Post-Acute Sequelae of COVID-19 (PASC):
Pathophysiology and Workup

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Advancing Integrated Psychiatric Care for the Medically Ill

Disclosures

- DoD CDMRP W81XWH-20-1-0928
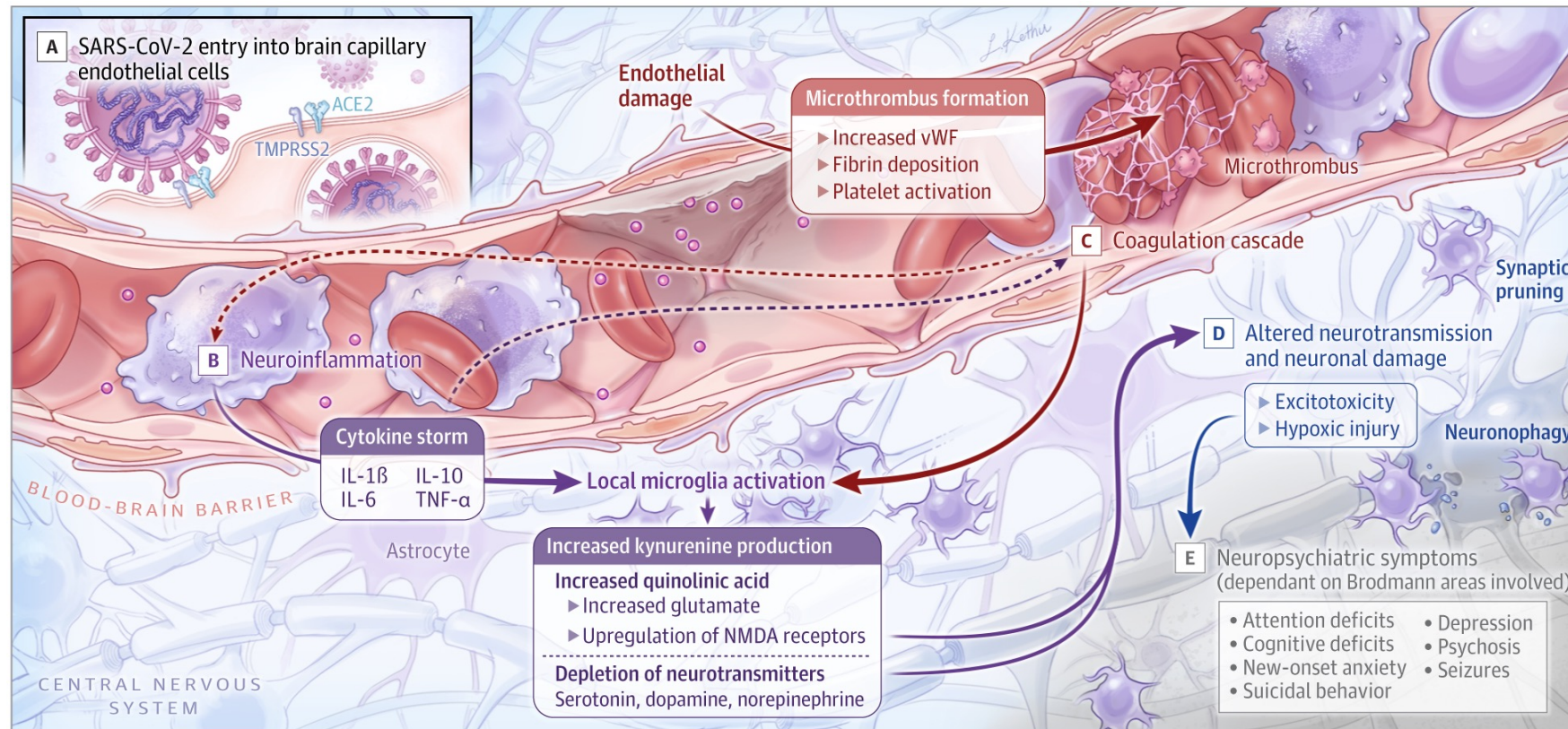- DoD CDMRP W81XWH-17-1-0432

