





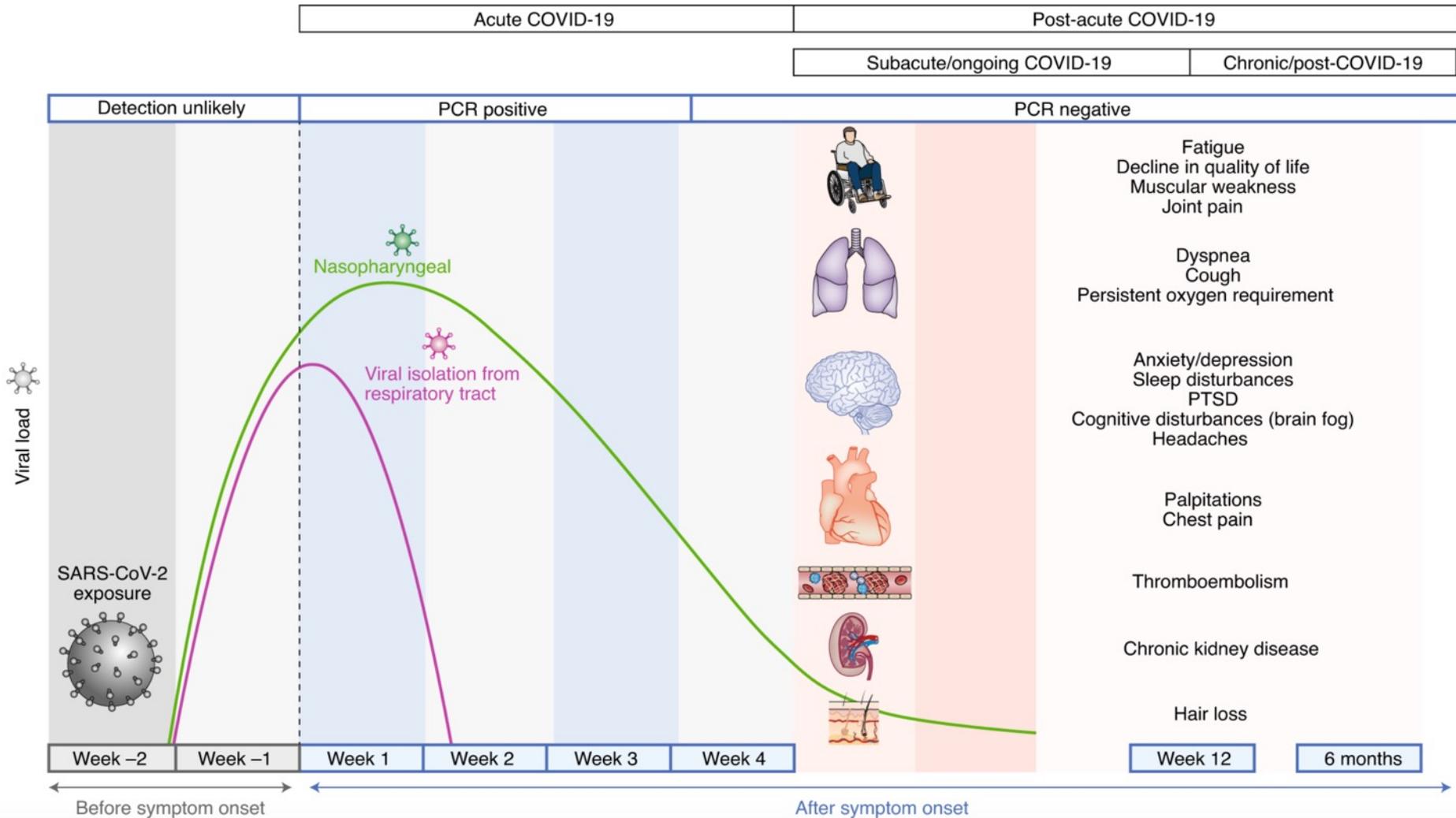


# What is “Long COVID”?

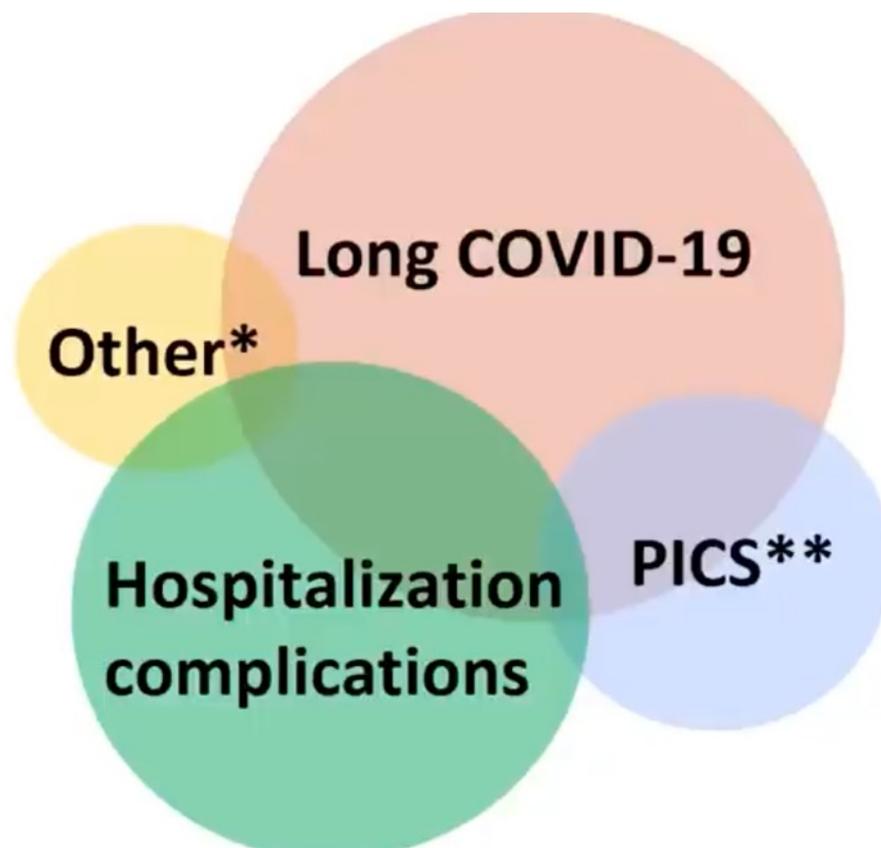
- Some patients with COVID-19 continue to have symptoms for weeks, or even months after initial infection, regardless of the severity of initial disease
- Currently there is no clearly delineated consensus definition for the condition: terminology has included “long COVID,” “post-COVID syndrome” and “post-acute COVID-19 syndrome”
- Patients often referred to as by the lay public as “long haulers”
- NIH announced a terminology in February 2021, referring to it collectively as **Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)**

# WHO Definition

"Post COVID-19 condition occurs in individuals with a **history of probable or confirmed SARS-CoV-2 infection**, usually **3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis**. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which **generally have an impact on everyday functioning**. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children."



# Long COVID may overlap with other complications of acute COVID-19 illnesses



\*GBS, multisystem inflammatory disorder, etc.

\*\* Post-ICU syndrome

# Epidemiology

- True incidence and prevalence is unknown
- Most estimates suggest that 10%-30% of acute infections lead to Long COVID
- Early data from Wuhan- 6-month follow-up of patients hospitalized Jan-May 2020
  - More than 75% reported still having symptoms after 6 months-- fatigue or muscle weakness, sleep difficulties, and anxiety or depression
  - Over half had significant persistent lung abnormalities
- May be easier to ask “How prevalent are persistent symptoms after COVID as compared to e.g. influenza?”



