

# Nonlethal effects of SARS-CoV-2 infection:

Science Circle  
October 29th 2022

Stephen Gasior, Ph.D.  
a.k.a. Stephen Xootfly  
Researcher

Company that has nothing to do with this talk  
Former University Biology Instructor

# Nonlethal effects of SARS-CoV-2 infection:

Yo! Wife! What's your name? I can't  
smell my shrunk penis but also  
going to just lie down and take a nap

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# **Nonlethal Covid**

Basics of Covid

history

life-cycle and infection

“-omics” study

Smell

Shrinkage

Toes

Brain Fog

Fatigue

# Coronavirus history

Severe  
Acute  
Respiratory  
Syndrome  
SARS  
  
coronavirus

**SARS-CoV-1** was first discovered in Asia in February 2003. The outbreak lasted approximately six months as the disease spread to more than two dozen countries in North America, South America, Europe, and Asia before it was stopped in July 2003.

## **Symptoms of SARS**

In general, SARS begins with a high fever. Other symptoms may include headache, an overall feeling of discomfort, and body aches. Some people also have mild respiratory symptoms at the outset. About 10 percent to 20 percent of patients have diarrhea. After 2 to 7 days, SARS patients may develop a dry cough. Most patients develop pneumonia.

**Deaths:** 774

**Confirmed cases:** 8,096



# Coronavirus history

Middle

East

Respiratory  
Syndrome

MERS

coronavirus

Most MERS patients developed severe respiratory illness with symptoms of fever, cough and shortness of breath. Health officials first reported the disease in Saudi Arabia in September 2012. Through retrospective (backward-looking) investigations, they later identified that the first known cases of MERS occurred in Jordan in April 2012.

## Symptoms of MERS

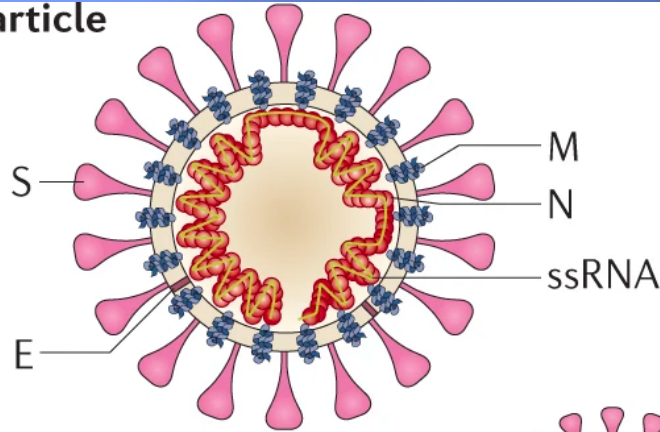
ibid SARS

**Deaths:** Approximately 35% of patients with MERS-CoV have died, but this may be an overestimate of the true mortality rate, as mild cases of MERS may be missed by existing surveillance systems (WHO).

**Confirmed cases:** 2574 (03 Aug 2021 from WHO)

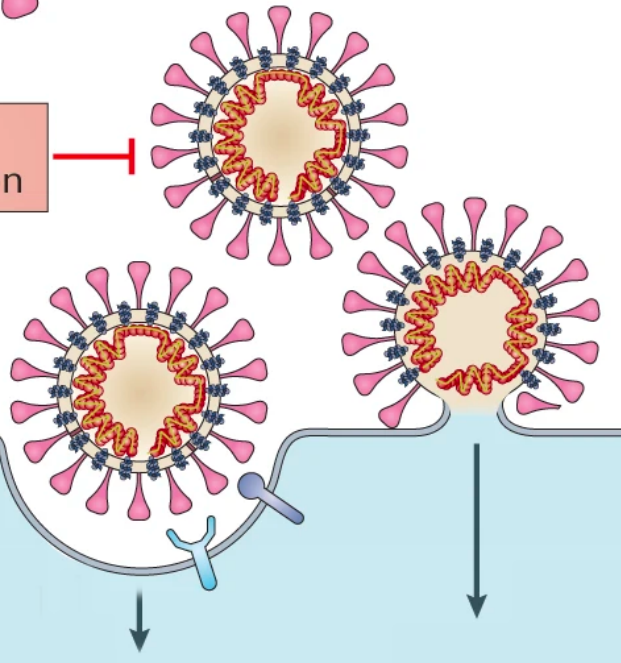
# Coronavirus Life Cycle

Viral particle



Attachment and virus neutralization

Receptor binding  
ACE2  
TMPRSS2  
(CoV-2)



Entry

“Crown”

Spike

Membrane

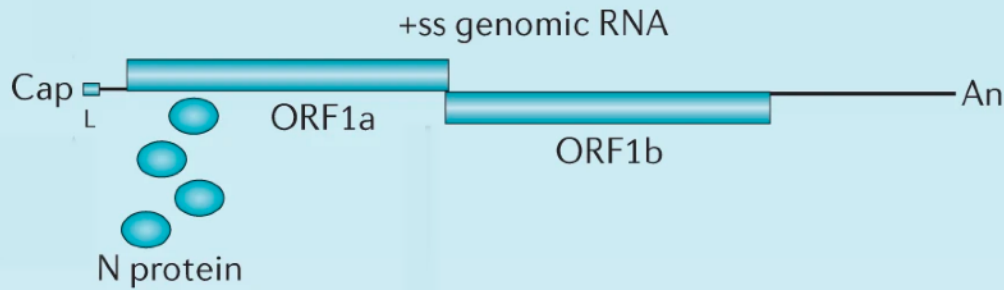
Envelope

Nucleocapsid

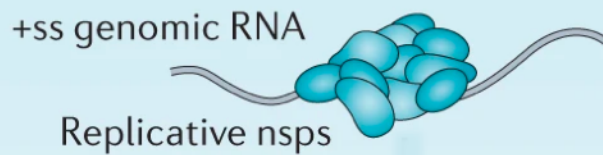
Angiotensin  
Converting Enzyme

V'kovski, Philip, et al. "Coronavirus biology and replication: implications for SARS-CoV-2." *Nature Reviews Microbiology* **19.3** (2021): 155-170.

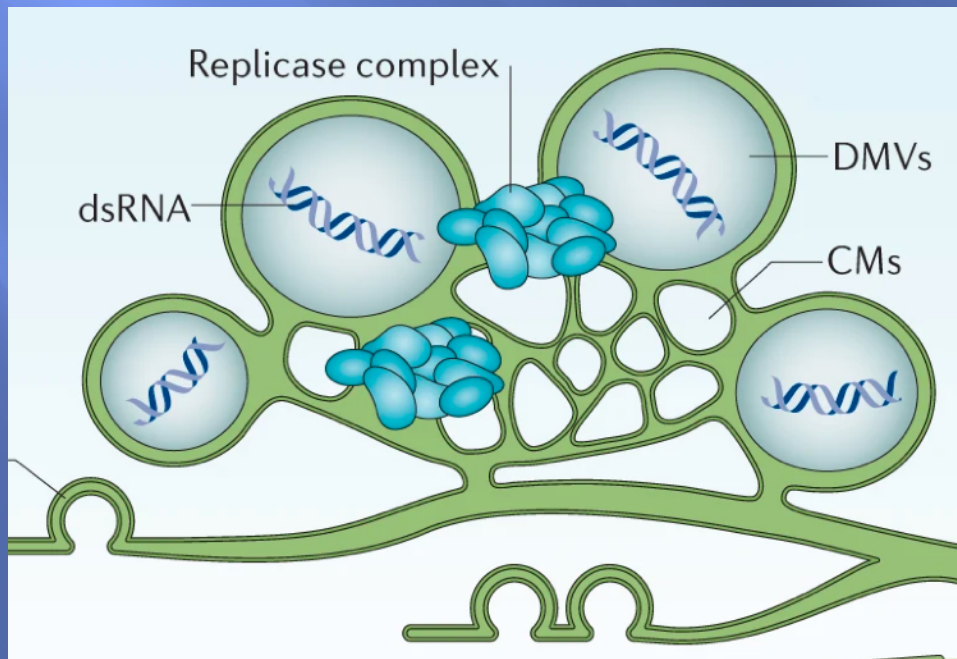
# Coronavirus Life Cycle



RNA makes 2 proteins



Proteins get processed into multiple proteins



create dsRNA (RNA dependent RNA Polymerase) replication complexes in the Endoplasmic Reticulum

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# Coronavirus Life Cycle

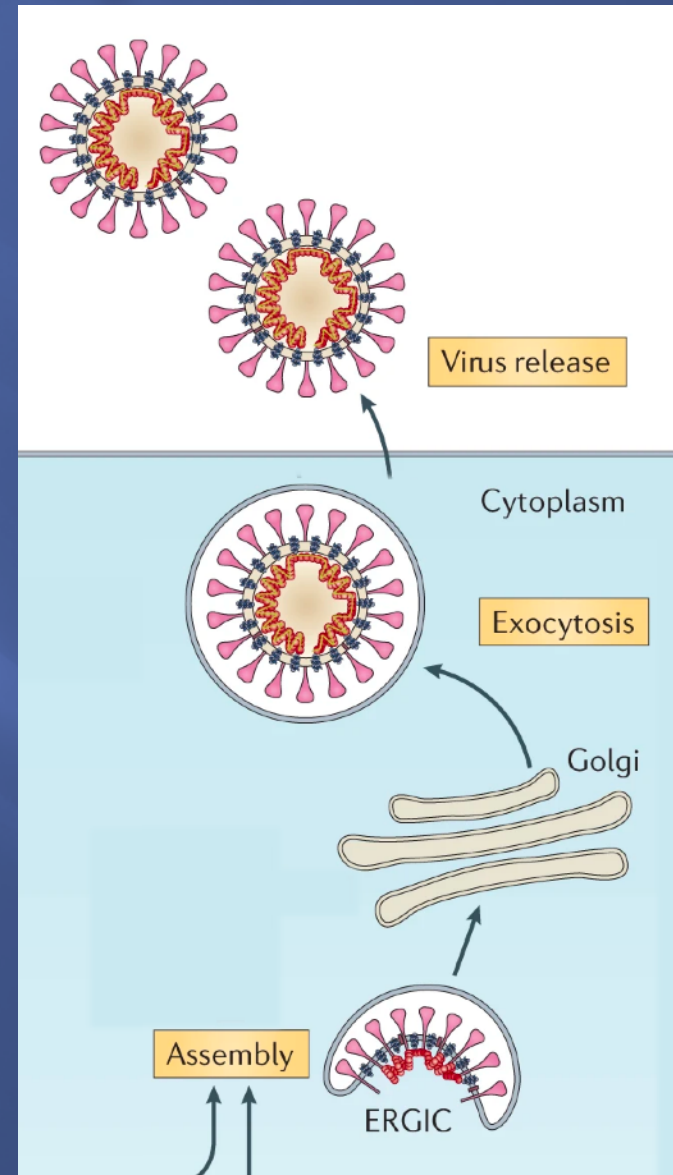
Package up and export

**Virion factory!!!**

This process damages cells and  
invokes inflammation

Damaged cells and overreactive  
inflammation account for Severe  
Acute Symptoms and death