- NIH PASC Investigator Consortium Phase 1 participant

Outline

- How might COVID-19 lead to PASC?
  - 2 trajectories
- Candidate pathophysiologies
  - End-organ damage
  - Ongoing inflammation
  - Immune dysfunction
  - Dysautonomia
- Tentative clinical workup for PASC
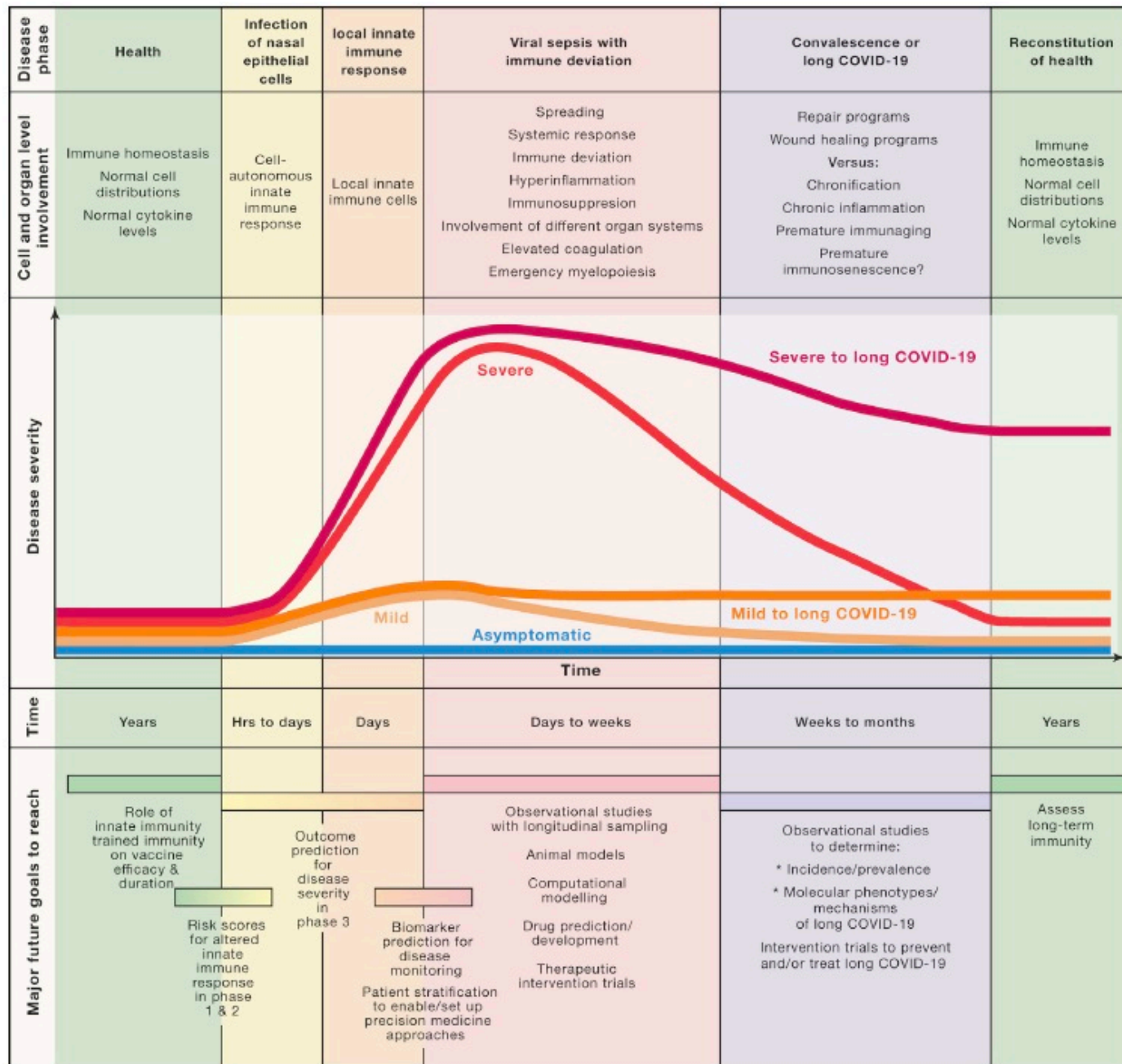
How might COVID-19 lead to PASC?