# Characterizing Long COVID

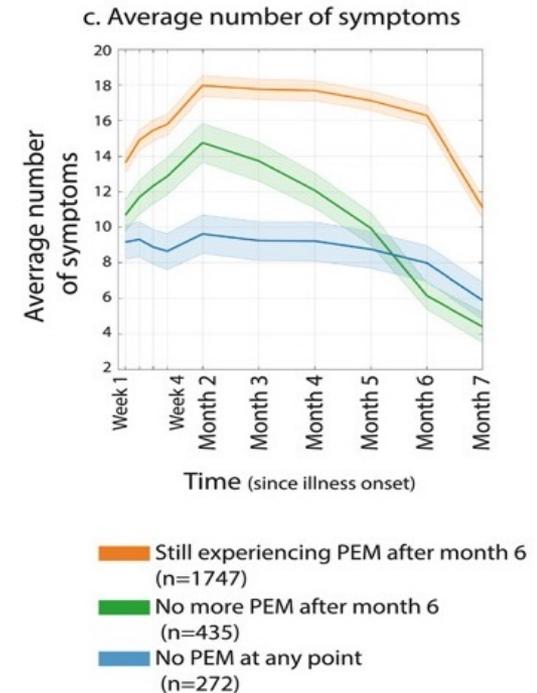


## “Patient led research for COVID-19”

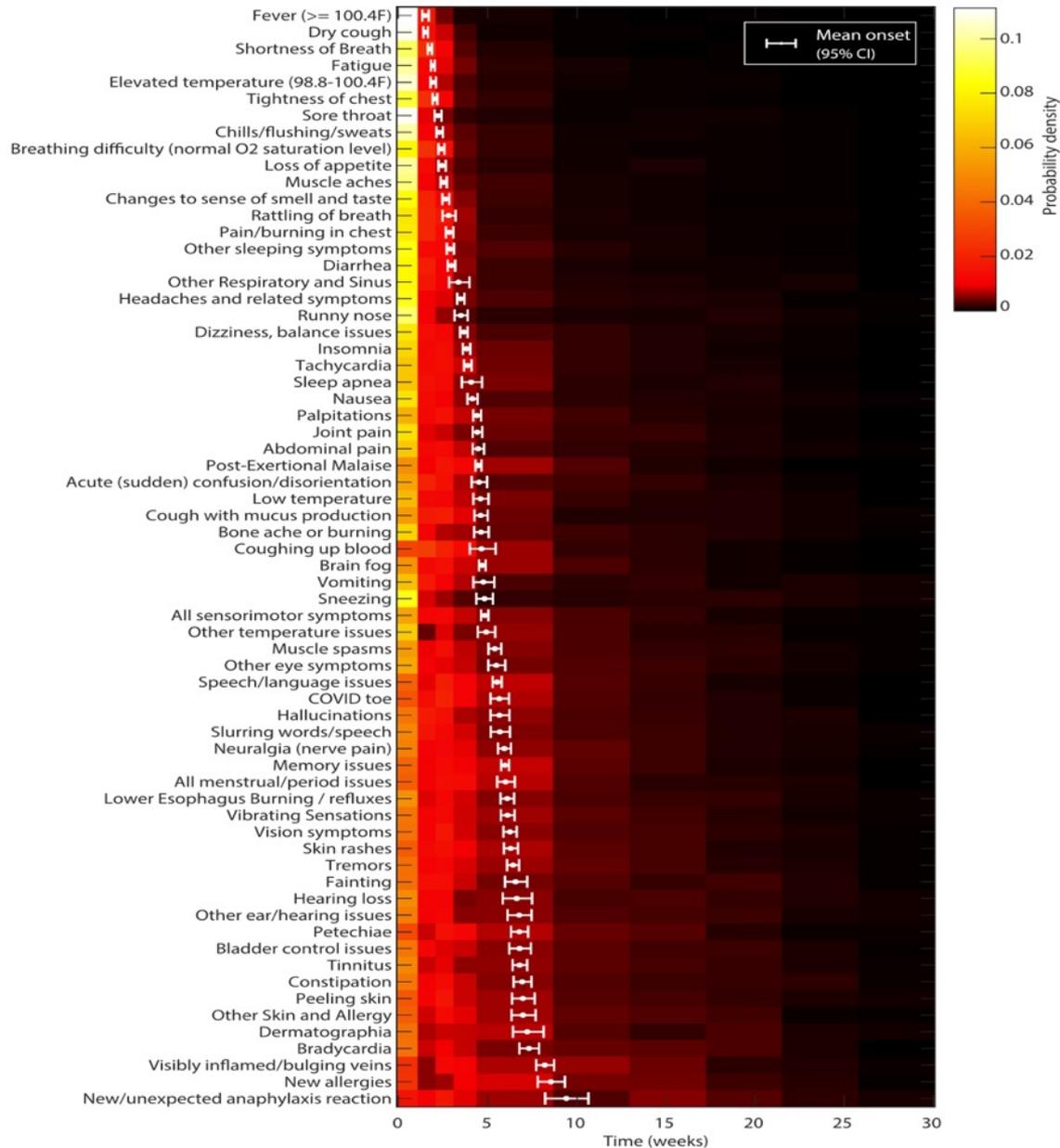
- Online survey of people with suspected and confirmed COVID-19, distributed via COVID-19 support groups (e.g. Body Politic) and social media (e.g. Twitter, Facebook)
- 3762 participants (1020 confirmed, 2742 suspected COVID-19) with illness lasting over 28 days and onset prior to June 2020
  - Global cohort- over 56 countries represented
  - 78.9% women, 85.3% white
  - Non-hospitalized (56.7% no care, 34.9% ER/urgent care)
- Survey of 203 symptoms (10 organ systems)
- Measured the impact on life, work, and return to baseline health

# Characterizing Long COVID

- Most common symptoms **fatigue** (77.7%) **post-exertional malaise** (72.2%), and **cognitive dysfunction** (55.4%)
  - *Majority (88%) reported having some form of cognitive dysfunction or memory loss affecting their daily lives*
- Those who had prolonged symptoms > 6 months reported having an average of 14 symptoms
- Similar findings between:
  - Confirmed and suspected cases
  - Men and women
- Nearly half could not work full-time 6 months after developing prolonged symptoms

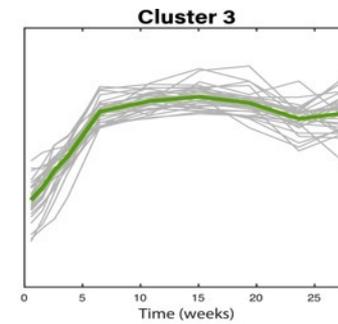
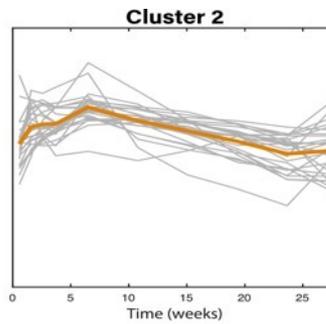
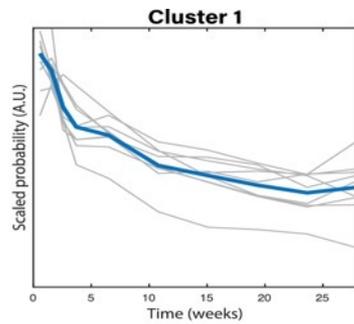