(very risk factor dependent for  
Covid-19)



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# The new coronavirus on the block

In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China - **SARS-CoV-2**

**Deaths:** 6,578,440

**Confirmed cases:** 627,631,619

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Asymptomatic/Usually mild/Severe

Acute but also frequently Chronic

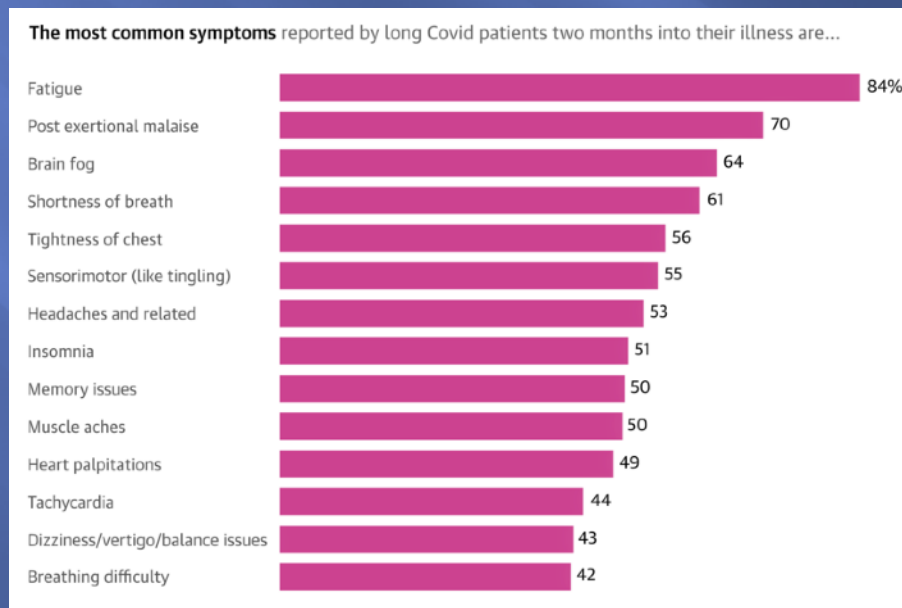
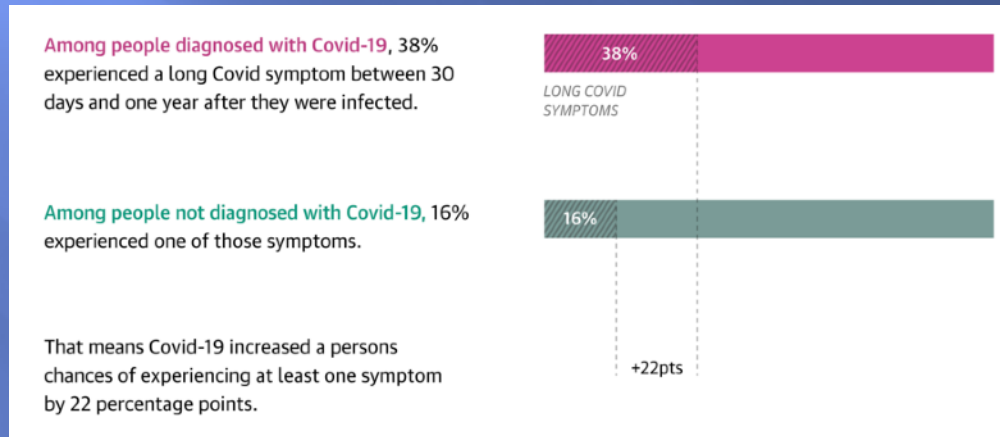
Respiratory/Inflammatory/Multi-Tissue  
Syndrome

A/Um/S/AfC/RIMTS-CoV



# Long Covid

“The astounding impact and reach of long Covid, in numbers and charts” *The Guardian* Wed 12 Oct 2022



# Long Covid

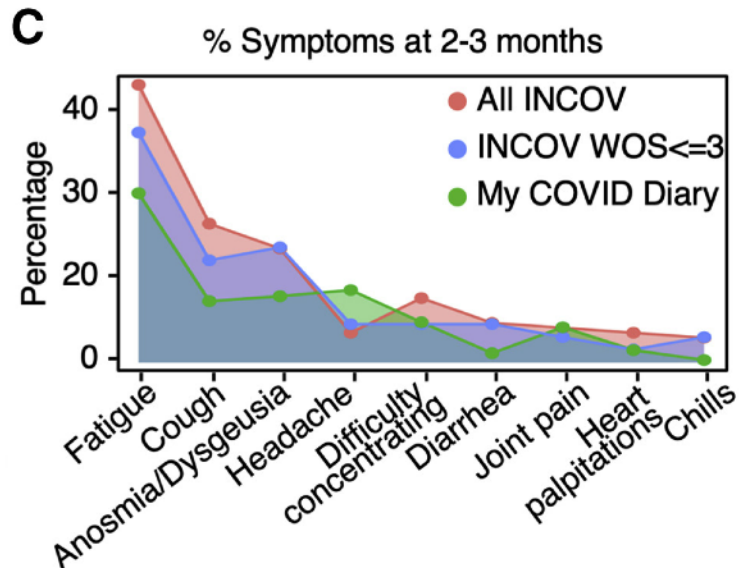
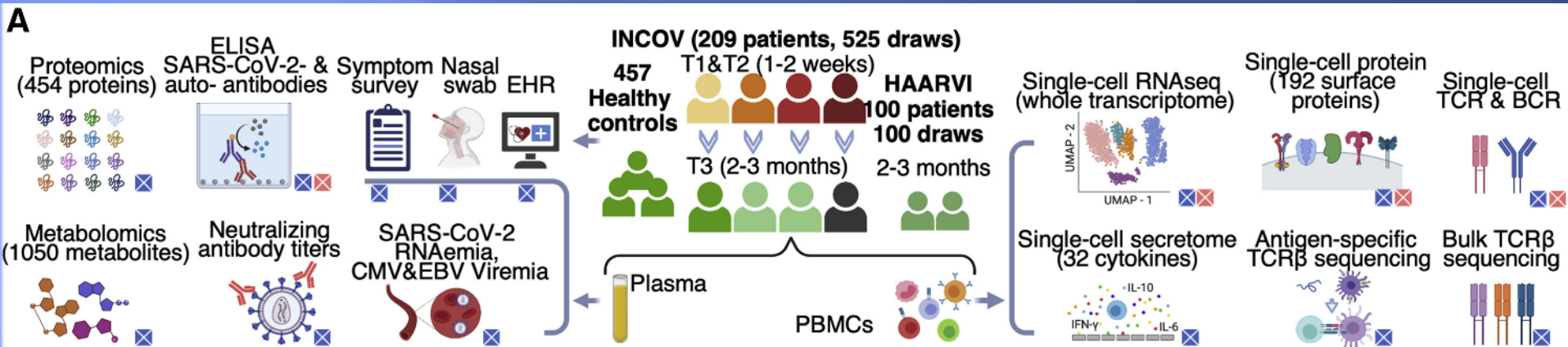
“The astounding impact and reach of long Covid, in numbers and charts” *The Guardian* Wed 12 Oct 2022

They [the study on next slides] found that long Covid symptoms have a high correlation with four factors:

- High levels of the virus RNA in blood.
  - Pre-existing type 2 diabetes.
  - High levels of Epstein-Barr virus DNA in blood.
  - The presence of “autoantibodies” that attack the person’s own body.
- + [SLG - distinct patterns of immune cell populations]

# Long Covid -omics

-omics to study post-acute sequelae

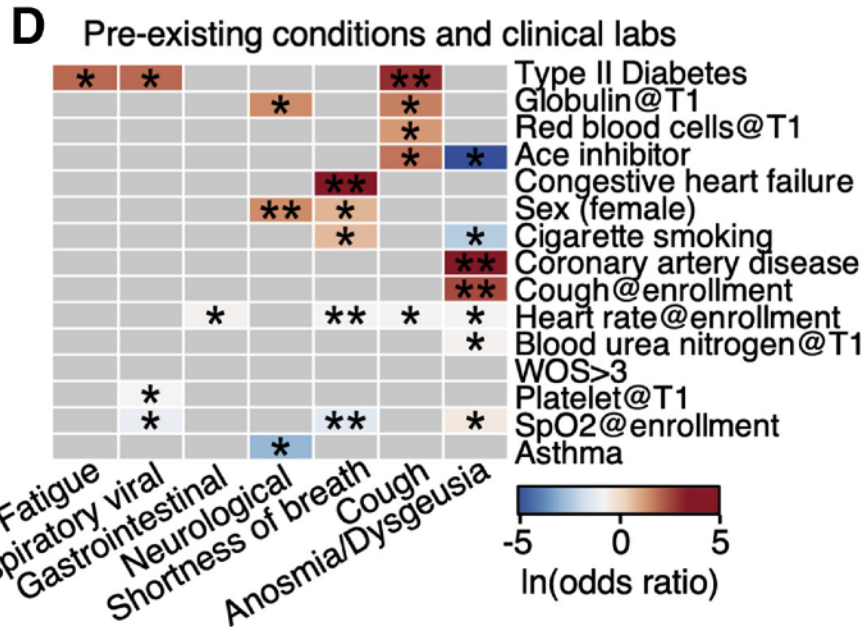


drawing blood and analyzing cell/protein/RNA distributions

Su, Y., Yuan, D., Chen, D. G., Ng, R. H., Wang, K., Choi, J., ... & Heath, J. R. (2022). Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*, 185(5), 881-895.