SARS-CoV-2 Infection → microthrombus formation → hypoxic/ischemic injury

SARS-CoV-2 Infection → immune system activation → neuroinflammation

2 Trajectories to PASC

1) <mark>Severe Infection</mark> →
   Acute care hospitalization
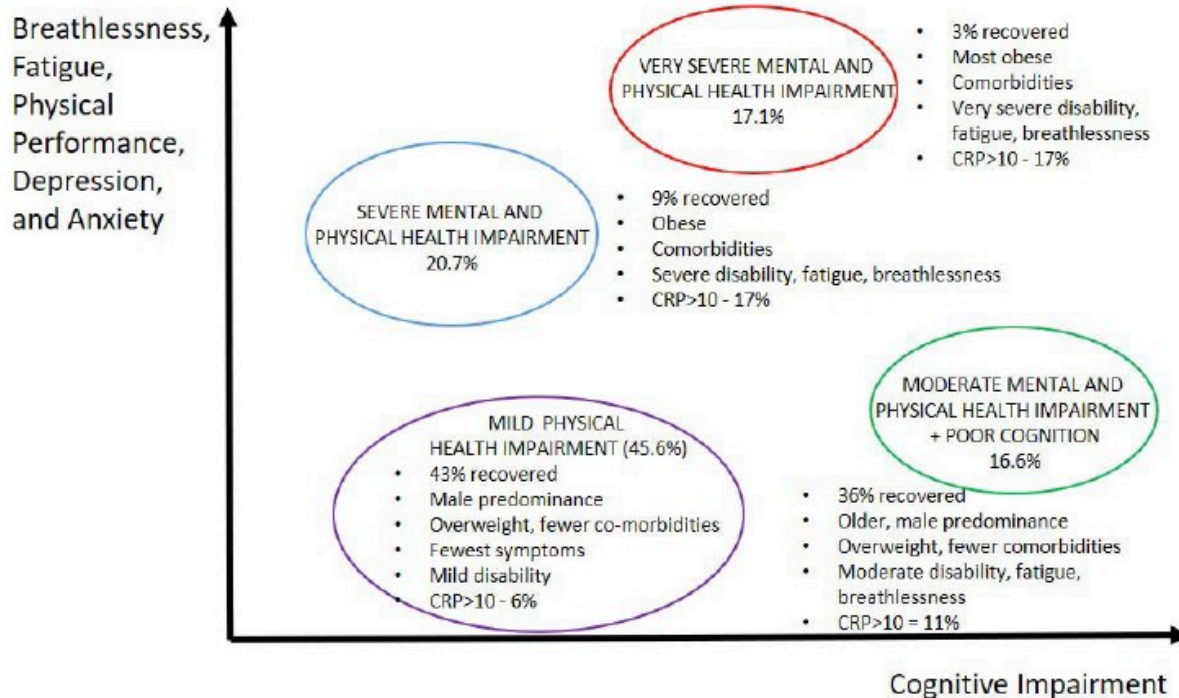
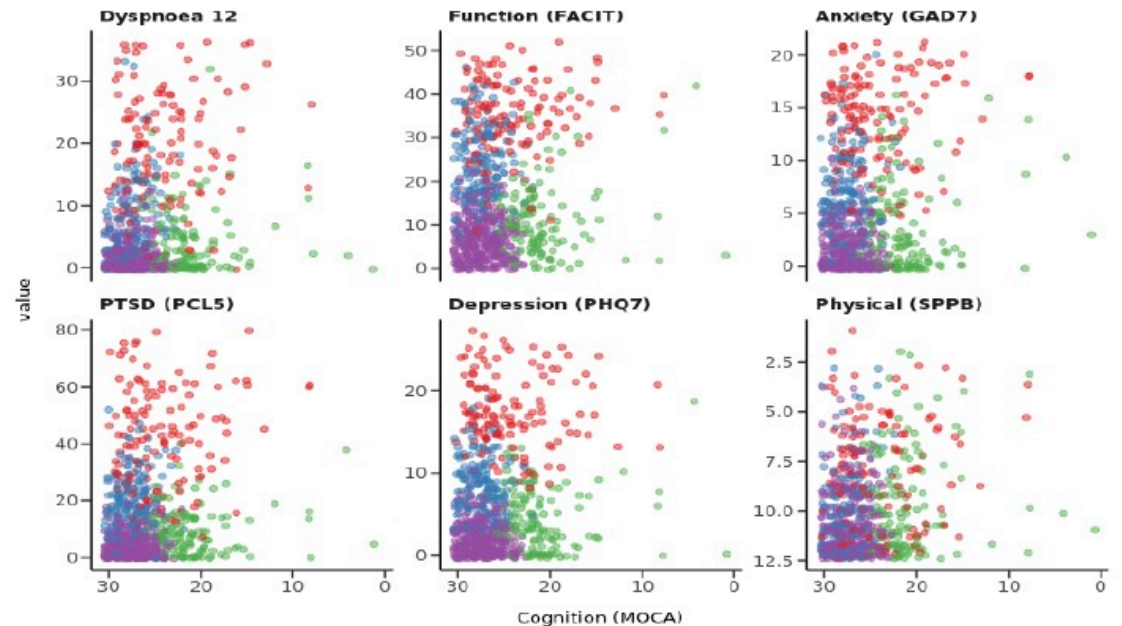2) <mark>Mild Infection</mark> → Ambulatory Care

