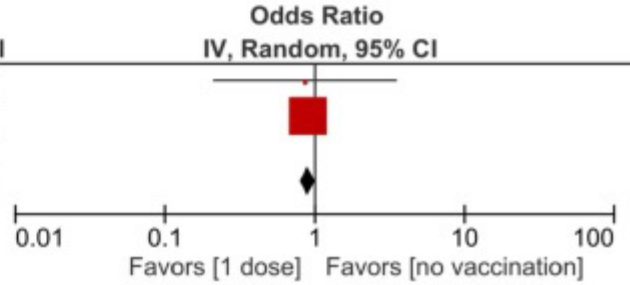
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.06 (P = 0.002)



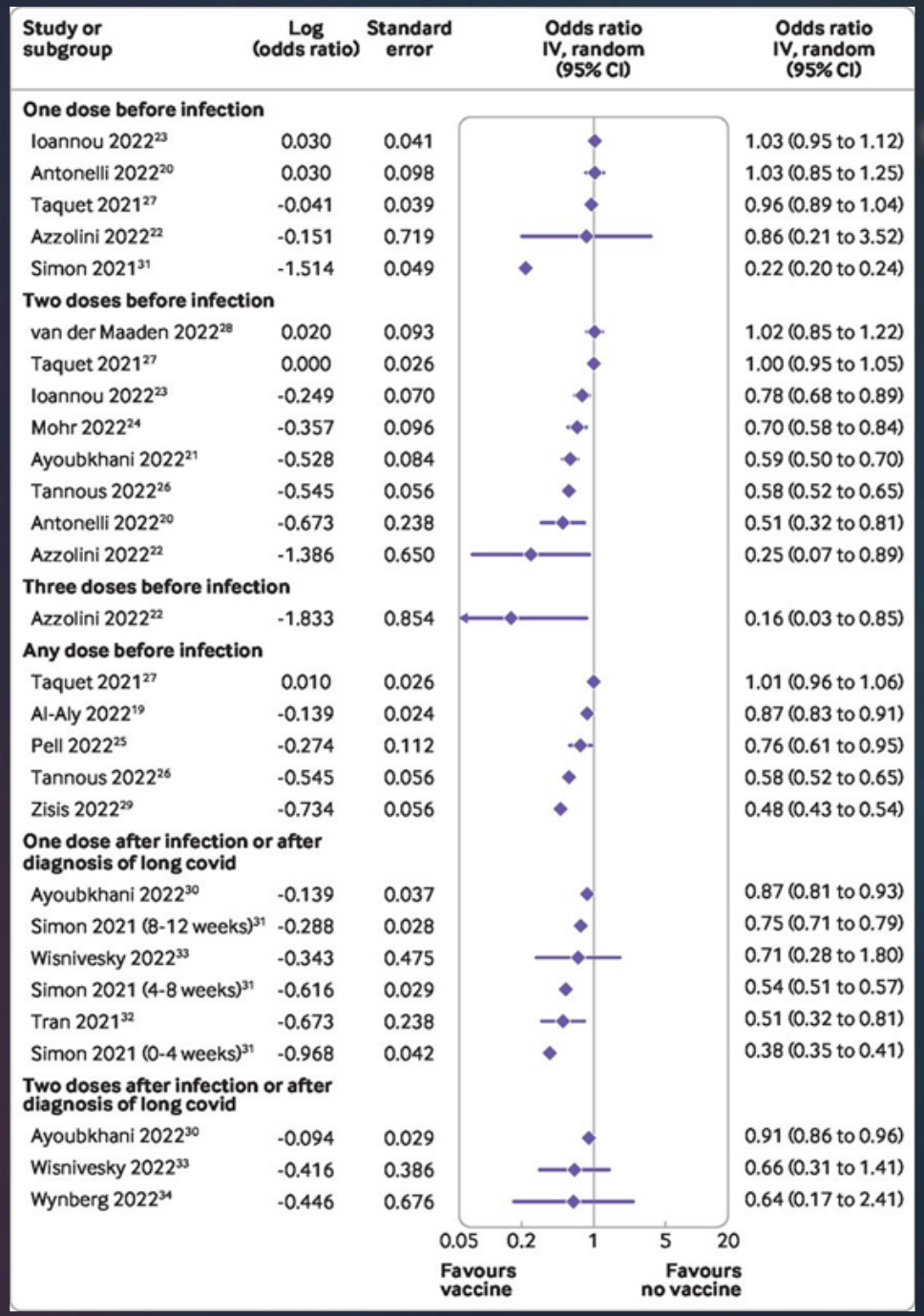

c) one-dose vaccination vs. no vaccination

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Azzolini [17] | -0.1508 | 0.7147 | 0.7% | 0.86 [0.21, 3.49] |
| Meza-Torres [22] | -0.1054 | 0.0588 | 99.3% | 0.90 [0.80, 1.01] |