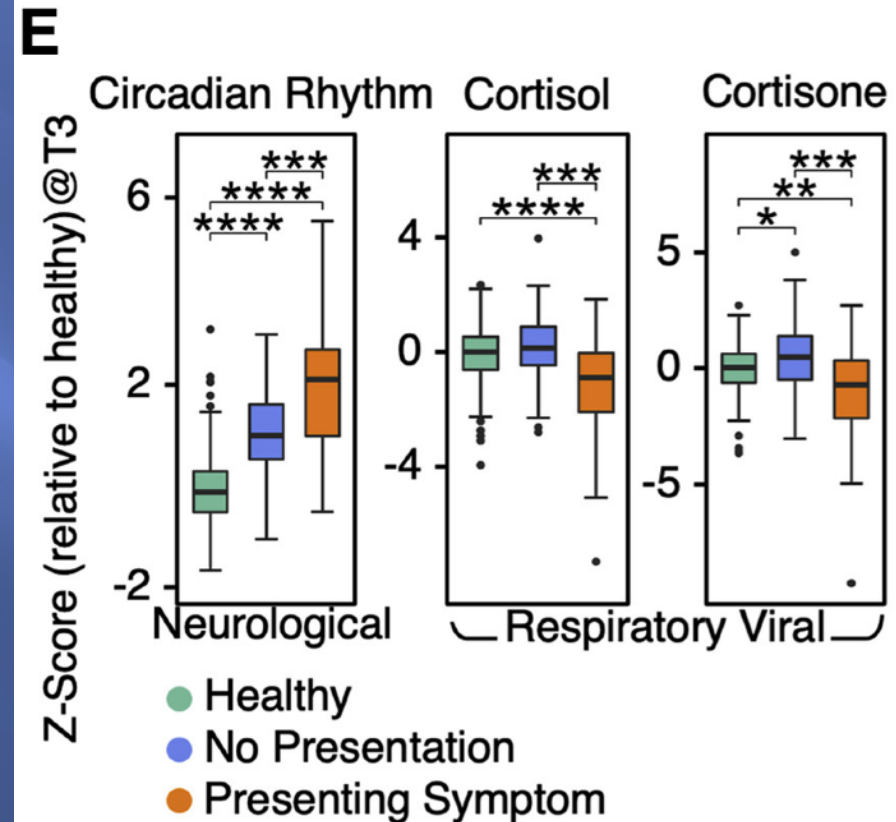
# Long Covid -omics

-omics to study post-acute sequelae



symptoms showing significant  
to clinical symptoms

(focus on the red — worse!  
but note the blue “protective”)



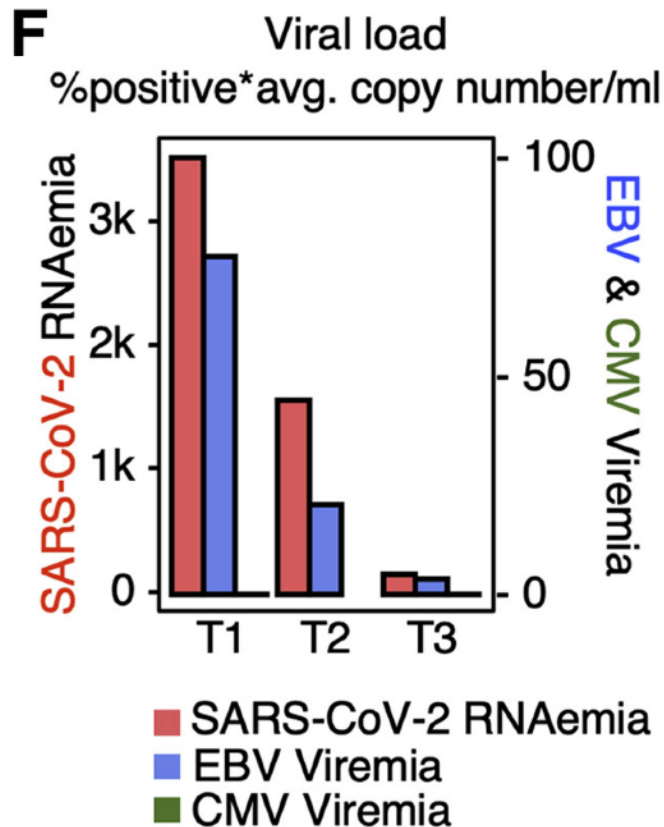
cortisol derangement

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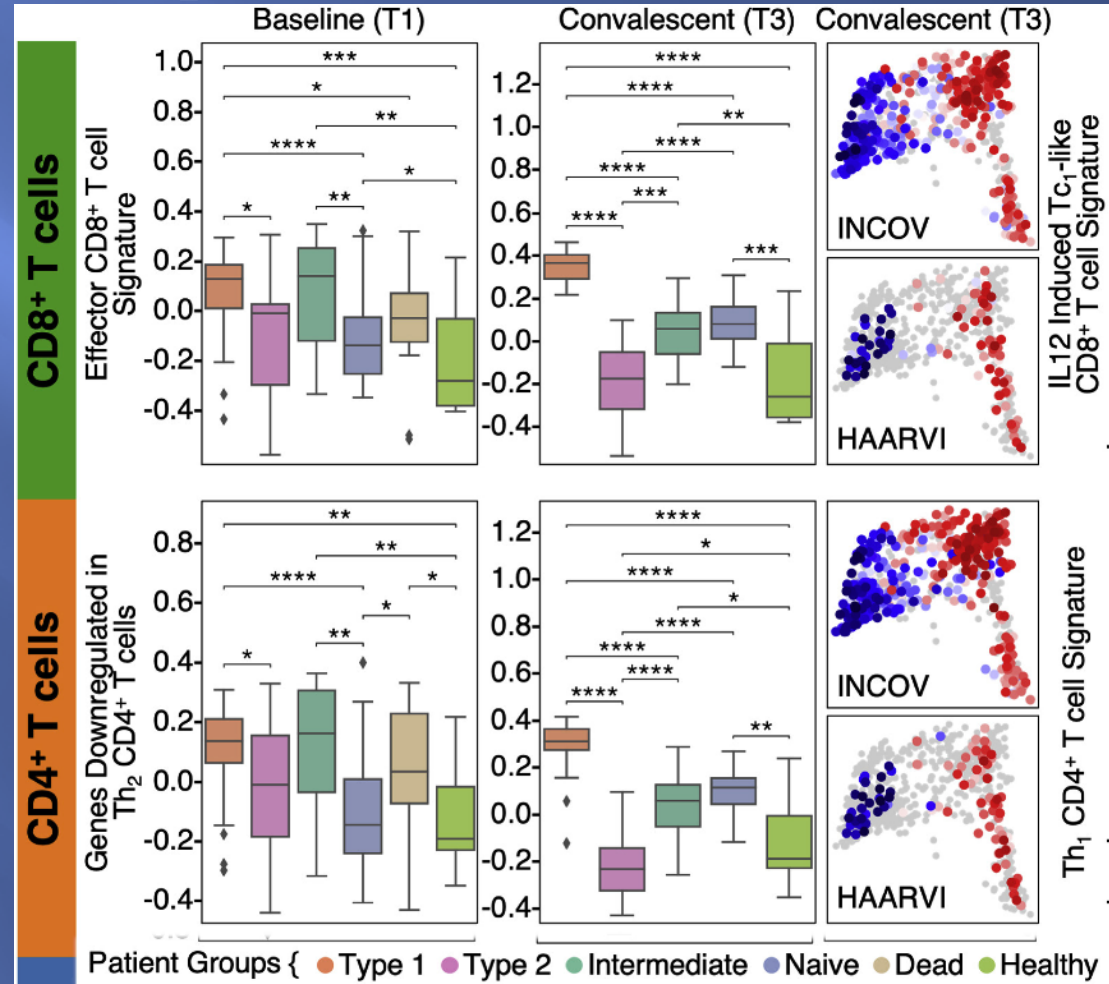


# Long Covid -omics

-omics to study post-acute sequelae



other virii activated



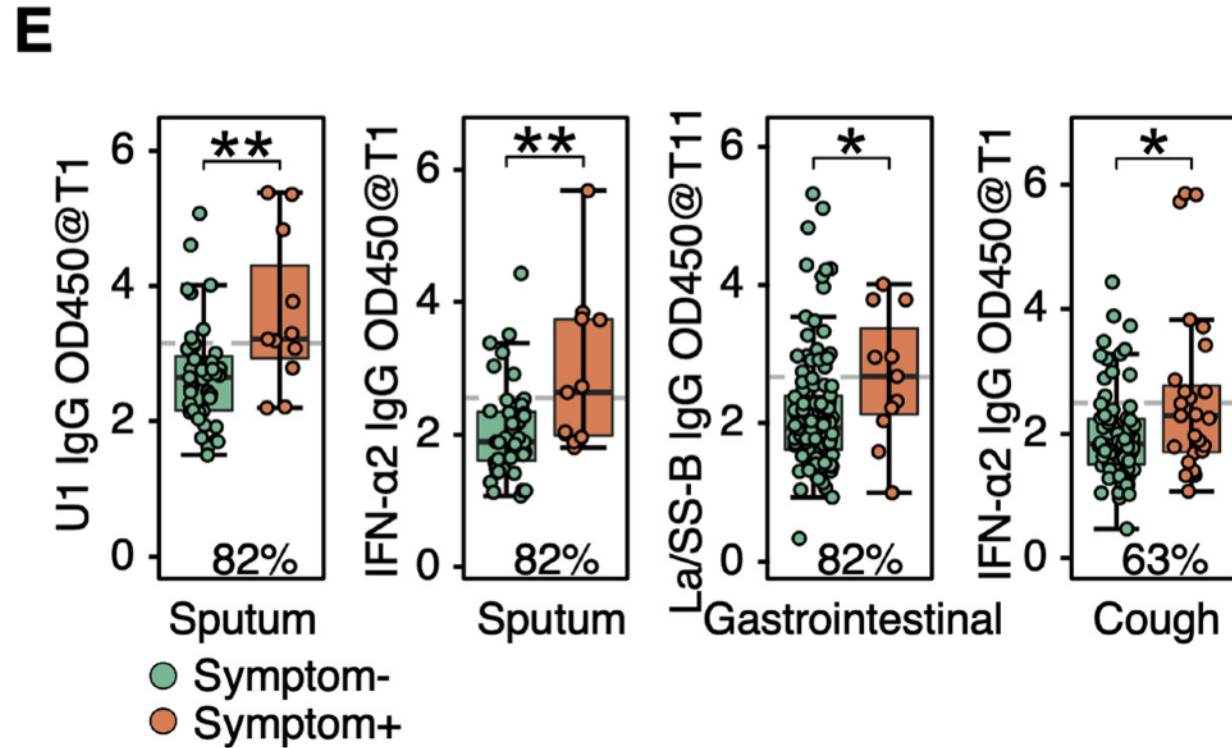
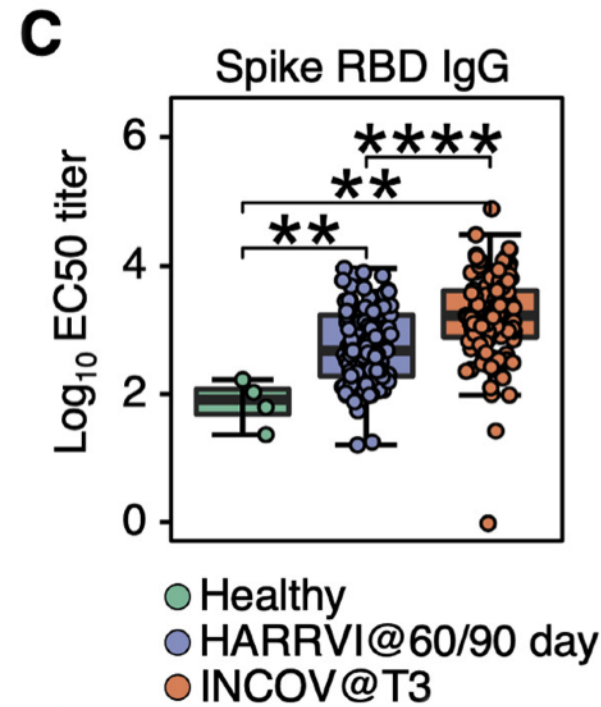
T-cells are part of adaptive immunity