Schultze, Sept 2021

Trajectory to PASC 1: Post-hospitalization

The Post-hospitalisation COVID-19 study (PHOSP-COVID)

1077 discharged hospitalized COVID pts
Assessed at 5 mo post-discharge
29% fully recovered; 20% with new disability
4 phenotypes of recovery identified

Breathlessness, Fatigue, Physical Performance, Depression, and Anxiety

VERY SEVERE MENTAL AND PHYSICAL HEALTH IMPAIRMENT 17.1%
- 3% recovered
- Most obese
- Comorbidities
- Very severe disability, fatigue, breathlessness
- CRP>10 - 17%

SEVERE MENTAL AND PHYSICAL HEALTH IMPAIRMENT 20.7%
- 9% recovered
- Obese
- Comorbidities
- Severe disability, fatigue, breathlessness
- CRP>10 - 17%

MODERATE MENTAL AND PHYSICAL HEALTH IMPAIRMENT + POOR COGNITION 16.6%

MILD PHYSICAL HEALTH IMPAIRMENT (45.6%)
- 43% recovered
- Male predominance
- Overweight, fewer co-morbidities
- Fewest symptoms
- Mild disability
- CRP>10 - 6%

- 36% recovered
- Older, male predominance
- Overweight, fewer comorbidities
- Moderate disability, fatigue, breathlessness
- CRP>10 = 11%

Cognitive Impairment

- 1: Very severe mental/physical impairment
- 2: Severe mental/physical impairment
- 3: Moderate mental/physical impairment + poor cognition
- 4: Mild impairment

Dyspnoea 12   Function (FACIT)   Anxiety (GAD7)
PTSD (PCL5)   Depression (PHQ7)   Physical (SPPB)
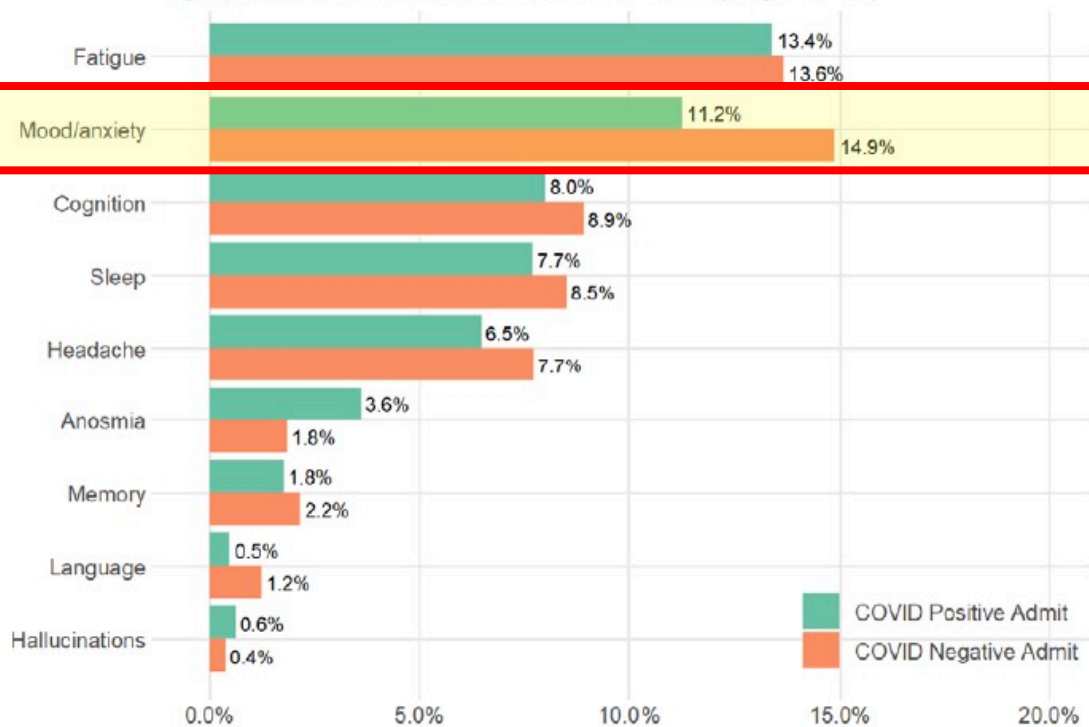
Cognition (MOCA)