| **Total (95% CI)** | | | **100.0%** | **0.90 [0.80, 1.01]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)



# The Effect of Covid-19 Vaccine Doses on Long Covid.

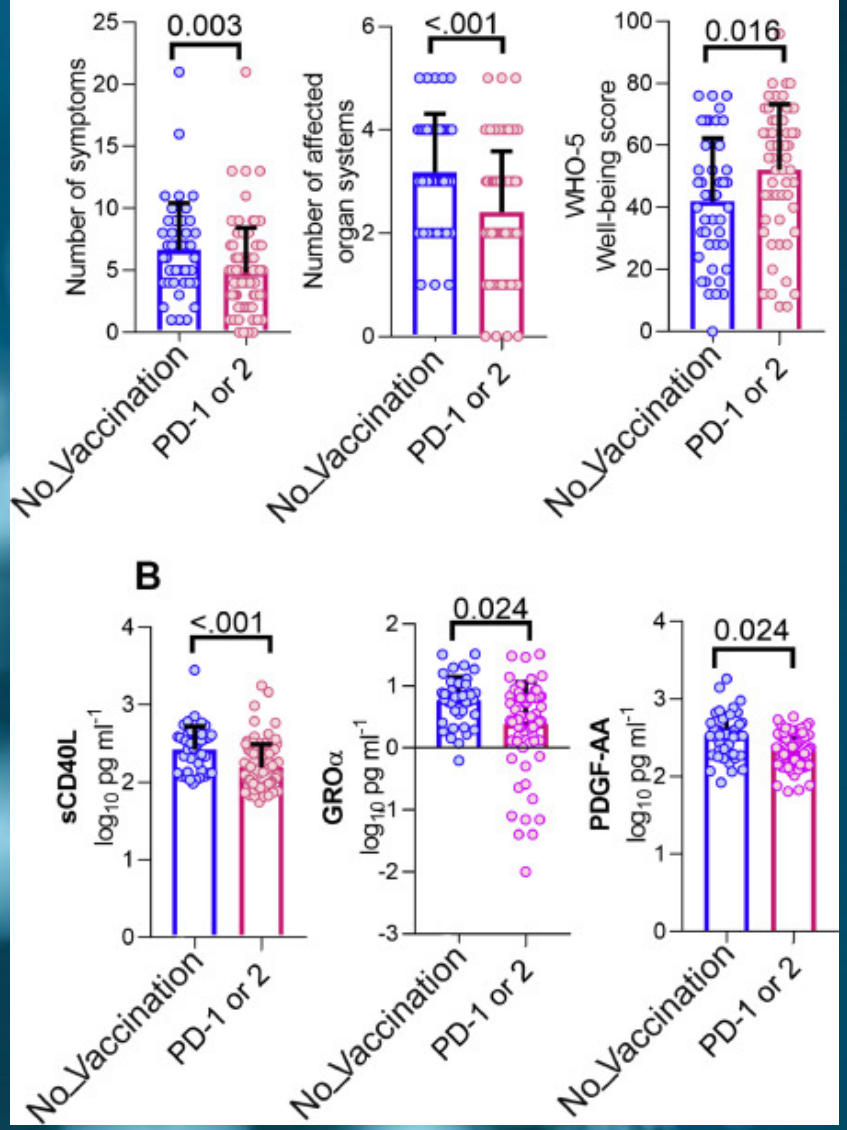



Forest plot of the effect of covid-19 vaccine doses on long covid. Only relevant outcomes from all reported outcomes in individual studies were chosen. IV=inverse variance