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# Long Covid -omics

-omics to study post-acute sequelae (PASC)

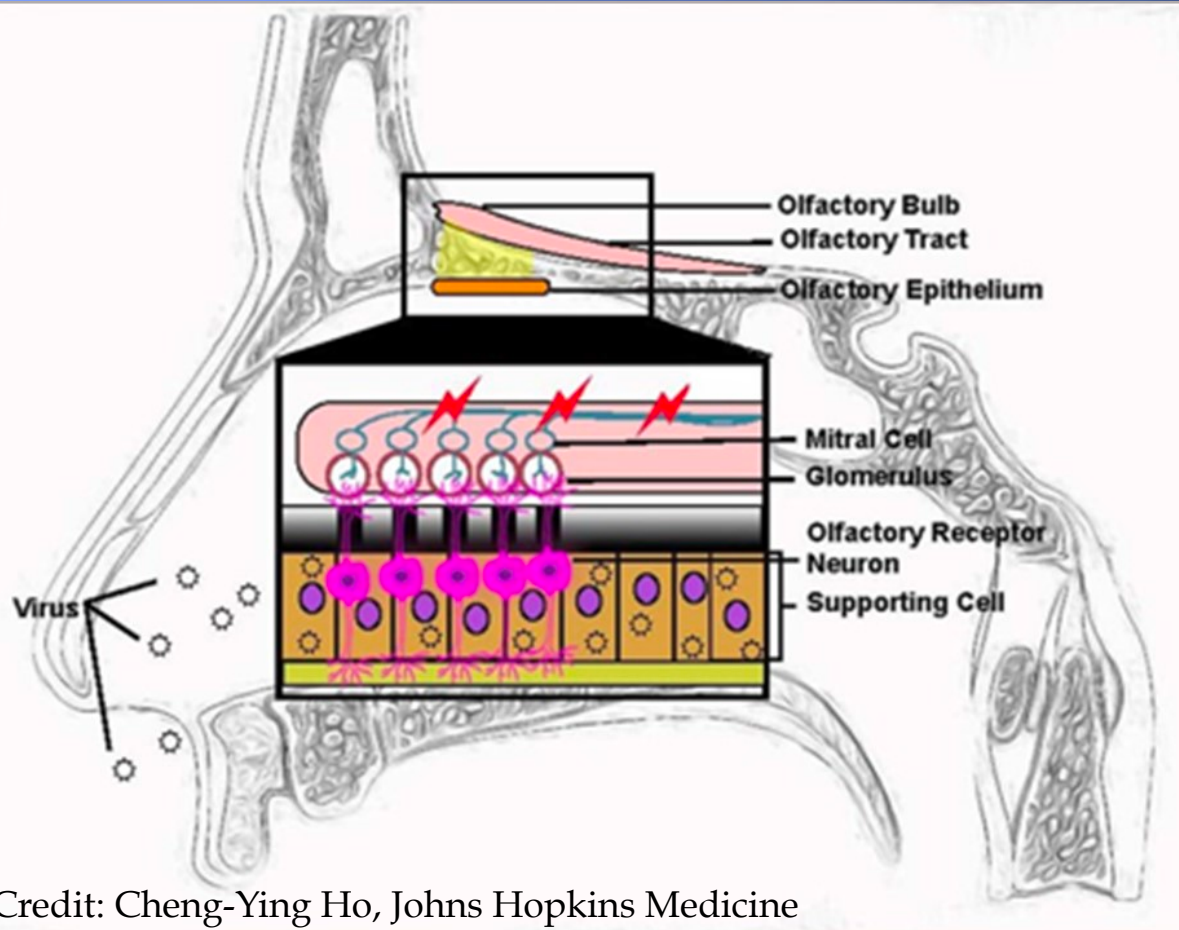


Covid-19 anybody persists  
(month 3)

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Boxplots showing all significant  
PASC- autoantibody (T1) relationships

# Nonlethal Covid: anosmia



SARS-CoV-2 NOT  
found in olfactory  
neurons

found in support  
cells

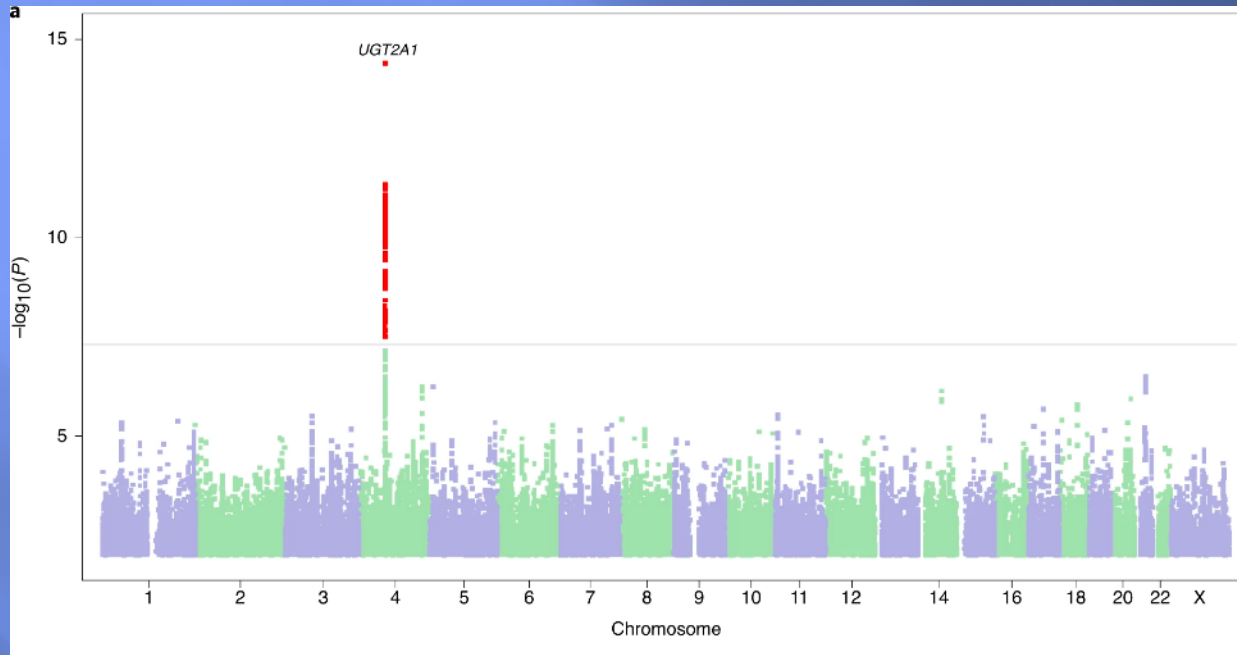
Ho, Cheng-Ying, et al.  
"Postmortem Assessment of  
Olfactory Tissue Degeneration and  
Microvasculopathy in Patients  
With COVID-19." *JAMA  
neurology* (2022).

Credit: Cheng-Ying Ho, Johns Hopkins Medicine

To conduct their investigation, Ho and her colleagues collected tissues from the olfactory bulb at the base of the brain — a region that transmits nerve impulses carrying information about odors — of 23 persons who died from COVID-19 and a control group of 14 who died from other causes and who had no detectable SARS-CoV-2 at the time of their deaths.

# Nonlethal Covid: anosmia

The *UGT2A1/UGT2A2* locus is associated with COVID-19-related loss of smell or taste.

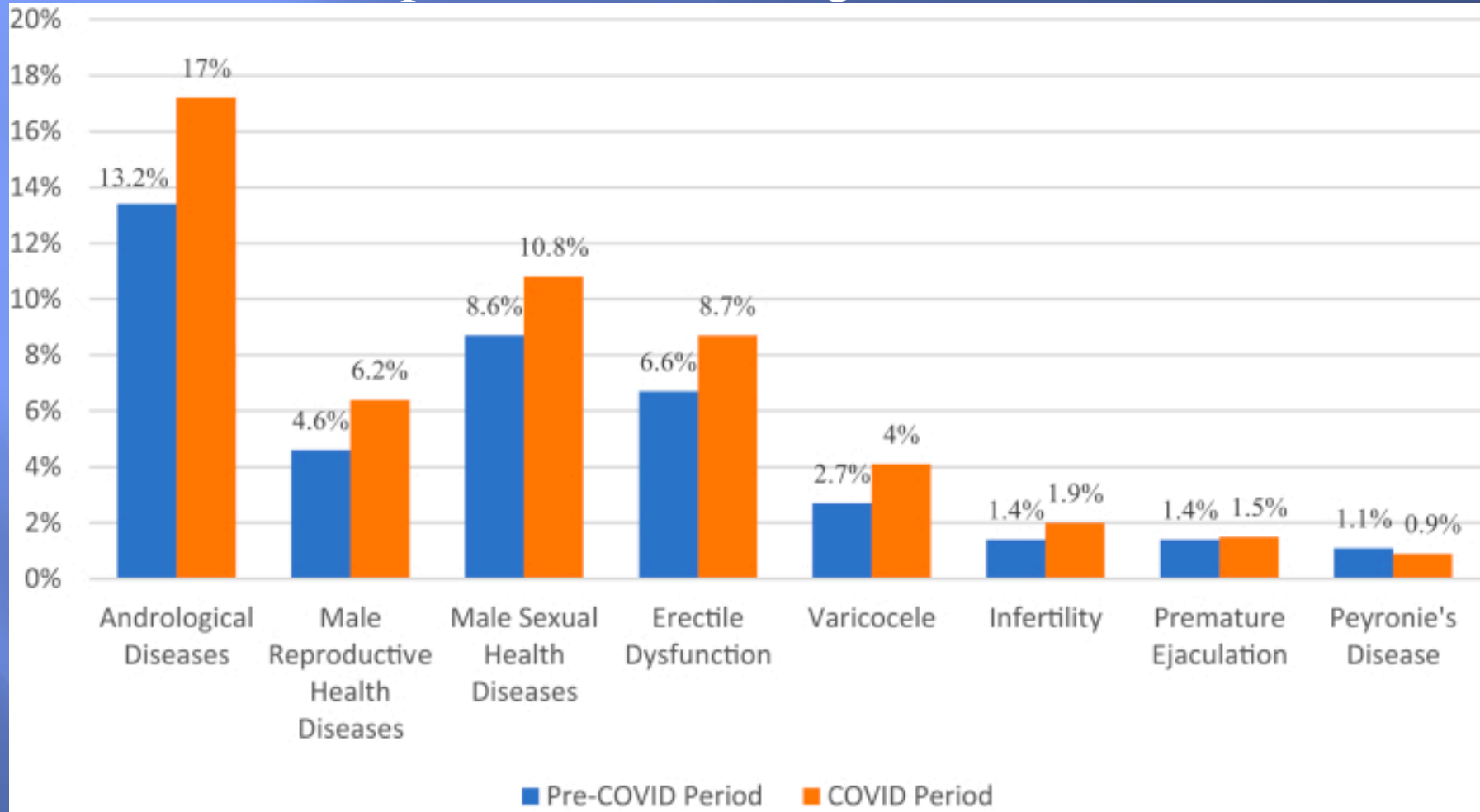


Shelton, J. F., Shastri, A. J., Fletez-Brant, K., Aslibekyan, S., & Auton, A. (2022). *Nature Genetics*, 54(2), 121-124.