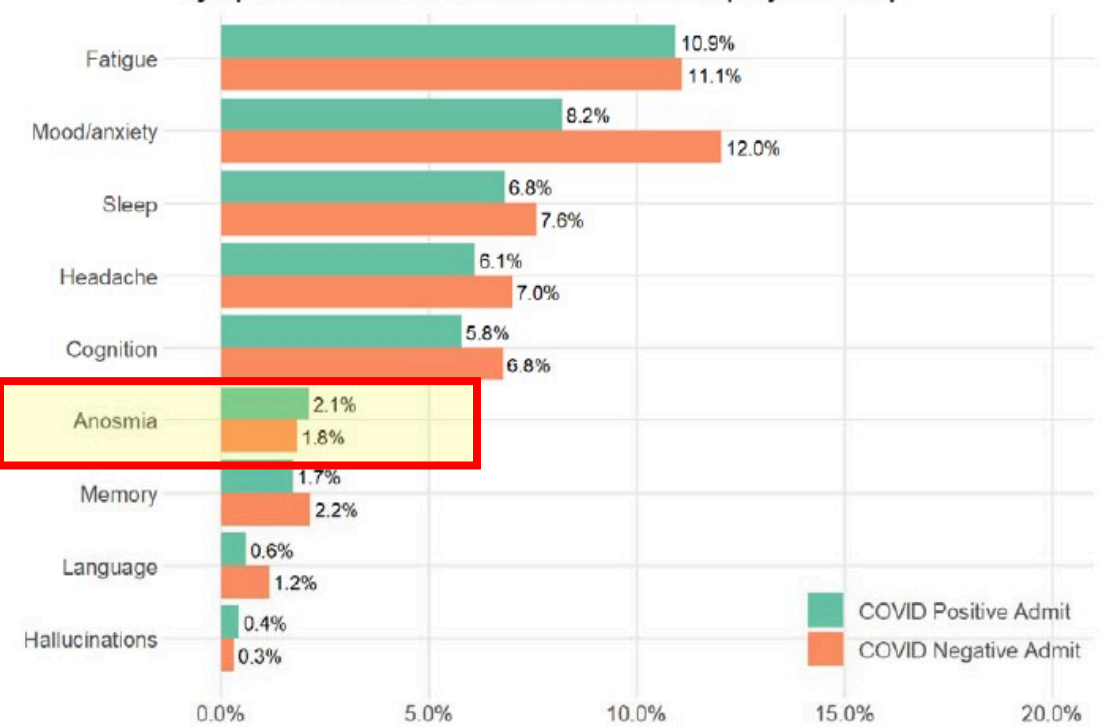# Is PASC a specific or nonspecific effect?