# Characterizing Long COVID



# Characterizing Long COVID

- Triggers for relapses:
  - Physical activity (70.7%)
  - Stress (58.9%)
  - Exercise (54.4%)
  - Mental activity (46.2%)
  - Menstruation (~35%)



<b>Cardiovascular</b>		25. Fainting 19. Pain/burning in chest 33. Tachycardia	49. Bradycardia 38. Palpitations 64. Visibly inflamed/bulging veins
<b>Dermatologic</b>		30. COVID toe	53. Dermatographia 55. Other Skin and Allergy 42. Peeling skin 54. Petechiae 44. Skin rashes
<b>Gastrointestinal</b>	9. Diarrhea 2. Loss of Appetite 4. Vomiting	26. Abdominal pain 18. Nausea	45. Constipation 43. Gastroesophageal reflux
<b>HEENT (Head, ears, eyes, nose, throat)</b>	7. Runny nose 6. Sore Throat		48. Hearing loss 51. Other ear/hearing issues 39. Other eye symptoms 58. Tinnitus 59. Vision symptoms
<b>Immunologic/ Autoimmune</b>			65. New allergies 63. New anaphylaxis reaction
<b>Musculoskeletal</b>		32. Bone ache or burning 21. Muscle aches 15. Tightness of Chest	37. Joint pain 40. Muscle spasms
<b>Neuropsychiatric</b>		20. Acute (sudden) confusion/disorientation 12. Changes to sense of smell and taste 22. Dizziness, unsteadiness or balance issues 31. Hallucinations 29. Headaches and related symptoms 35. Insomnia 27. Other sleeping symptoms 34. Sleep apnea 36. Slurring words/speech	41. All sensorimotor symptoms 47. Brain fog 61. Memory issues 50. Neuralgia (nerve pain) 62. Speech/language issues 52. Tremors 56. Vibrating Sensations
<b>Pulmonary/ Respiratory</b>	3. Dry cough 5. Rattling of breath	14. Breathing difficulty (normal O2 saturation level) 17. Cough with mucus production 10. Coughing up Blood 24. Other Respiratory and Sinus 16. Shortness of Breath 13. Sneezing	
<b>Reproductive/ Genitourinary/ Endocrine</b>			60. All menstrual/period issues 46. Bladder control issues
<b>Systemic</b>	8. Elevated temperature (98.8-100.4F) 1. Fever ( $\geq 100.4F$ )	11. Chills/flushing/sweats 28. Fatigue 23. Low temperature	39. Other temperature issues 57. Post Exertional Malaise

# “More than 50 long-term effects of COVID-19: a systematic review and meta-analysis”

- A total of 18,251 publications were identified, of which 15 met the inclusion criteria
- Estimated prevalence of 55 long-term effects
  - 21 meta-analyses were performed
  - 47,910 patients were included (age 17–87 years old)
  - Follow-up time ranged 14 to 110 days post-infection
- Key findings:
  - 80% of patients still had 1 or more symptoms at time of follow-up



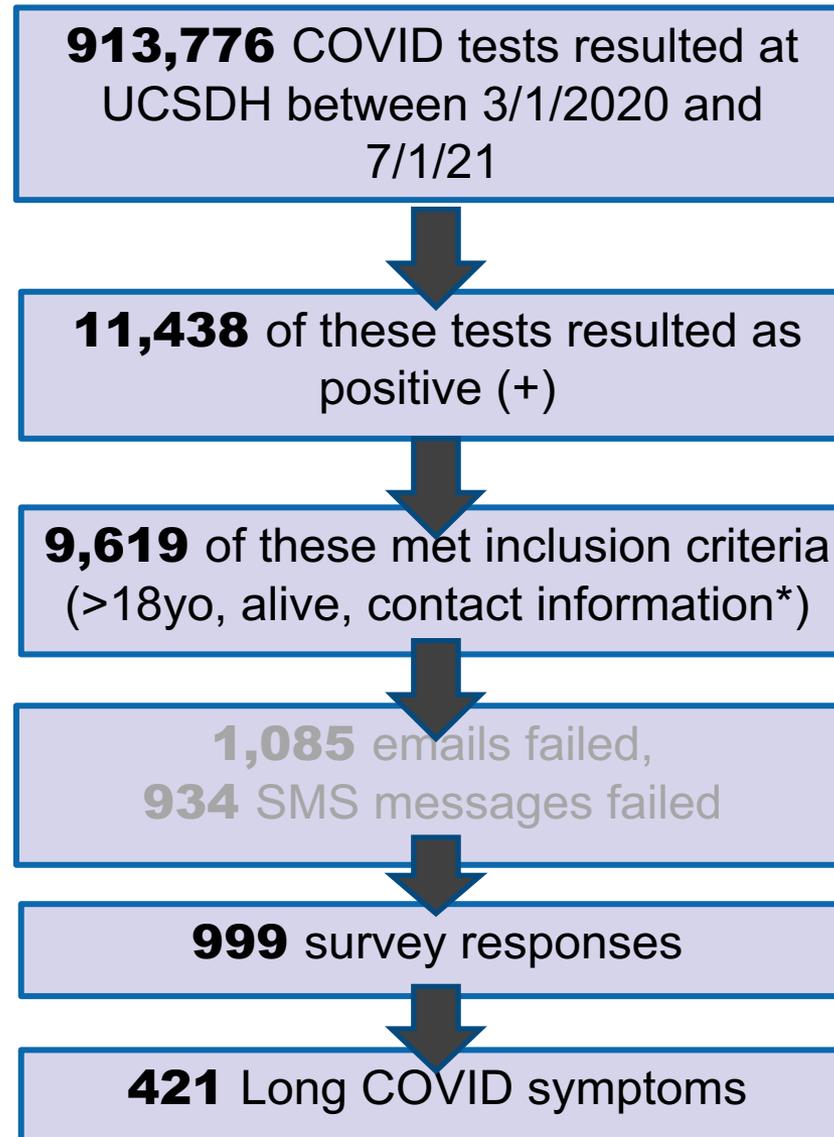
# “More than 50 long-term effects of COVID-19: a systematic review and meta-analysis”

- Key findings:
  - 80% of patients has 1 or more symptoms
    - Most common symptoms: fatigue (58%), headache (44%), attention deficit ( 27%), hair loss (25%), dyspnea (24%)
  - Lab tests and other examinations abnormal in a subset of patients
    - Abnormal lung imaging→ CXR or CT (24%)
    - Elevated levels of pro-inflammatory biomarkers:
      - d-dimer (20%), NT-proBNP (11%), CRP (8%), ferritin (8%), procalcitonin (4%), IL-6 (3%)

# UC San Diego Health post-COVID outreach study “CARES MORE”

- True incidence is unknown, most estimates suggest that 10%-30% of acute infections lead to Long COVID
  - Suspected that only a small sub-set of patients with Long COVID have been diagnosed and/or linked to care
  - Disproportionate number of patients seen in our clinic are self-referred or under Worker’s Comp programs
- Lack of systematic, population-based follow-ups with large cohorts of ambulatory patients to characterize the prevalence of Long COVID
- To guide programmatic planning, we needed empirical data on the potential number of patients experiencing Long COVID symptoms who may benefit from specialized services at our institution