We performed a multi-ancestry genome-wide association study (n=69,841) and identified a genome-wide significant locus in the vicinity of the *UGT2A1* and *UGT2A2* genes. Both genes are expressed in the olfactory epithelium and play a role in metabolizing odorants. These findings provide a genetic link to the biological mechanisms underlying COVID-19-related loss of smell or taste.

# Nonlethal Covid: shrinkage

Pre/Post Covid prevalence of diagnosis



Duran, Mesut Berkan, et al. "Variations in the number of patients presenting with andrological problems during the coronavirus disease 2019 pandemic and the possible reasons for these variations: a multicenter study." *Sexual Medicine* 9.1 (2021): 100292.



# **Nonlethal Covid: shrinkage**

Pre/Post Covid prevalence of diagnosis

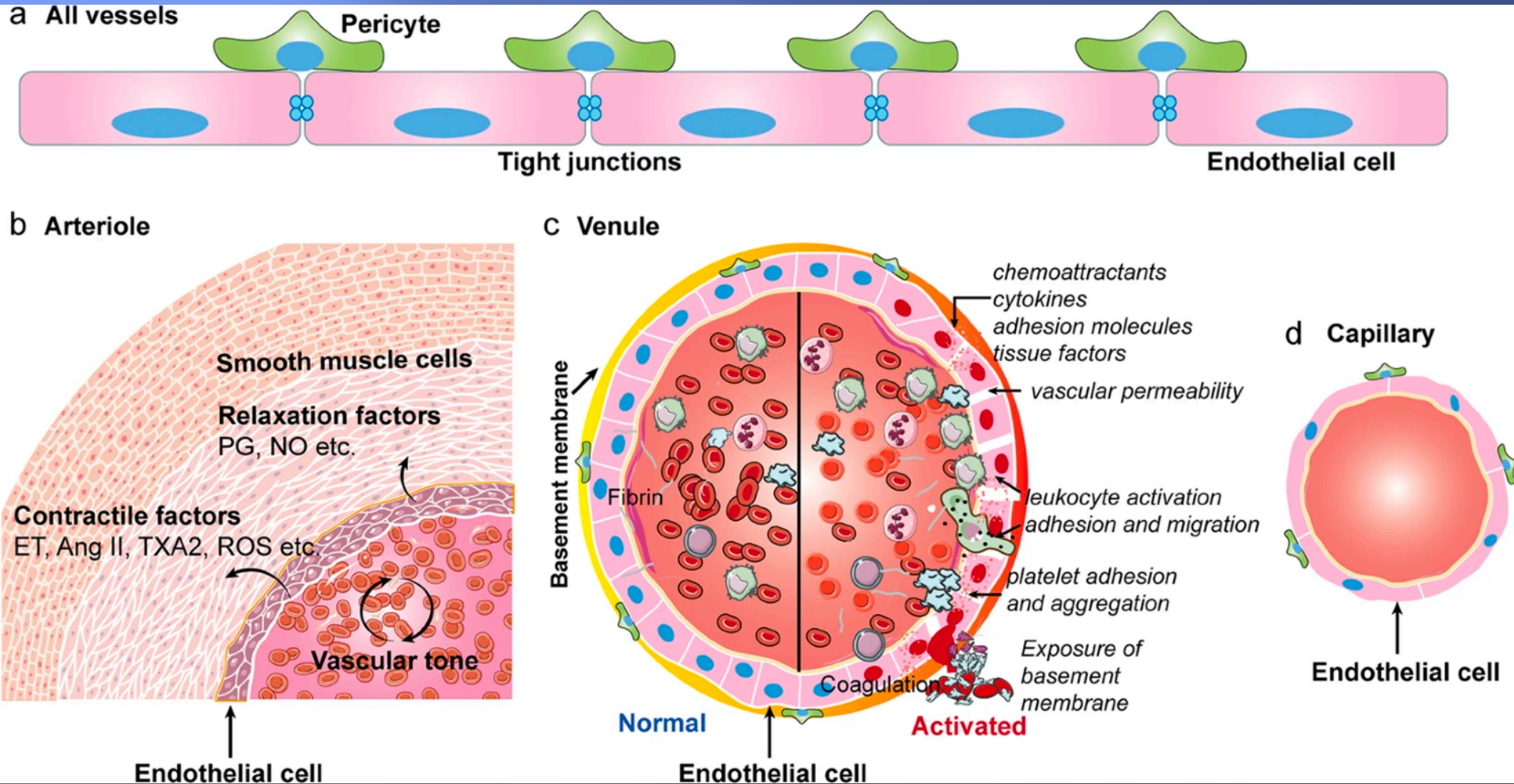
Patients with **COVID-19** were **3.3 times more likely to have erectile dysfunction** with 95% CI (2.8, 3.8). The association became stronger with odds ratio 4.8 (95% CI (4.1, 5.7)) after adjusting for age groups. .... After adjusting for race, COVID-19 patients were 2.6 (95% CI (2.2, 3.1)) times more likely to have erectile dysfunction. The **odds ratio were 1.6, 1.8, 1.9 and 2.3** after adjusting for **respiratory disease, obesity, circulatory disease and diabetes**, respectively.

Katz, J., et al. "Increased odds ratio for erectile dysfunction in COVID-19 patients." *Journal of Endocrinological Investigation* 45.4 (2022): 859-864.



# Nonlethal Covid: shrinkage

## Endothelium basics



Jin, Yuefei, et al. "Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches." *Signal transduction and targeted therapy* 5.1 (2020): 1-13.

# Nonlethal Covid: toes

The research indicates that the lesions may be a side effect of the immune system's shift into high gear in response to exposure to the virus, which can damage cells and tissues in the process.



high levels of Type 1 interferon and high levels of an antibody that can inadvertently attack the body's own cells.

‘Covid toes’ may be caused by a powerful immune response, a new study finds.

Roni Caryn Rabin Oct. 6, 2021 Updated Oct. 13, 2021 The New York Times



## **Nonlethal Covid: brain fog**

evaluated 22 adults reporting cognitive PASC and 10 not reporting cognitive symptoms after mild SARS-CoV-2 ; performed structured interviews, neuropsychological testing, and optional cerebrospinal fluid (CSF) evaluations

—abnormal oligoclonal banding (OCB) patterns were identified in 69% (9/13) of participants with cognitive PASC compared to 0% of cognitive controls ( $p = 0.03$ )

—Cognitive PASC participants had a higher number of pre-existing cognitive risk factors (2.5 vs. 0;  $p = 0.03$ ) and higher proportion with abnormal CSF findings (77% vs. 0%;  $p = 0.01$ )

Apple, Alexandra C., et al. "Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19." *Annals of clinical and translational neurology* 9.2 (2022): 221-226.

# **Nonlethal Covid: brain fog**

- mice: mild respiratory led to persistently impaired hippocampal neurogenesis, decreased oligodendrocytes, and myelin loss ... elevated CSF cytokines/chemokines including CCL11.
- Systemic CCL11 administration specifically caused hippocampal microglial reactivity and impaired neurogenesis.
- humans: post-COVID infection with symptoms, exhibit elevated CCL11 levels.

Fernández-Castañeda, Anthony, et al. "Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation." *Cell* 185.14 (2022): 2452-2468.

# Nonlethal Covid: brain fog

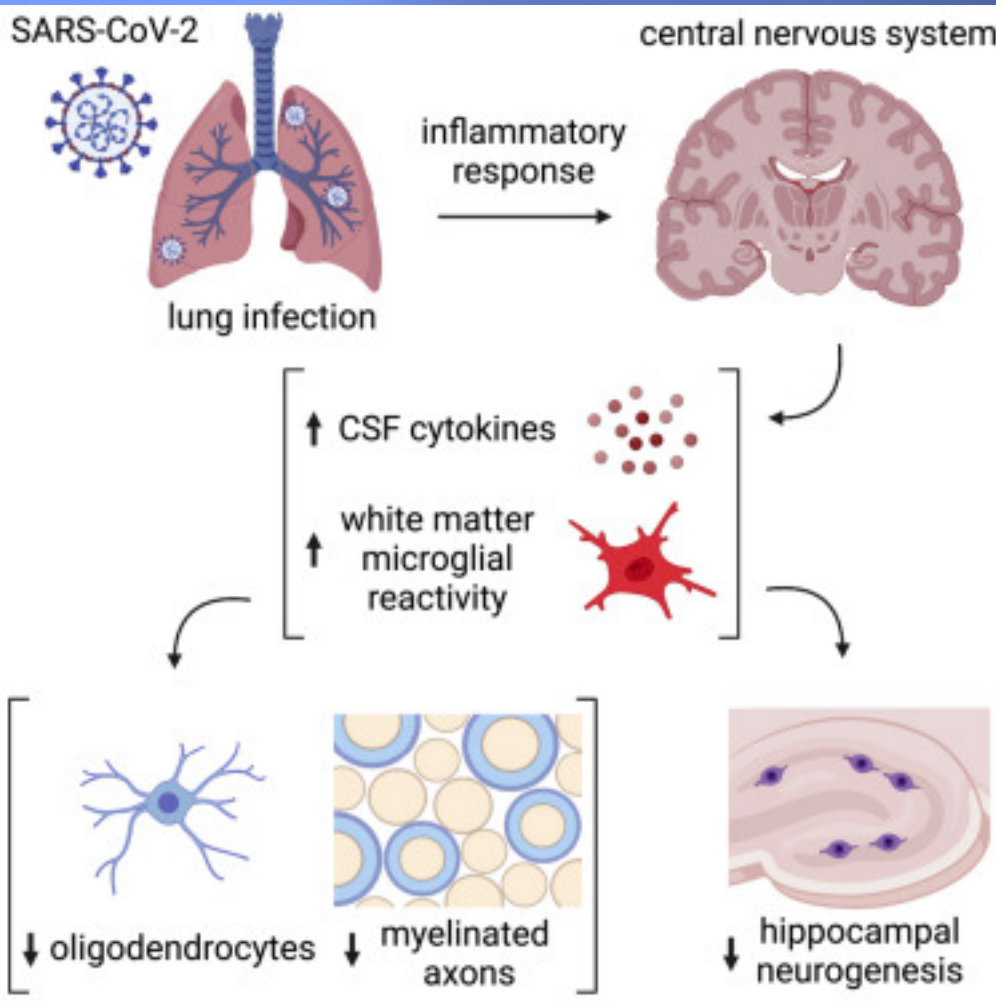
— resembles the syndrome of cancer-therapy-related cognitive impairment, commonly known as “chemo fog.”