EHR study of 6,619 COVID+ admits and 36,342 non-COVID admits from 6 hospitals
Symptoms at 31-90 days and 91-150 days post-discharge assessed
No difference in symptom rates between COVID+ and COVID- groups

Symptom Prevalence in Post-acute Period (Days 31-90)

Symptom Prevalence in Post-acute Period (Days 91-150)

Castro et al, 2021

Trajectory to PASC 2: Mild then worsening

3762 respondents to internet survey w/ confirmed or suspected COVID infection tracking symptoms over 7 months
<mark>Symptoms can worsen over time, fluctuate</mark>

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

Hannah E. Davis[a,1], Gina S. Assaf[a,1], Lisa McCorkell[a,1], Hannah Wei[a,1], Ryan J. Low[a,b,1], Yochai Re'em[a,c,1], Signe Redfield[a], Jared P. Austin[a,d], Athena Akrami[a,b,1,*]
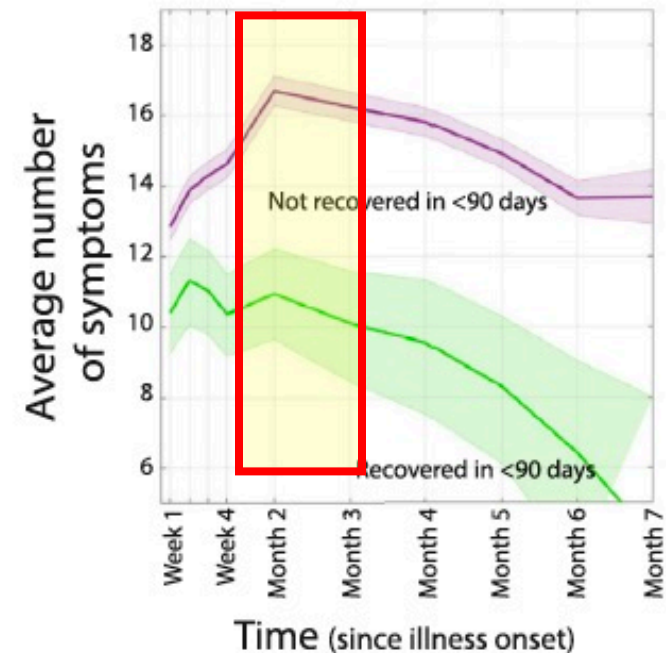
a. Probability of having symptoms after T
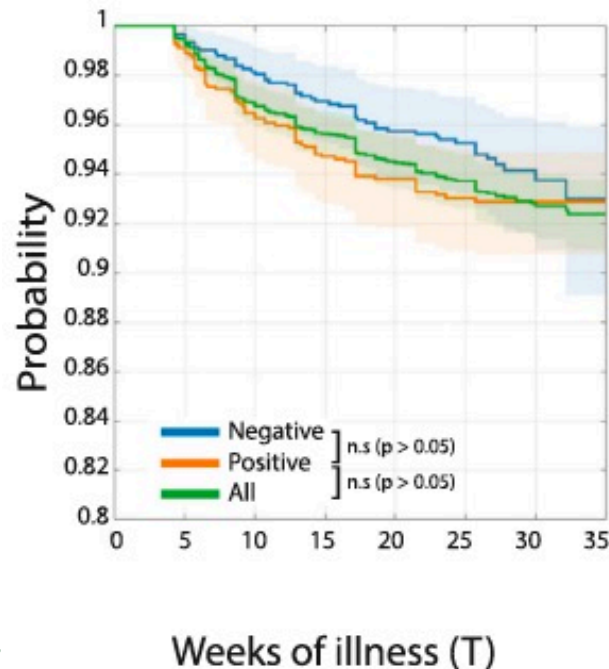
b. Symptom severity score over time
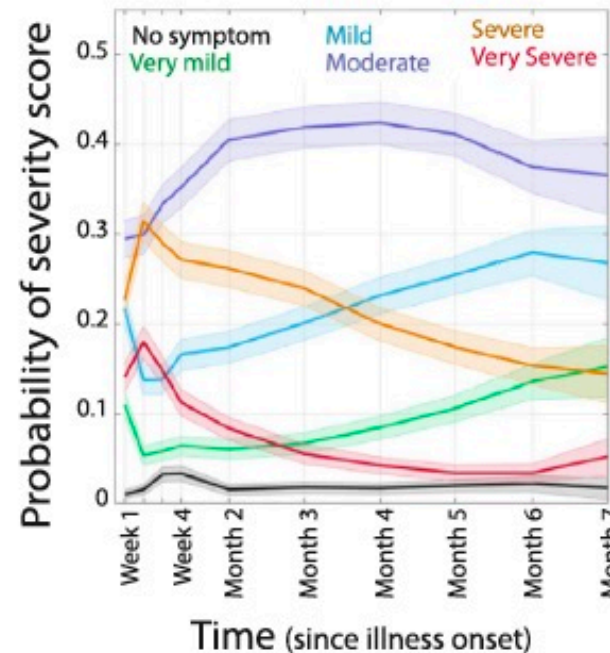
c. Average number of symptoms over time

Specific or Non-specific?