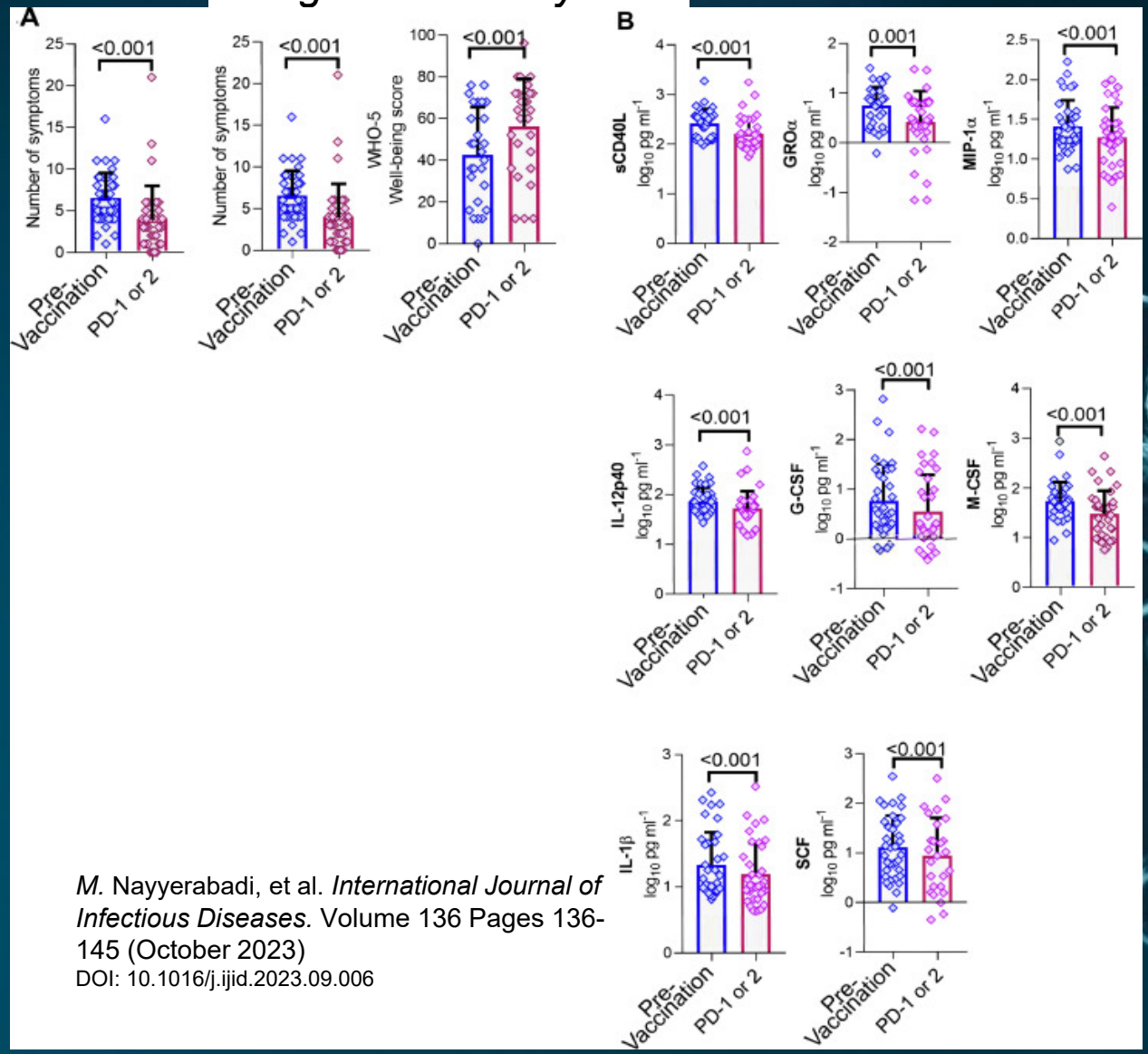
Byambasuren O, et al. BMJMED 2023;2:e000385. doi:10.1136/bmjmed-2022-000385