— particular reactivity of the microglia which are support cells for neurons

— reactive astrocytes can assume a range of reactive states

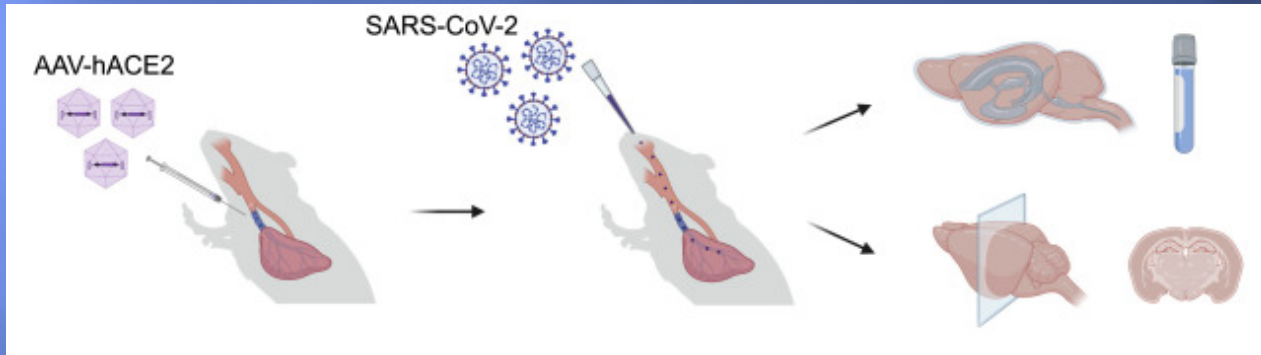
— and invasive macrophages

resulting in dysregulation of myelin-forming oligodendrocytes and hippocampal neural precursor cells.

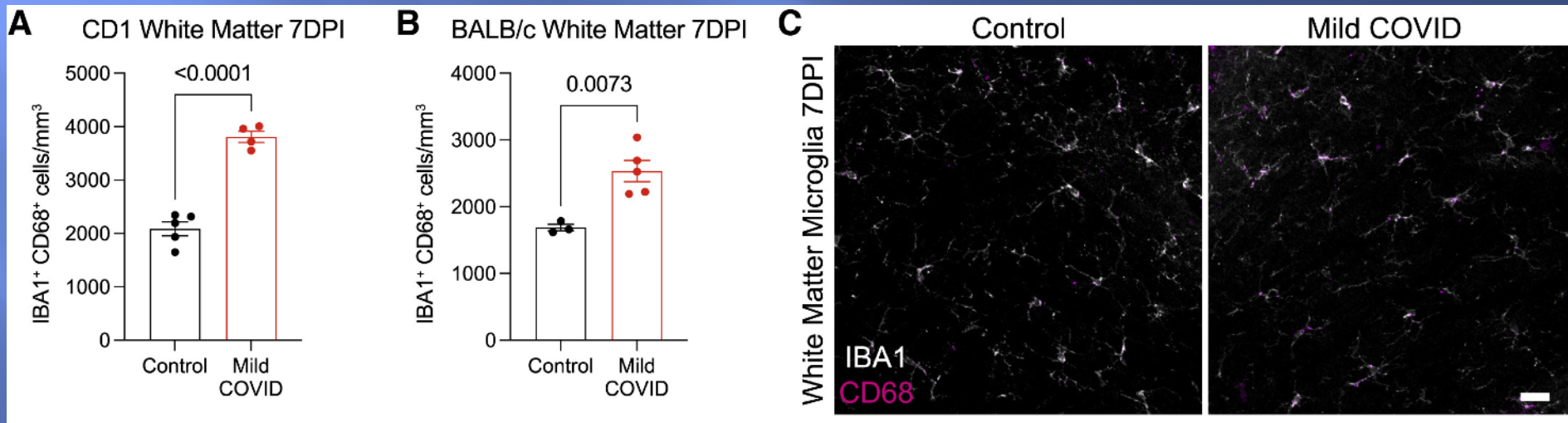




# Nonlethal Covid: brain fog



## Mouse model of COVID infection



IBA1 and CD68 on same cells is marker of inflammation

# **Nonlethal Covid: fatigue**

analyzed a cohort of individuals followed systematically for 8 months after COVID-19 infection according to a predefined schedule (LC)

compared them to healthy donors unexposed to SARS-CoV-2 before December 2019 (UHC)

and individuals who had been infected with prevalent human coronaviruses (HCoV)

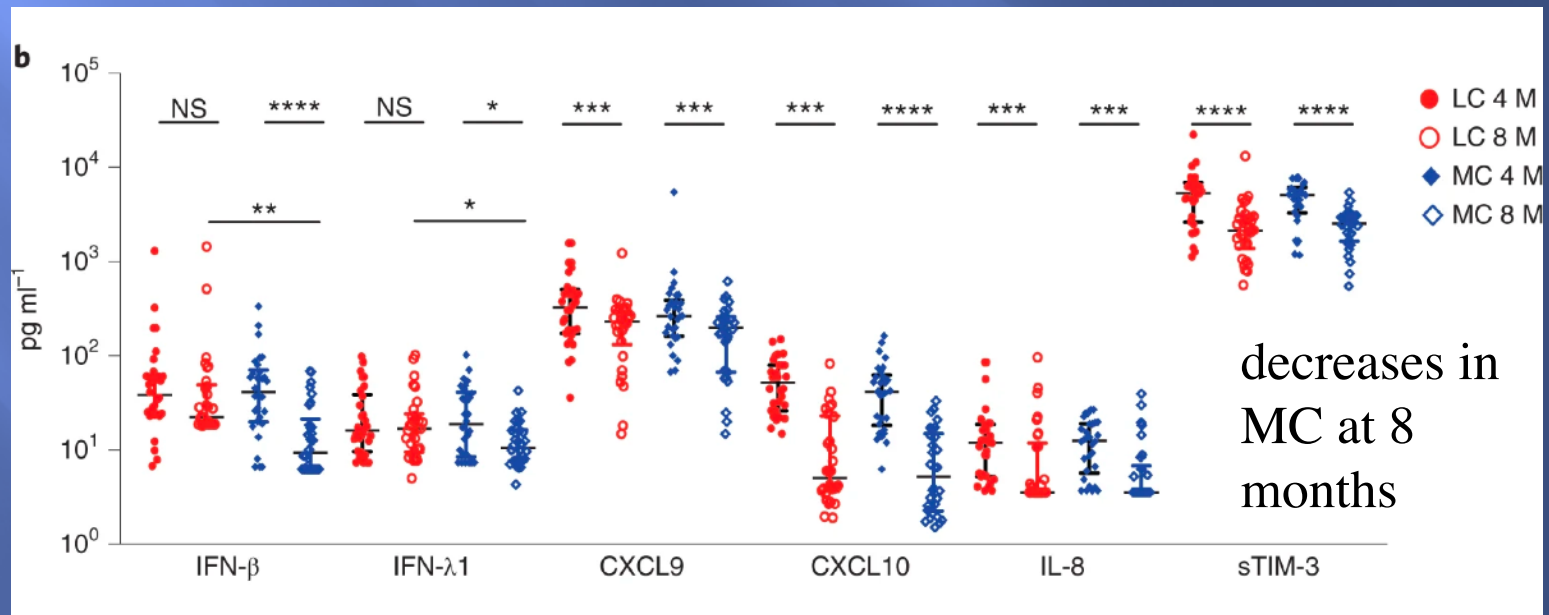
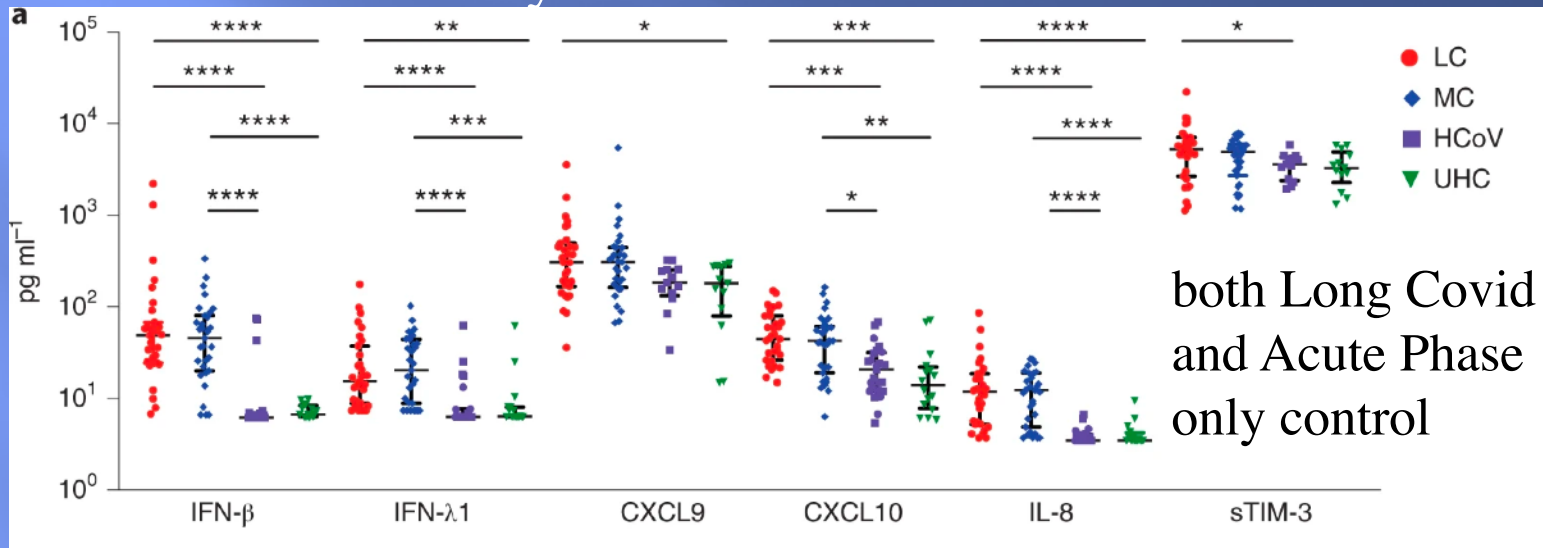
Of the 147 patients recruited, 31 participants (21.08%) were designated as LC based on the occurrence of one of three major symptoms (fatigue, dyspnea or chest pain) at month 4

age and gender matched with 31 asymptomatic matched controls (MCs) who HAD acute symptoms but from the same cohort who did not report symptoms at month 4 after infection (MC)

Phetsouphanh, Chansavath, et al. "Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection." *Nature immunology* 23.2 (2022): 210-216.