# Outreach survey to UCSDH Patients



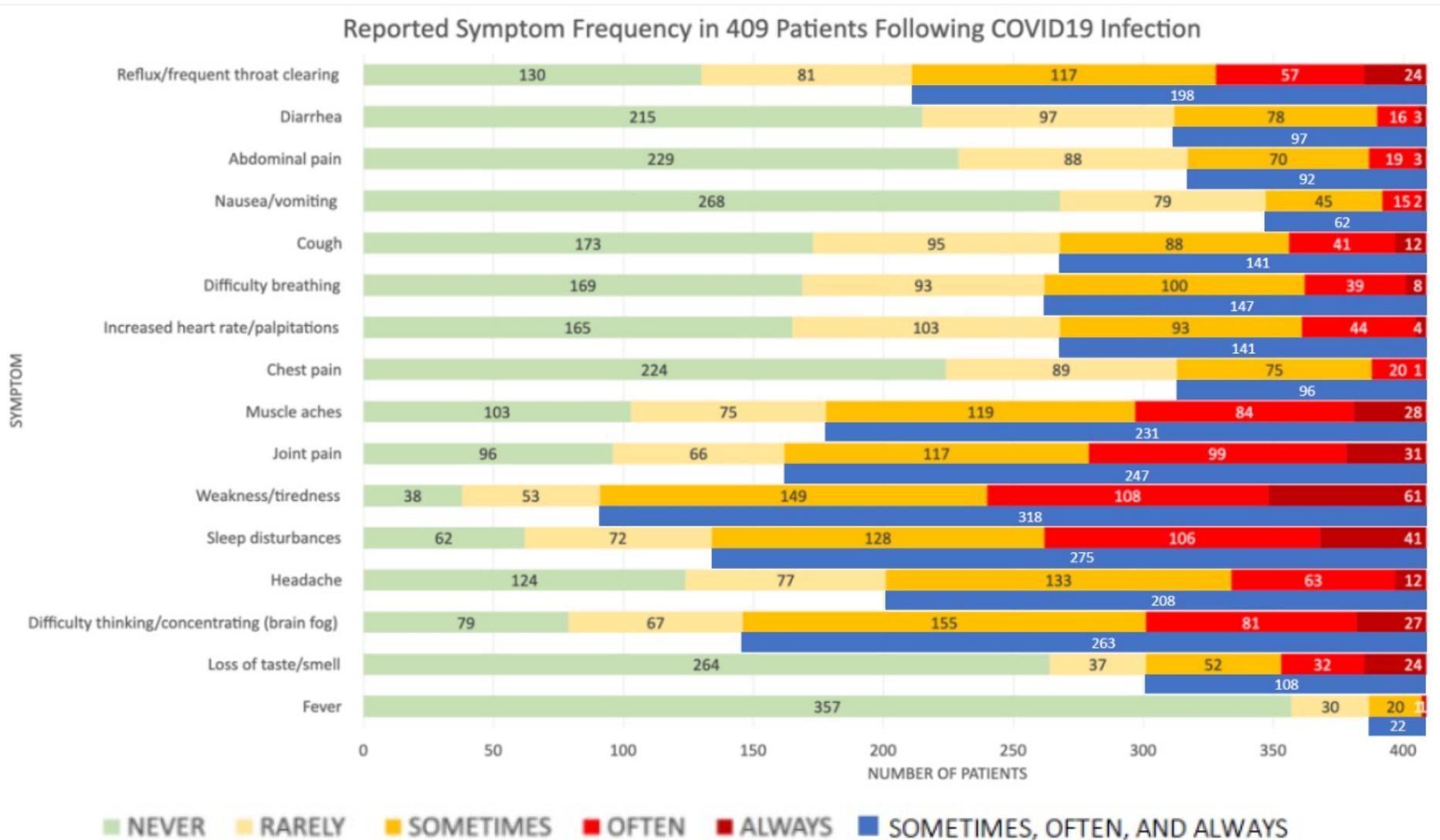
# Survey Respondents

- Demographics:
  - 59% female, 41% male
  - Average age 51.5 years
  - 53% white, 9% Asian, 4% Black, 23% mixed-race
  - Median Healthy Places Index (HPI) 57 (range 0-99)
- Hospitalized for COVID-19: 14.8%
- Only 8.4% received monoclonal antibody treatment
- Equal response rates by distribution channel (email vs text)

# Key Findings

- Of the survey respondents, **46.3% reported having Long COVID symptoms**
  - 343 (83.9%) had at least three symptoms (**mean of six symptoms**)
- Impact on daily functioning:
  - 75/216 (**34.7%**) reported having to miss work/school due to symptoms
  - 143/216 (**66.2%**) reported disruption of daily activities due to symptoms
- Impact on mental health:
  - 23% with positive screening for anxiety (GAD-2  $\geq$  3)
  - 22% with positive screening for depression (PHQ-2  $\geq$  3)

# Long COVID Symptoms in patients testing positive



# Implications for health systems

- Only 123 patients (approx. 25%) reported seeking medical care for their Long COVID symptoms→ suggesting the majority of Long COVID patients at UCSDH have NOT yet engaged in care for their symptoms
  - Estimate that hundreds of Long COVID patients not currently in care
- Survey did not capture full Delta surge (and was pre-Omicron) so anticipate a further increase in Long COVID patients
  - Future/repeat surveys to those testing positive may be useful
- In preparing for our *New Normal* with ongoing COVID transmission, need to anticipate the potential burden of Long COVID patients on the health system
  - Primary care visits, specialty referrals, mental health services, physical therapy, etc.

# Clinical Manifestations and Evaluation

# General themes in Long COVID

- Patients typically present with a constellation of symptoms, many organ systems involved
- Does not seem to correlate with severity of COVID infection; most had mild to moderate COVID (some even were asymptomatic)
- Can present as persistence of COVID symptoms but also new symptoms can start weeks to months after recovery from initial acute illness
- Symptoms often wax and wane
- Diagnostic testing often normal
- Often a strong psychosocial component
- “Unmasking” of other conditions, e.g. reflux, asthma, sleep issues
  - Some patient may end up getting diagnosed with other specific conditions, including asthma, POTS, reactive arthritis, depression, anxiety, PTSD

# Our approach to Long COVID workup and management

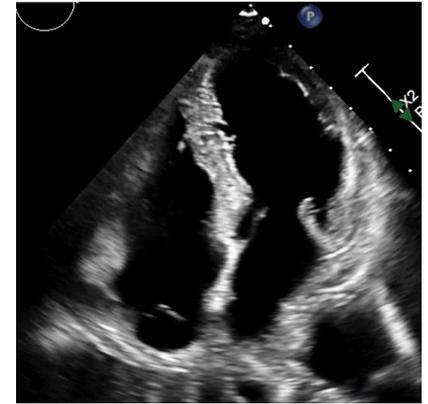
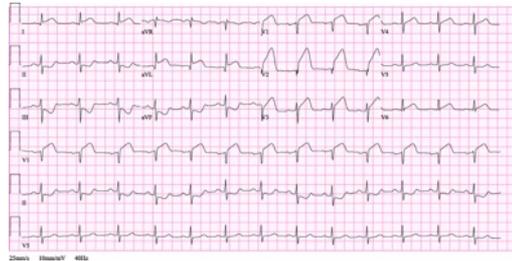
- Work-up should be limited, focus on ruling-out clinically concerning signs and symptoms
  - Symptom-based work-up– e.g. tilt-table testing for POTS symptoms
  - "normal" test results and ruling-out other serious conditions can be therapeutic for some patients
- Cognitive testing can help identify true deficits (e.g. MOCA)
- Physical rehabilitation is a key component
  - Pulmonary rehab and/or physical therapy
  - Slow, step-wise progression in any physical activity
- Integrative approaches to treating pain and fatigue
- Addressing mental health issues and sleep disturbances important-- The Five Pillars of Health
- Focus on ***healing*** rather than ***therapies***