# Vaccination After Developing Long COVID: Impact on Clinical Presentation, Viral Persistence, and Immune Responses

## *Cross-sectional study*



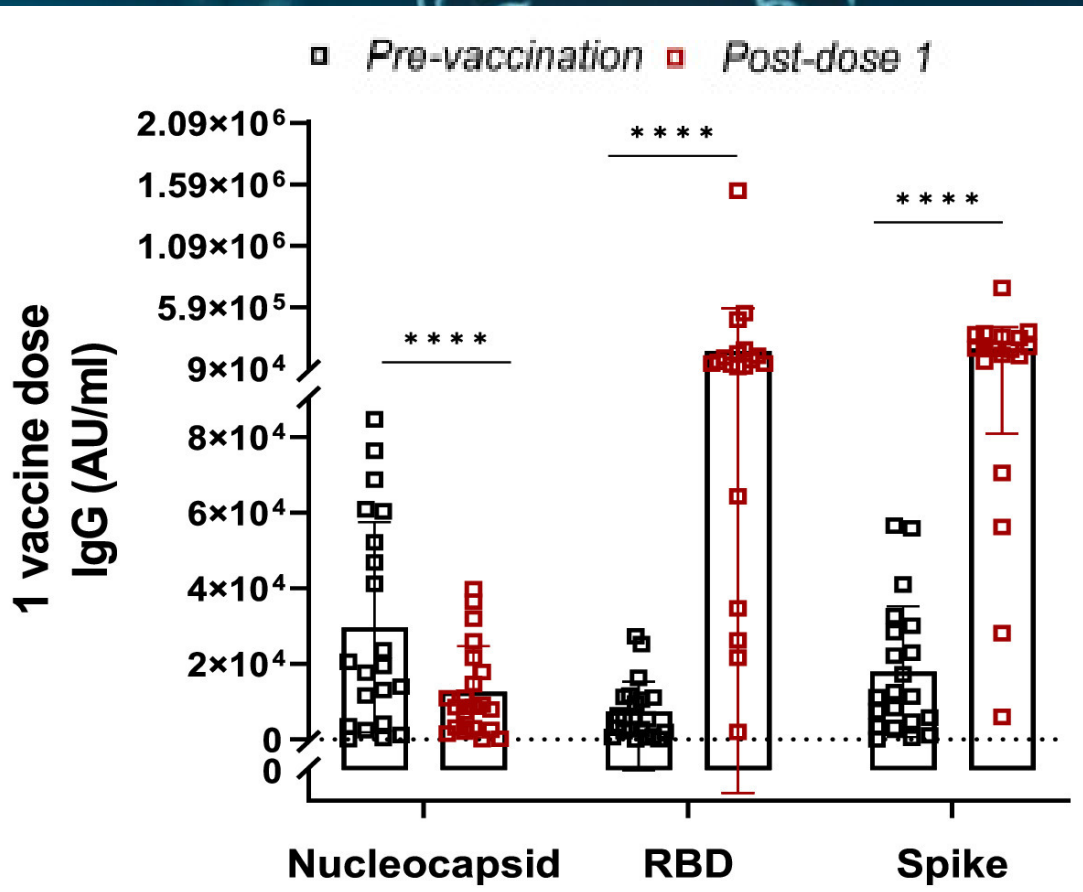

## *Longitudinal study*

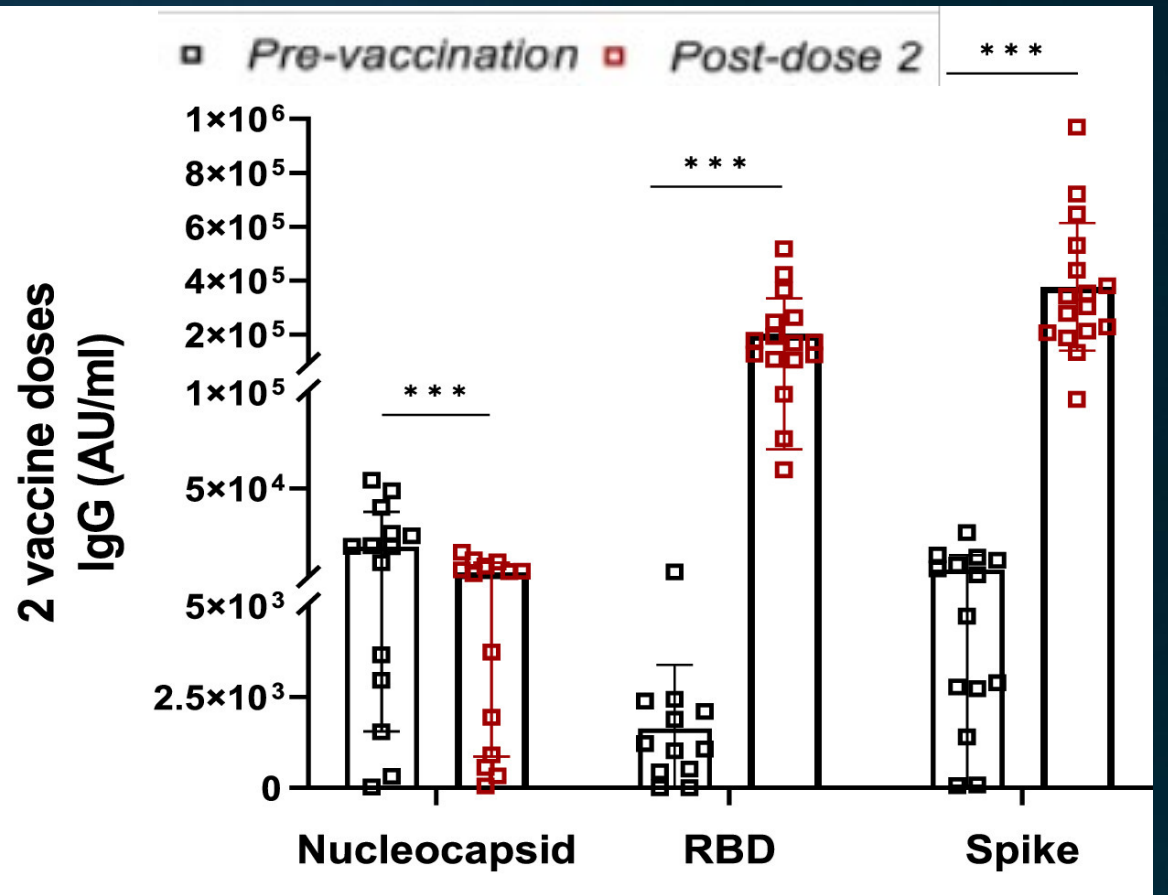



*M.* Nayyerabadi, et al. *International Journal of Infectious Diseases.* Volume 136 Pages 136-145 (October 2023)
DOI: 10.1016/j.ijid.2023.09.006

Study shows higher pro-inflammatory responses associated with PCC symptoms and brings forward a possible role for vaccination in mitigating PCC symptoms by decreasing systemic inflammation.

# Vaccination After Developing Long COVID: IgG Immune Response




*Maryam Nayyerabadi, et al; IJID*, Vol 136. Pages 136-145 (November 2023) DOI: 10.1016/j.ijid.2023.09.006

# COVID Vaccination After Long COVID Linked to Better Outcomes

## Vaccination linked to lower cytokines

The five most common PCC symptoms reported at the beginning of the study were **fatigue (81.9%), trouble with concentration (47.0%), trouble with memory (39.8%), headache (32.5%)** and **shortness of breath at rest (31.3%)** during all follow-ups.