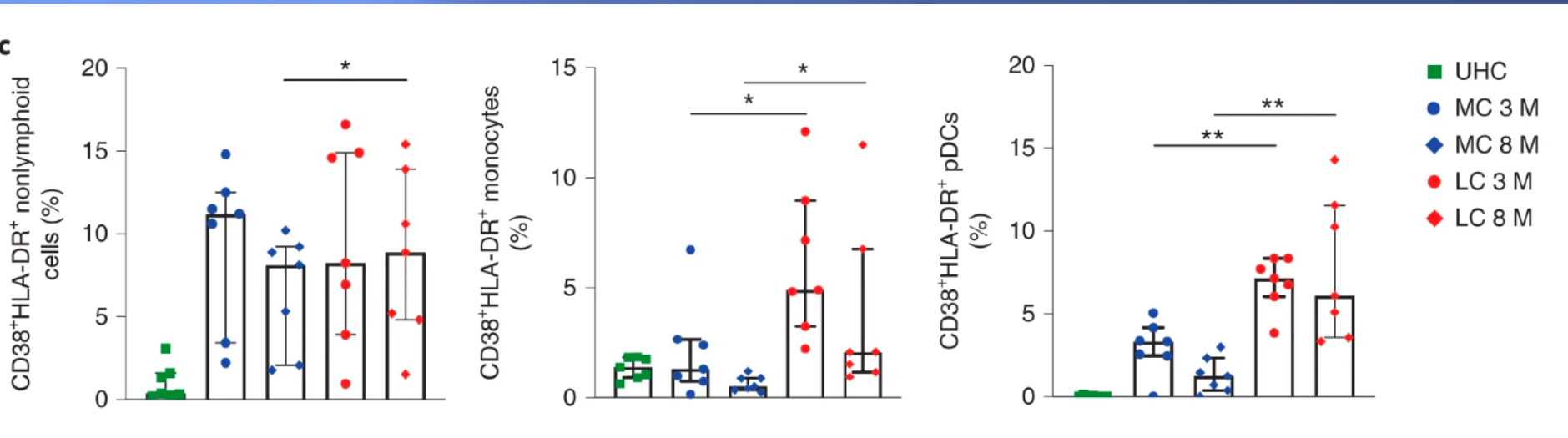
# Nonlethal Covid: fatigue

Inflammatory markers elevated at 4 months



# Nonlethal Covid: fatigue

Persistence of activated nonlymphoid (myeloid) cells

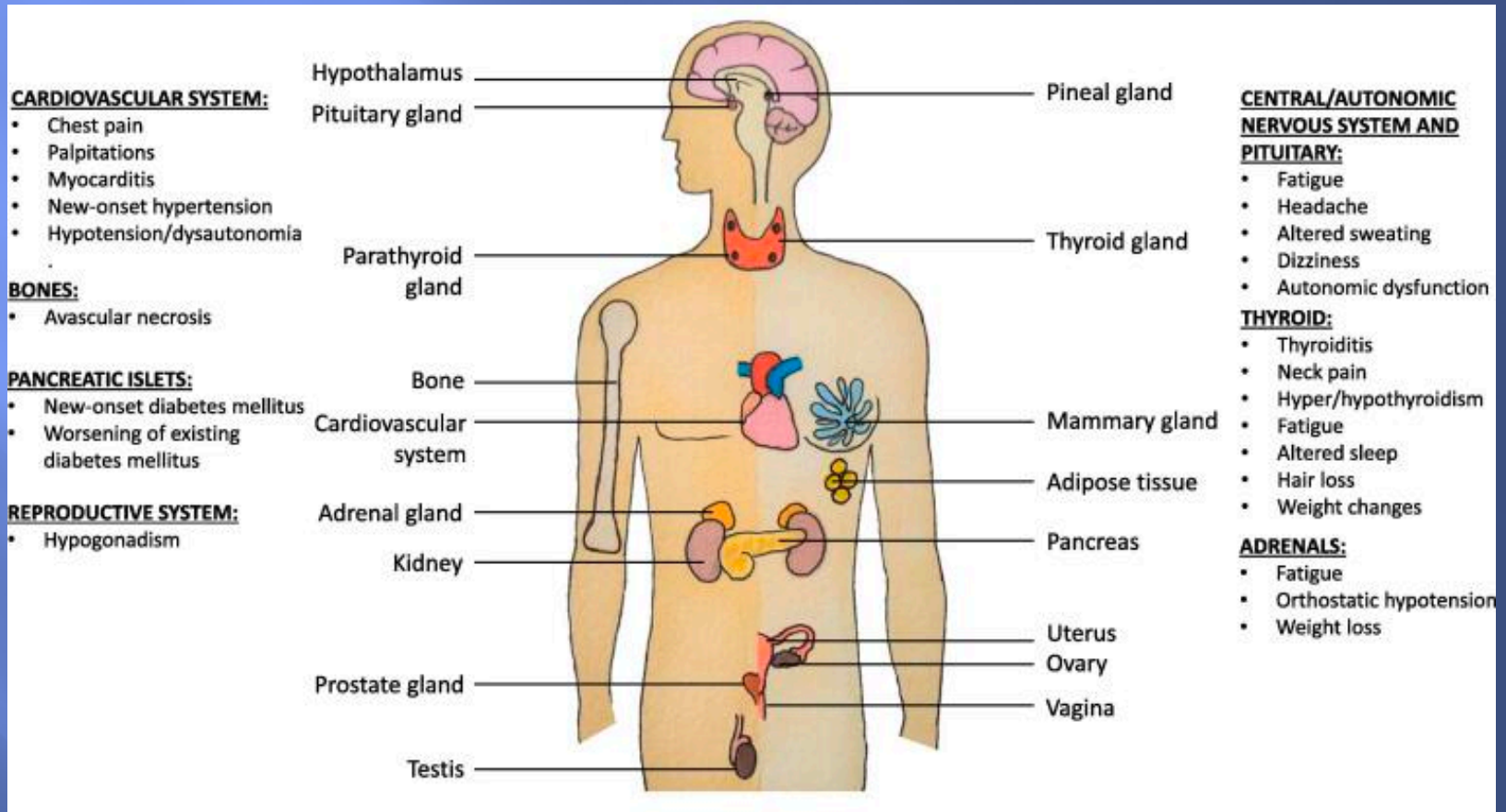




# Nonlethal Covid: fatigue

The endocrine connection to Long-COVID syndrome

All these endocrine organs have ACE2 receptors



Bansal, R., Gubbi, S., & Koch, C. A. (2022). COVID-19 and chronic fatigue syndrome: An endocrine perspective. *Journal of Clinical & Translational Endocrinology*, 27, 100284.

# **Nonlethal Covid: fatigue**

citing other work:

- On postmortem examination, SARS-CoV RNA was found in the pituitary gland, parathyroid, pancreas and adrenal gland
- In another study, both parafollicular and follicular cells were found to be apoptotic explaining the low serum triiodothyronine and thyroxine levels and the osteonecrosis of the femoral head associated with patients of SARS-CoV
- Evidence of hypocortisolism was found in 39% of sixty-one survivors of SARS prospectively recruited for hormonal derangements 3 months after recovery

ibid

# Nonlethal Covid: fatigue

citing other work:

—In autopsies of patients who died of SARS infection, evidence of viral genome, edema, and neuronal degeneration has been found in the hypothalamus

—In another study on recovered patients from previous SARS infection, hypocortisolism persisted for up to 1 year in the majority of patients along with central hypothyroidism and low dehydroepiandrosterone sulfate/DHEAS in some patients, supporting chronic corticotropin (ACTH) deficiency

ibid

# hypocortisolism

A disorder in which the adrenal glands don't produce enough hormones.  
(Addison's)

Specifically, the adrenal glands produce insufficient amounts of the hormone cortisol and sometimes aldosterone, too. When the body is under stress (e.g. fighting an infection), this deficiency of cortisol can result in a life threatening Addisonian crisis characterized by low blood pressure.

Symptoms tend to be non-specific and include fatigue, nausea, darkening of the skin, and dizziness upon standing.



# Nonlethal Covid: fatigue

“Hypocortisolism in survivors of severe acute respiratory syndrome (SARS)”