# Cardiovascular Manifestations of Long COVID

Two subtypes of Cardiac Long COVID:

- (1) Hospitalized and ICU patients with severe acute COVID infection

- Arrhythmias
- Myocardial infarction
- Acute heart failure



- (2) Younger, healthier patient with mild COVID

- Chronic dyspnea
- Tachycardia, palpitations

- Structurally normal heart
- “Normal” EKG and event monitor
- Negative troponin

# Cardiovascular Manifestations of Long COVID

- Long COVID Tachycardia
  - Dysautonomia
  - Postural Orthostatic Tachycardia Syndrome (POTS)
- Hypothesized that virus triggers autoantibodies that attack autonomic system
- Profound inflammatory/immune response leads dysregulation and dysautonomia

# Cardiovascular Manifestations of Long COVID

- Treatment of COVID-induced POTS:
  - Symptoms tend to improve with time from COVID infection
  - Lifestyle modifications
  - “Retraining” the autonomic nervous system with exercise
  - Ivabradine can be useful to lower HR and improve exercise tolerance

# Pulmonary Manifestations of Long COVID

- Post-COVID Respiratory symptoms are complex
  - Primary: SOB, impaired exercise tolerance, cough, chest pain
  - Secondary: dizziness, anxiety
- Multiple mechanisms:
  - Post-viral airway hyperresponsiveness
    - Transient, asymptomatic respiratory virus infection augments airway smooth muscle response
  - Neurogenic cough
  - Reflux (GERD/LPR)
  - Asthma
  - OSA

# Pulmonary Manifestations of Long COVID

*Aberrant immune cell regulation in airways of patients with persistent respiratory disease following SARS-CoV-2 infection*

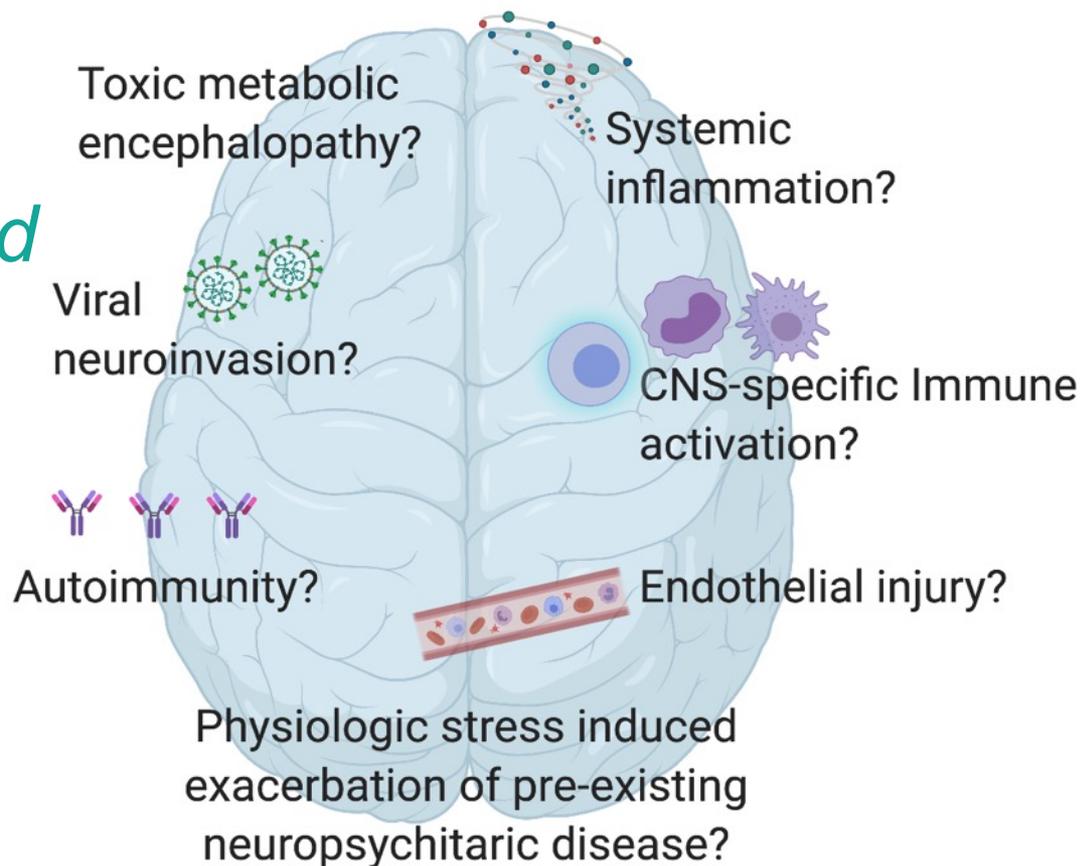
- Previously hospitalized patients with persistent respiratory symptoms or radiological abnormalities in the lungs >3 months post discharge
- Key findings:
  - Increased activated CD8+ and CD4+ tissue-resident memory (Trm) cells and altered monocyte pool
  - Airway proteome altered
  - Elevation in proteins associated with ongoing cell debt, loss of barrier integrity, and immune cell recruitment
  - Not reflected in peripheral blood
  - Dd not correspond to initial severity of illness (based on level of respiratory support)

# Neurologic Manifestations of Long COVID “NeuroPASC”

- NeuroPASC is common, but poorly defined, variable, non-specific
  - Does not require that acute COVID illness be severe
- Poor cognitive performance on objective testing is frequent; other findings range from abnormal sensation to ataxia
- Symptoms and signs are disabling (work, school, social functioning)
- Improvement over 6 to 12 months occurs in many, but not all
- Neuroimaging demonstrates vulnerable brain regions involved in memory, attention, executive function
- Leading candidates for neuropathogenesis: autoimmunity, endothelial dysfunction (viral entry into CNS is rare)
- Many treatments under investigation

# Pathophysiology/Mechanisms of NeuroPASC

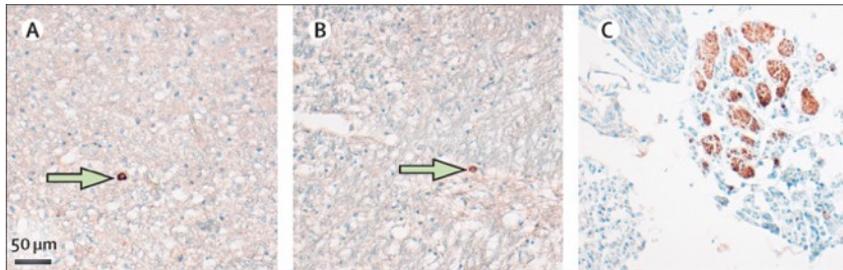
*How does a respiratory virus lead to neurological complications?*



*Adapted from Farhadian, Seilhean, and Spudich, Current Opinion in Neurology, 2021*  
Matschke et al Lancet Neurology, Nov 2020  
Meinhardt, J., Radke, J., Dittmayer, C. et al. Nat Neurosci (2020).  
Song and Zhang et al JEM  
Lee et al NEJM 2021