**After vaccination, 77.8%**, 7.4%, and 14.8% of participants reported **improved**, worsened and unchanged well-being scores, respectively, the authors said. And **86%**, 8.3% and 5.6% of participants reported **fewer**, more, and the same **number of PCC symptoms**, respectively.

> **“We observed a significant reduction in systemic inflammatory cytokine/chemokine levels post-vaccination, independent of number of vaccine doses received.”**

**16 cytokines and chemokines were significantly decreased after vaccination** in participant blood samples, a sign that inflammatory proteins were mitigated by vaccination.

**"High inflammatory cytokine/chemokine levels have been correlated with increased acute COVID-19 severity and poor prognosis,"** the authors concluded. **"We observed a significant reduction in systemic inflammatory cytokine/chemokine levels post-vaccination, independent of number of vaccine doses received.“** - CIDRAP

# Review Estimates 69% 3-dose Vaccine Efficacy Against Long COVID

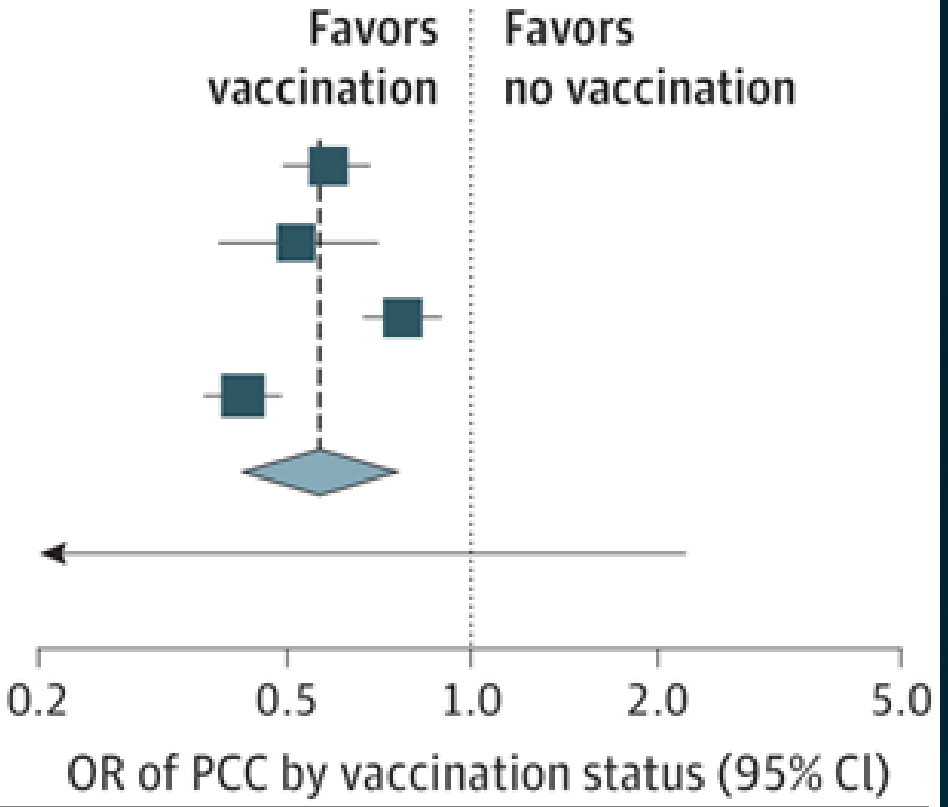
| Vaccinated individuals | COVID-19 vaccine before/after COVID-19 infection** | Studies included (*n*) | Participants [vaccinated + unvaccinated] (*n*) | Pooled Diagnostic Odds Ratio [DOR] (95% CI) | $I^2$ test for heterogeneity | Vaccine effectiveness* (95% CI) |
|---|---|---|---|---|---|---|
| Fully vaccinated | Before/After | 24 | 620,221 | 0.680 | 0% | 32.0% |
| | | | | (0.523, 0.885) | | (11.5%, 47.7%) |
| Fully vaccinated | Before | 21 | 618,841 | 0.631 | 0% | 36.9% |
| | | | | (0.518, 0.769) | | (23.1%, 48.2%) |
| Fully vaccinated | After*** | 5 | 396,101 | 1.303 | 19.9% | – |
| | | | | (0.890, 1.907) | | |
| Fully vaccinated | Before (Omicron era) | 7 | 25,414 | 0.684 | 50.1% | 31.6% |
| | | | | (0.542, 0.862) | | (13.8%, 45.8%) |
| Booster dose (1st) | Before | 3 | 5,948 | 0.313 | 0% | 68.7% |
| | | | | (0.278, 0.353) | | (64.7%, 72.2%) |