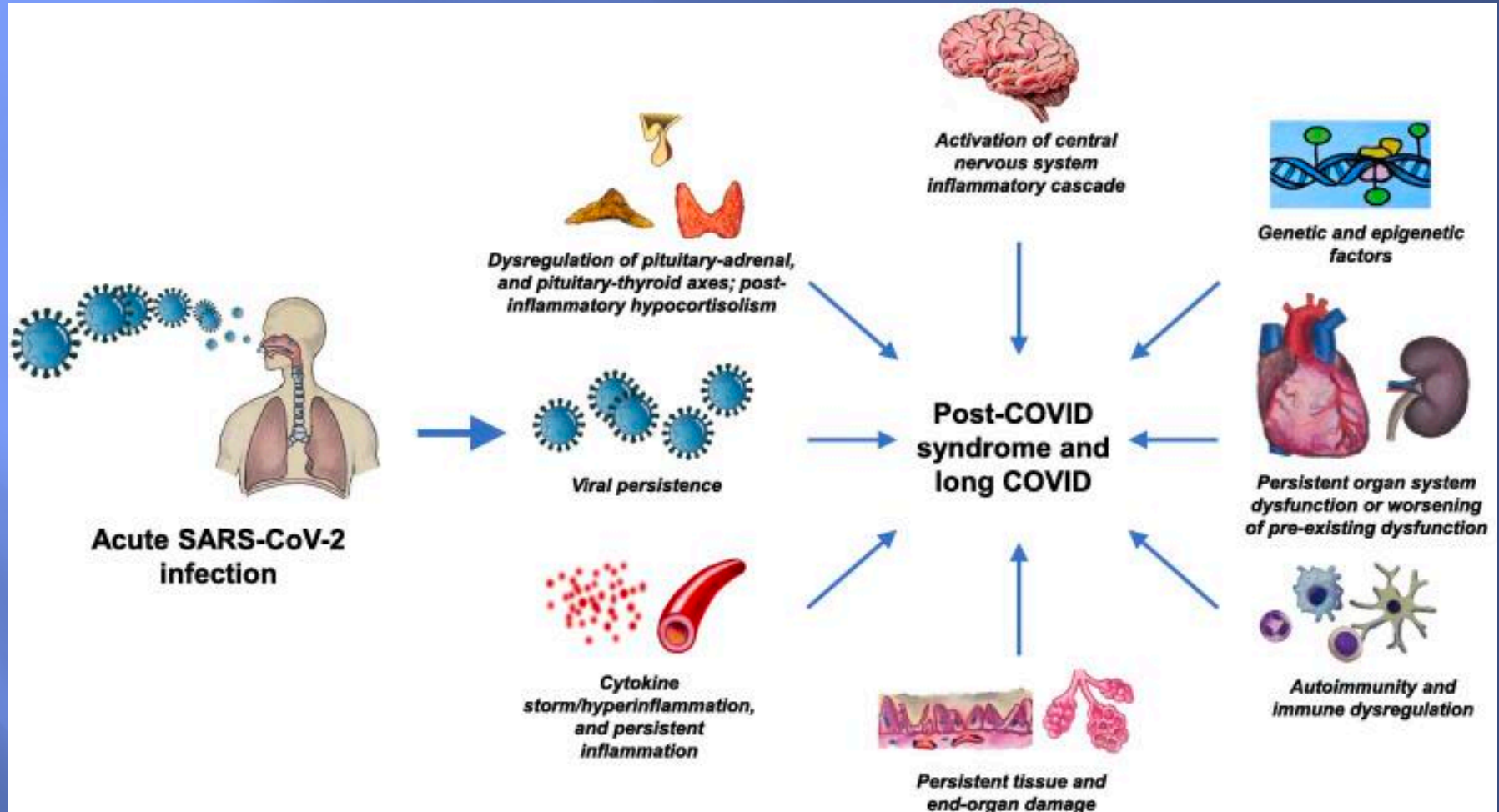
**Design, patients, measurements** Sixty-one survivors of SARS prospectively recruited were analysed for hormonal derangements 3 months following recovery.

**Results** Twenty-four (39·3%) patients had evidence of hypocortisolism. The hypothalamic–pituitary–adrenal (HPA) axis dysfunction of the majority resolved within a year. Two (3·3%) of the hypocortisolic cohort had transient subclinical thyrotoxicosis. Four (6·7%) were biochemically hypothyroid, being comprised of three with central hypothyroidism and one with primary hypothyroidism.

“Pending future SARS epidemics, adequately powered clinical studies to clarify this could prove daunting. In vitro studies and animal models of SARS might better define the endocrine lesions.”

Leow, Melvin Khee-Shing, et al. *Clinical endocrinology* 63.2 (2005): 197-202.

# Nonlethal Covid: overview



Bansal, R., Gubbi, S., & Koch, C. A. (2022). COVID-19 and chronic fatigue syndrome: An endocrine perspective. *Journal of Clinical & Translational Endocrinology*, 27, 100284.

# Long Covid-Economic Impacts

“The astounding impact and reach of long Covid, in numbers and charts” *The Guardian* Wed 12 Oct 2022

A 2022 study estimates will cost the US between \$149bn and \$362bn in medical expenses and lost income. This doesn't account for disability benefits, social services and other costs.

Among people who report long Covid symptoms...

Not working as a result of the sickness

23%

Reduced work hours as a result of the sickness

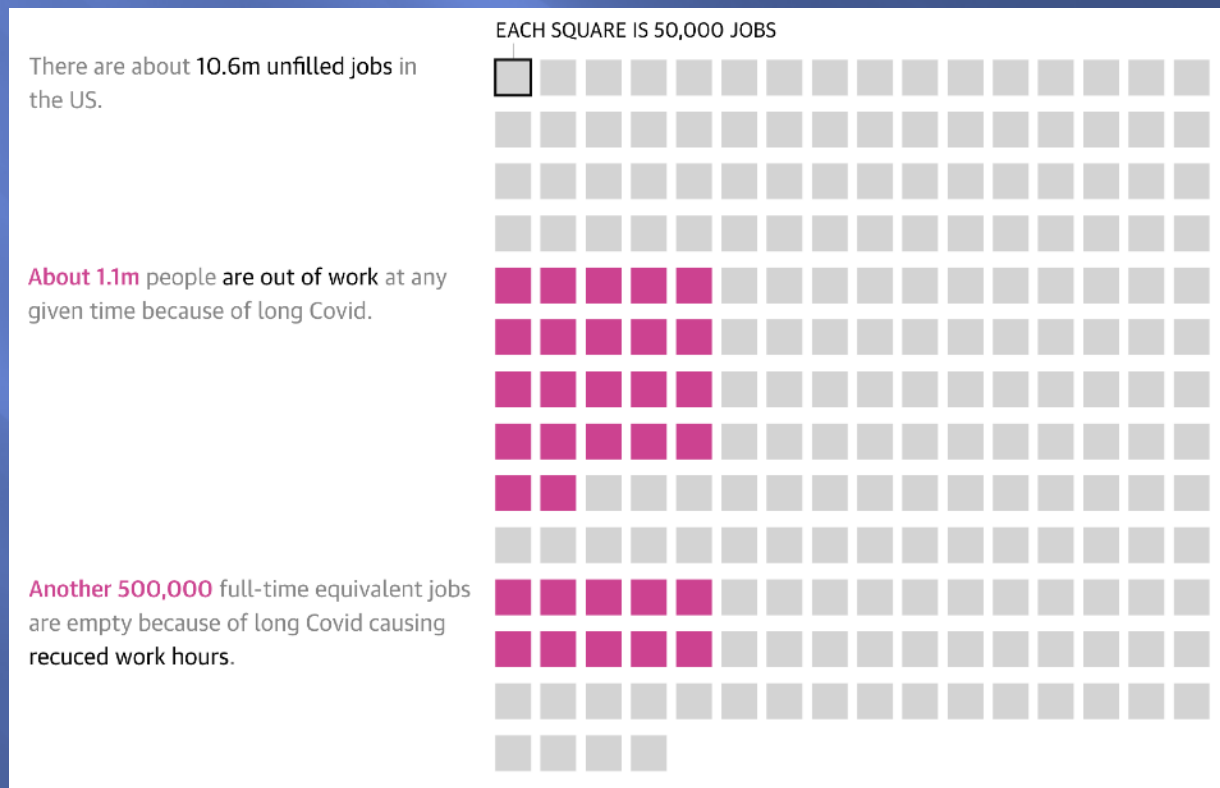
46%



# Long Covid-Economic Impacts

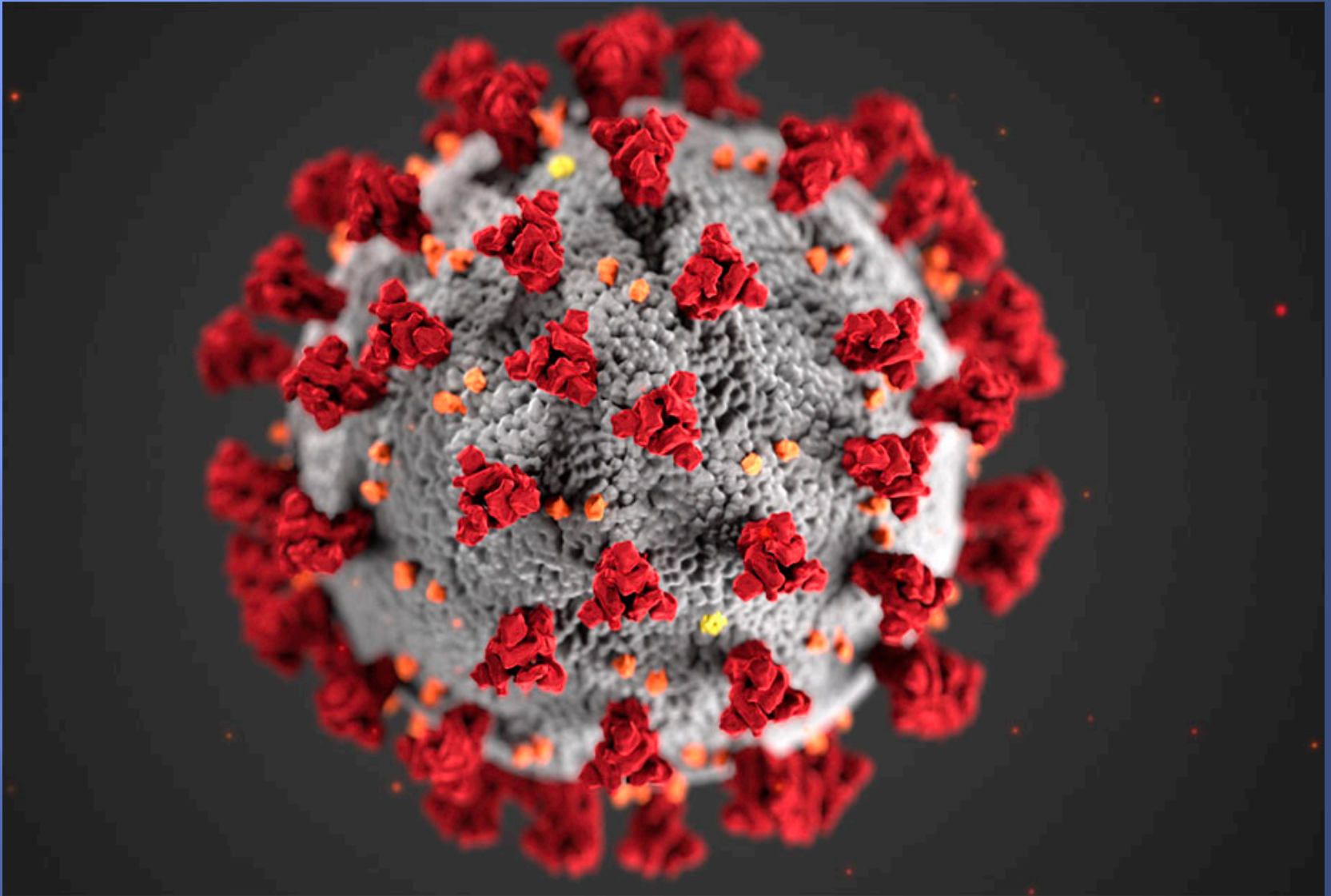
“The astounding impact and reach of long Covid, in numbers and charts” *The Guardian* Wed 12 Oct 2022

According to a Brookings Institution analysis, long Covid shrunk the workforce by about 1.6 million full-time equivalent workers at any given time in the first 20 months of the pandemic.





# Nonlethal Covid: Questions?



<https://www.cdc.gov/dotw/covid-19/index.html>