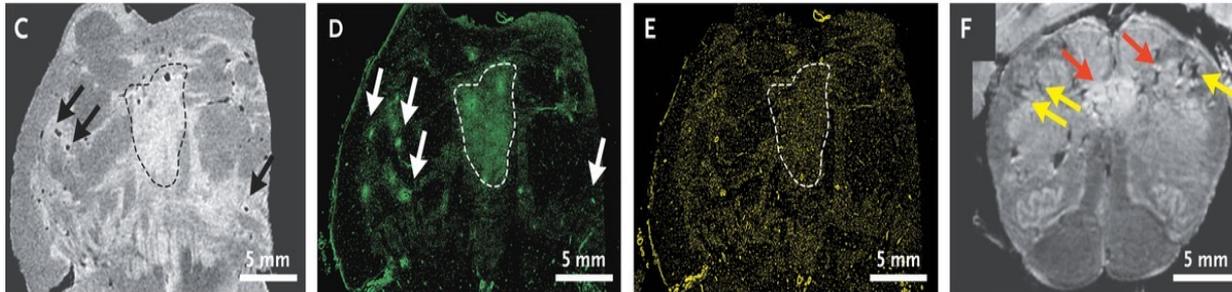
*Courtesy of Shelli Farhadian, Yale*

# Pathophysiology/mechanisms of NeuroPASC: Human brain autopsy studies of viral neuro-invasion



**German cohort I (43 brains):  
53% positive for SARS-CoV-2 RNA  
or protein**

*- viral presence not associated with  
neuropath changes - generally mild*

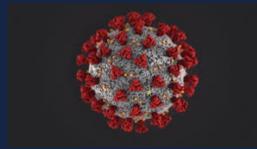


**NYC cohort (13 patients):  
SARS-CoV-2 RNA not  
detected in any**

*-widespread microvascular  
injury by MR microscopy*

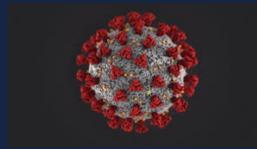
*Matschke et al Lancet Neurology, Nov 2020  
Meinhardt, J., et al Nat Neurosci (2020  
Lee et al NEJM 2021*

- Neurons not infected
- Vascular epithelium infected and inflamed



# UCSD NeuCovid Collaboration: Neuro-PASC longitudinal data to date

- Early on in neuro-PASC prominent symptoms are *headache and fatigue*
- Later in neuro-PASC *memory and inattention* symptoms predominate
- Most improve over follow-up but takes 3-6 months
- 2/3 have some persistent symptoms >6 months



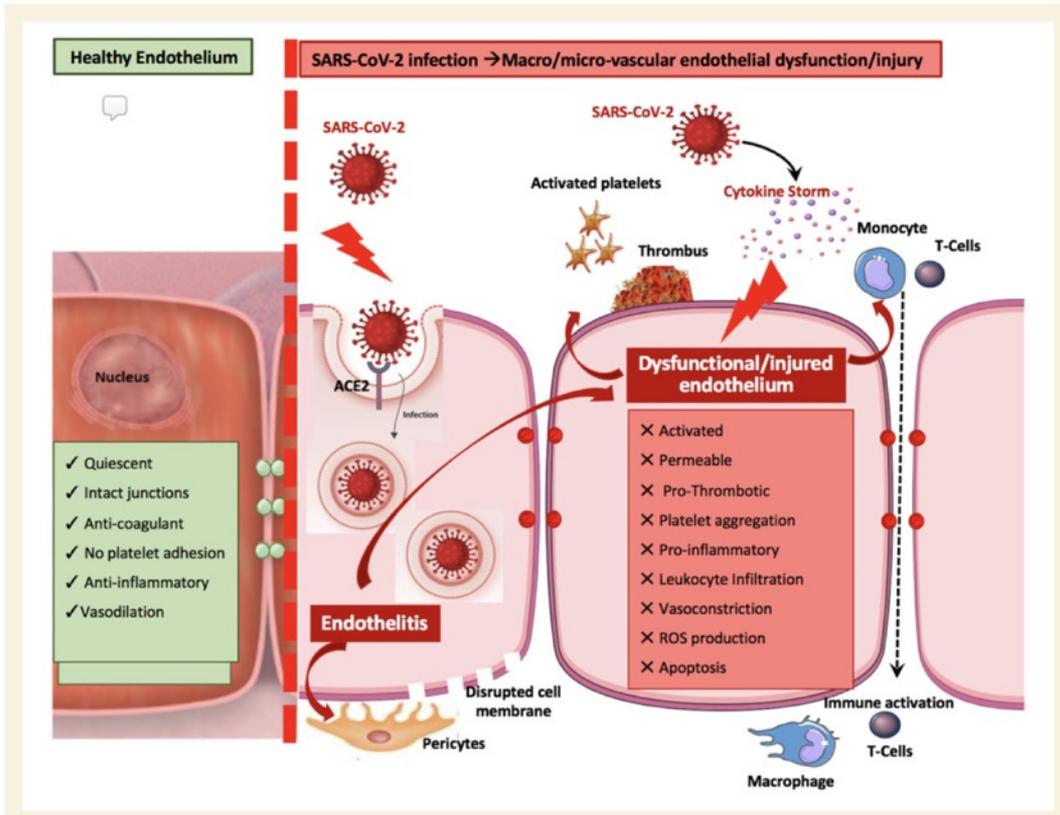
# UCSD NeuCovid Collaboration: Neuro-PASC longitudinal data to date

- While most get better, 10-15% of neuro-PASC worsen over time including screening cognitive scores
- Potentially alarming phenotype of tremor, ataxia and cognitive changes (PASC-TAC) emerged in ~7% of our cohort

# What causes Long COVID/PASC?

- Underlying pathophysiology is still largely unknown
- Potential mechanisms include:
  - Virus-specific pathophysiologic changes
  - Perturbation of immune and inflammatory responses by the acute viral infection
  - Expected sequelae of post-critical illness
  - Viral infection triggering autoimmunity
  - Long term viral persistence
  - Fibrosis and other changes in lungs, heart, other organs
- Autonomic nervous system dysregulation (& vagus nerve damage)
- Psychological component in large subset
- No clear correlation with antibody levels or severity of disease