Receiving a complete COVID-19 vaccination prior to contracting the virus resulted in a significant reduction in post-COVID conditions throughout the study period, including during the Omicron era. Vaccine effectiveness demonstrated an increase when supplementary doses were administered.

Marra, A., Kobayashi, T., Callado, G., Pardo, I., Gutfreund, M., Hsieh, M., . . . Rizzo, L. (2023). The effectiveness of COVID-19 vaccine in the prevention of post-COVID conditions: A systematic literature review and meta-analysis of the latest research. *Antimicrobial Stewardship & Healthcare Epidemiology, 3*(1), E168. doi:10.1017/ash.2023.447

# Association of Vaccination Status With Post–COVID-19 Condition (PCC), 2021 to 2022

| Source | OR (95% CI) |
|---|---|
| Ayoubkhani et al[18] | 0.59 (0.50-0.69) |
| Emecen et al[26] | 0.53 (0.40-0.71) |
| loannou et al[34] | 0.78 (0.68-0.90) |
| Zisis et al[12] | 0.43 (0.37-0.49) |
| Total (random effects) | 0.57 (0.43-0.76) |
| Prediction interval | (0.15-2.22) |
| Heterogeneity: $\chi^2_3 = 35.00$ ($P < .001$); $I^2 = 91\%$ | |




**Individuals who were vaccinated against COVID-19 with 2 doses had a significantly lower risk of developing PCC than individuals who had not been vaccinated. The dotted line represents the point of no difference between the 2 groups, and the dashed line represents the average effect of all studies when pooled together. OR indicates odds ratio.**

Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post−COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med.* 2023;183(6):566–580. doi:10.1001/jamainternmed.2023.0750

# Main Take Away

HEALTHWATCH ›

## Long COVID has affected nearly 7% of American adults, CDC survey data finds

CBS NEWS HEALTH WATCH

BY SARA MONIUSZKO

SEPTEMBER 26, 2023 / 1:32 PM / CBS NEWS

Epidemic Prevention/ Success Stories

## "VOICES" OF LONG COVID STRESS THE URGENCY OF COVID-19 VACCINATION

Awareness campaign spotlights COVID long-haulers to increase vaccine uptake


"I used to run 5 to 6 miles a day. Now, when I walk up a flight of stairs, I'm gasping for air ... I'm telling my Long COVID story because I don't want it to ruin other people's lives like it did mine."
-Rob, 22


"I can no longer remember some things that happened even way before I got COVID ... I'm telling my Long COVID story so that you won't have one to tell."
-Katelyn, 20

PUBLIC HEALTH

## Evidence grows that vaccines lower the risk of getting long COVID

March 24, 2022 · 5:00 AM ET

By Will Stone

CIDRAP

NEWS TOPICS & PROJECTS PODCASTS

## Vaccine may limit long-COVID impact, studies show, but controlled trials needed

Mary Van Beusekom, MS, March 1, 2023

Topics: COVID-19

## Review estimates 69% 3-dose vaccine efficacy against long COVID

Mary Van Beusekom, MS, October 13, 2023

Topics: COVID-19