# Endothelial dysfunction in Long COVID

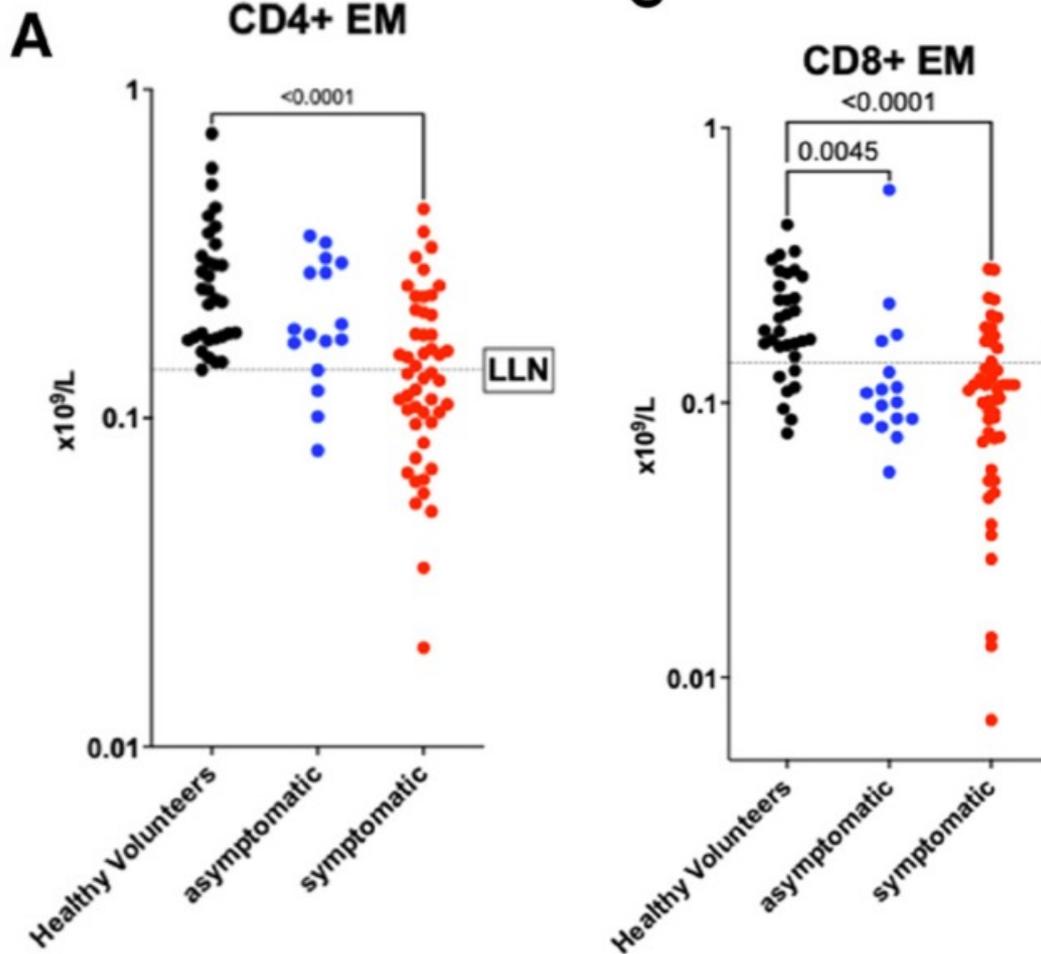


- SARS-CoV-2 infection of and subsequent damage to endothelial cells may explain some symptoms including autonomic dysfunction
- Microvascular damage in lungs, heart, other organs?
- Endothelial dysfunction has been described in other infections (e.g. VHFs)

# T cell perturbations

- Gylnee et al. observational study of patients previously diagnosed with mild COVID and initially recovered but then developed Long COVID
  - 49 Long-COVID patients, plus 16 post-COVID asymptomatic control patients, and health controls
  - Isolation and molecular analysis of T cells
- Key Findings:
  - Long COVID is associated with characteristic and specific alterations in circulating T cells up to 400 days after infection

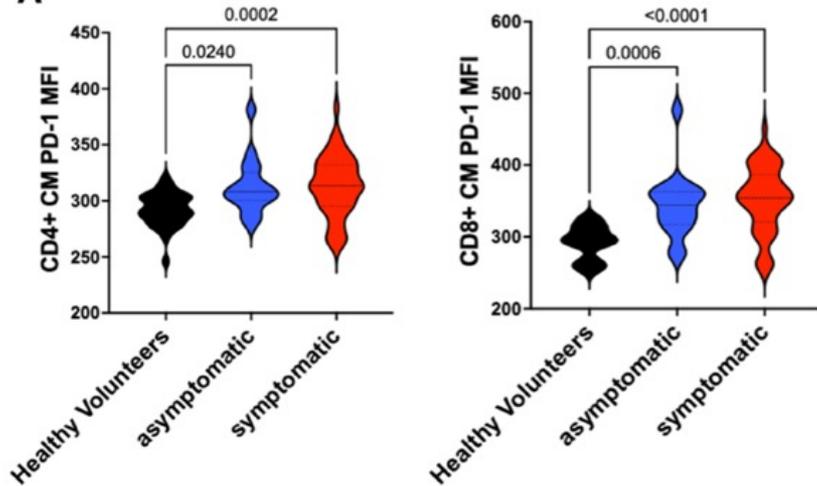
# T cell perturbations



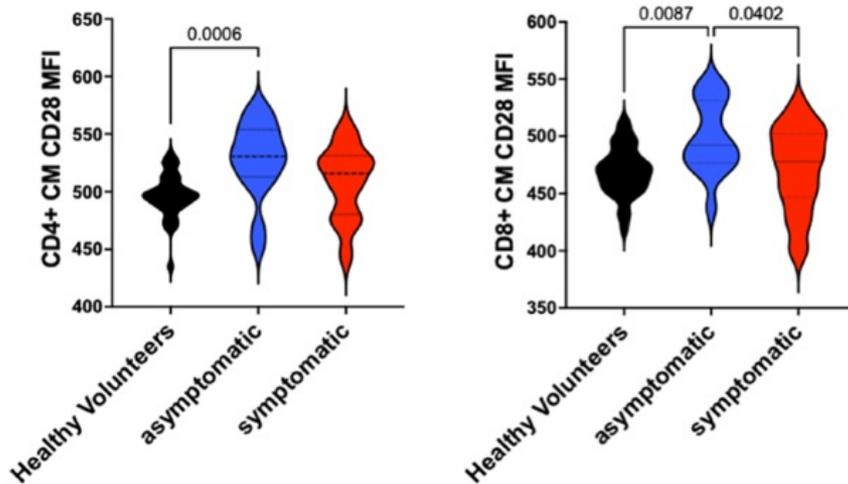
- Reduction in CD4+ and CD8+ effector memory cell numbers after COVID infection
- Significant difference in CD4+ between symptomatic and asymptomatic groups

# T cell perturbations

A



B



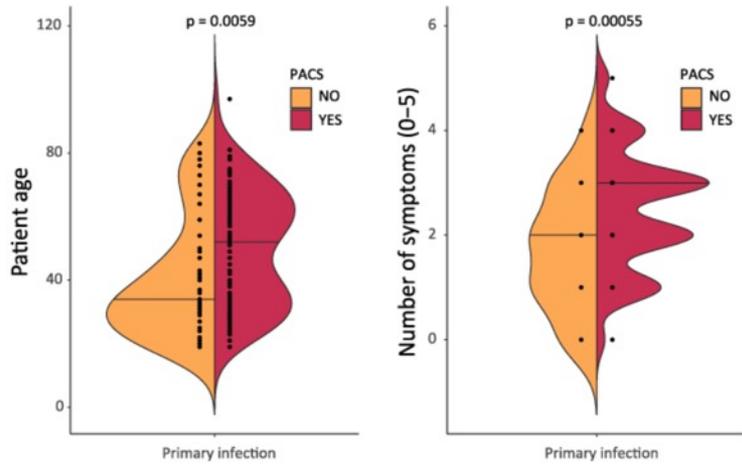
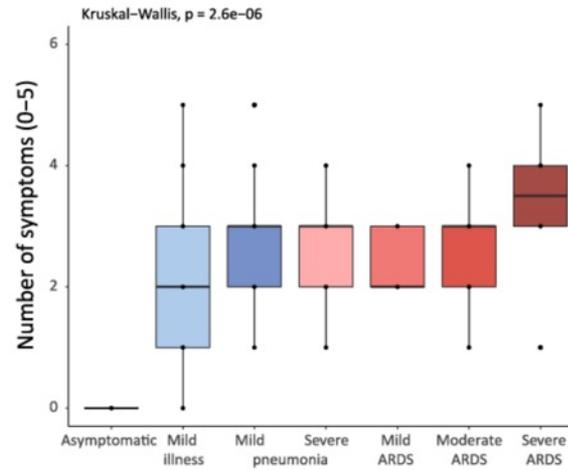
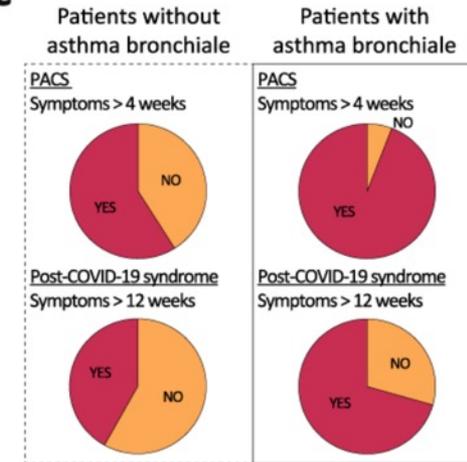
- PD-1 and CD28 levels distinguish patients with long COVID from the asymptomatic fully recovered group
- PD-1 is a marker of *T cell exhaustion* in chronic viral infection – increased after COVID infection
- CD28 is a modulator essential for signal transduction and T cell triggering- increased in those who had made an uneventful recovery from COVID-19
  - *May represent a 'healthy' immune response to SARS-CoV-2*

# Predictors of Developing Long COVID

# Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome

Carlo Cervia <sup>1</sup>, Yves Zurbuchen <sup>1</sup>, Patrick Taeschler<sup>1</sup>, Tala Ballouz<sup>2</sup>, Dominik Menges <sup>2</sup>, Sara Hasler <sup>1</sup>, Sarah Adamo <sup>1</sup>, Miro E. Raeber <sup>1</sup>, Esther Bächli<sup>3</sup>, Alain Rudiger<sup>4</sup>, Melina Stüssi-Helbling<sup>5</sup>, Lars C. Huber<sup>5</sup>, Jakob Nilsson<sup>1</sup>, Ulrike Held <sup>2</sup>, Milo A. Puhani <sup>2</sup> & Onur Boyman <sup>1,6</sup>✉

- Prospective multicentric cohort study (n= 215)
- Enrolled during primary infection → 1 year follow-up
- Predictors of developing PASC:
  - Immunoglobulin signature (based on total IgM and IgG3 levels)
  - Older age
  - History of asthma bronchiale
  - Five symptoms during primary infection

**a****b****c**

- Greater number of symptoms and more severe disease predicted risk for post-acute and chronic COVID syndromes
- Regardless of their COVID-19 severity, 71% of patients with history of asthma bronchiale developed Long COVID (symptoms > 12 weeks) versus 42% without a history of asthma bronchiale

# Multiple Early Factors Anticipate Post-Acute COVID-19 Sequelae

Yapeng Su  <sup>28</sup>  • Dan Yuan <sup>28</sup> • Daniel G. Chen <sup>28</sup> • ... Mark M. Davis • Jason D. Goldman   • James R. Heath  <sup>29</sup>  • [Show all authors](#) • [Show footnotes](#)

[Open Access](#) • Published: January 24, 2022 • DOI: <https://doi.org/10.1016/j.cell.2022.01.014>

- “Deep, multi-omics” biology approach (proteomics, metabolomics)
- Prospective study: time of infection and 2-3 months later
- n=209 (plus healthy controls)
- Assessment of autoantibodies, SARS-CoV-2-specific antibodies, global plasma proteomic and metabolomic profiles, and single-cell multi-omics characterizations of peripheral blood mononuclear cells
  - Each blood draw was paired with nasal swab and plasma measurements of SARS-CoV-2 viral load

## Key findings:

- Pre-existing type 2 diabetes is a risk factor for PASC
- Reactivation of latent viruses during initial infection may contribute to PASC
  - EBV viremia more common in those who develop persistent symptoms
- Subclinical autoantibodies negatively correlate with anti-SARS-CoV-2 antibodies
- Gastrointestinal-predominant subtype of PASC has a unique expansion of cytotoxic T cells
  - SARS-CoV-2-specific and CMV-specific CD8<sup>+</sup> T cells exhibited unique dynamics during post-infection recovery

# Role of Vaccination

# Vaccination in patients with Long-COVID

- Having Long COVID is **not a known contraindication to COVID vaccination**
- Several studies suggest that vaccination may improve or resolve symptoms in many patients
- Subset of patients report worsening or relapsing symptoms



# Effectiveness of vaccination against Long COVID

- UK Health Security Agency's rapid evidence briefing published in February 2022
- 15 studies reporting the efficacy of vaccination against Long COVID:
  - 7 examined role of vaccine prior to infection
  - 7 examined role of vaccine in people already with Long COVID
  - 1 looked at both
- All studies were observational
- Large heterogeneity in the definition of Long COVID

# Effectiveness of vaccination against Long COVID

- All 8 studies assessing effectiveness of vaccination before infection *suggested that vaccine reduced the likelihood of developing Long COVID symptoms*
  - People who were fully vaccinated and then developed COVID-19 were about half as likely as people who were unvaccinated or received only one dose of mRNA vaccine to develop post-COVID symptoms (> 28 days)
    - Retrospective cohort study by Simon et al. (2021, preprint, rated high quality) found vaccinated patients had an OR of 0.22 of developing any Long COVID symptoms up to 12 weeks later
    - Nested case-control study by Antonelli et al. (2022, rated medium quality) found fully vaccinated participants had an OR 0.51 partially vaccinated had similar OR to unvaccinated
  - Vaccine effectiveness against most post-COVID conditions was highest in adults over 60 years of age.

# Effectiveness of vaccination against Long COVID

- For studies measuring effect of vaccination on patients already experiencing Long COVID:
  - 3 of 4 studies suggested that *more patients reported improvement in symptoms after vaccination* (either immediately or over several weeks) compared to before
  - However, *some cases in all studies reported a worsening in symptoms post-vaccination*
  - In 3 of 5 studies looking at symptom changes after vaccination, more people reported unchanged symptoms than improvement or worsening
  - One study suggested that vaccination sooner after infection may lead to lower likelihood of Long COVID symptoms

# Clinical Challenges in Long COVID

- **Not all Post-COVID is Long COVID**
- Difficult to understand underlying pathophysiology and disease processes
- No standardized diagnostic criteria, no clear guidelines for evaluation and treatment → lack of uniformity even within institutions
- Need more large, prospective studies to better evaluate the natural course of COVID-19 infection, define the Long COVID syndrome, and identify the best rehabilitation techniques and clinical management strategies
- Resource-intensive condition, multidisciplinary teams needed
  - Potential to be a huge strain on health systems
  - Demand for ancillary services and support staff

# The UC San Diego Health Post-COVID Care Clinic

- Multidisciplinary, joint clinic structure
  - All patients seen by 3 providers (ID, Pulm, Rheum) at same visit
  - Referral to other subspecialties as indicated
- Neurocognitive screening
- Majority referred for pulmonary rehab/PT and Integrative Med
- Patient support group (starting March 2022)
- Since September 1, 2021: 246 completed visits (>140 unique patients)
- Opportunities to participate in clinical trials
- Patients can be self-referred or referred by PCP
- <https://health.ucsd.edu/specialties/infectious-disease/Pages/post-covid-care.aspx>

# The UC San Diego Health Post-COVID Care Clinic



**Lucy E Horton, MD, MPH**



**Angela K Wang, MD**



**Susan J Lee, MD**



**Ronald J Ellis, MD**



**Nicholas J Phreaner, MD**



**Arpi Minassian, PhD**



**Jennifer Graves, MD, PhD, MAS**

*"Healing is a matter of time, but it is sometimes also a matter of opportunity." - Hippocrates*