Prevalence and Predictors of Prolonged Cognitive and Psychological Symptoms Following COVID-19 in the United States

Jennifer A. Frontera[1]*, Ariane Lewis[1], Kara Melmed[1], Jessica Lin[1], Daniel Kondziella[2,3], Raimund Helbok[4], Shadi Yaghi[5], Sharon Meropol[1], Thomas Wisniewski[1], Laura Balcer[1] and Steven L. Galetta[1]

999 respondents to a community survey
19 COVID+ with prolonged symptoms, 57 COVID+ recovered, 923 negative

After controlling for demographics, PMH, stressors, COVID+ status predictive of NeuroQOL cognitive symptoms but not depression, anxiety, fatigue, or sleep
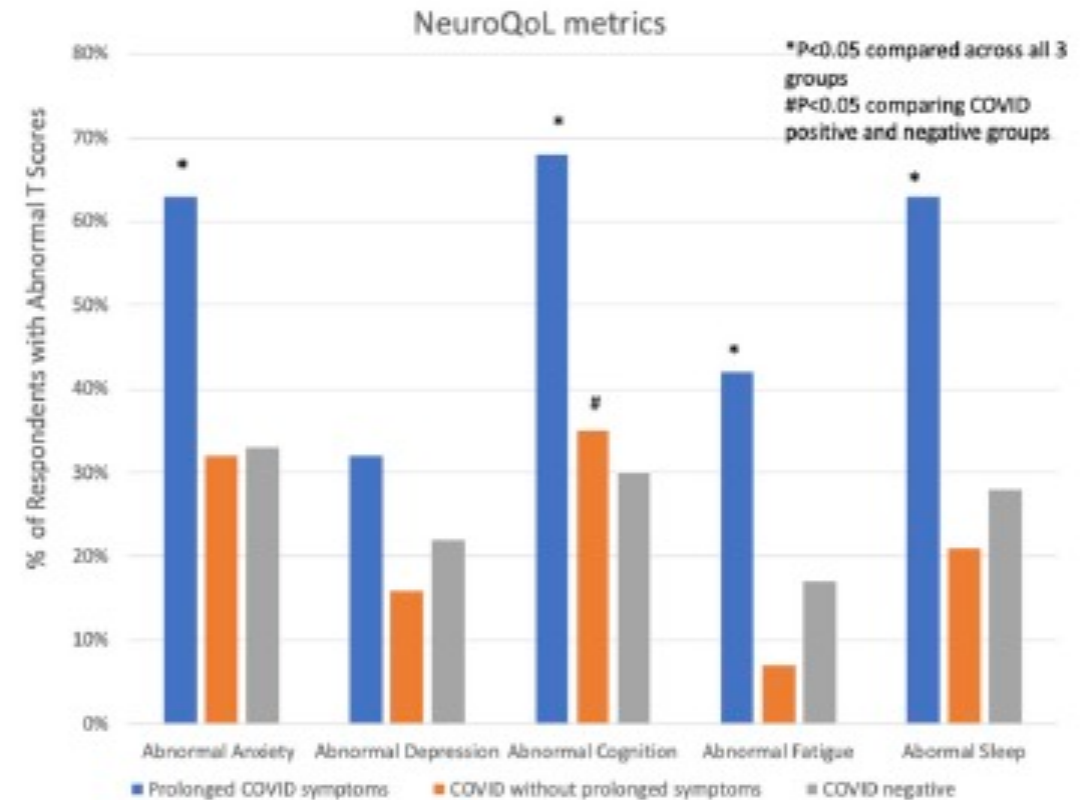
Mechanisms of PASC after COVID-19

- Direct viral invasion of tissue

- Viral-induced inflammation and organ damage

- Viral-induced immune reaction + autoimmunity

- Post-ICU syndrome (metabolic disarray , mechanical ventilation, delirium, deconditioning, sedative effects, PTSD)

- Complications of treatments (steroids, hydroxychloroquine, antivirals)
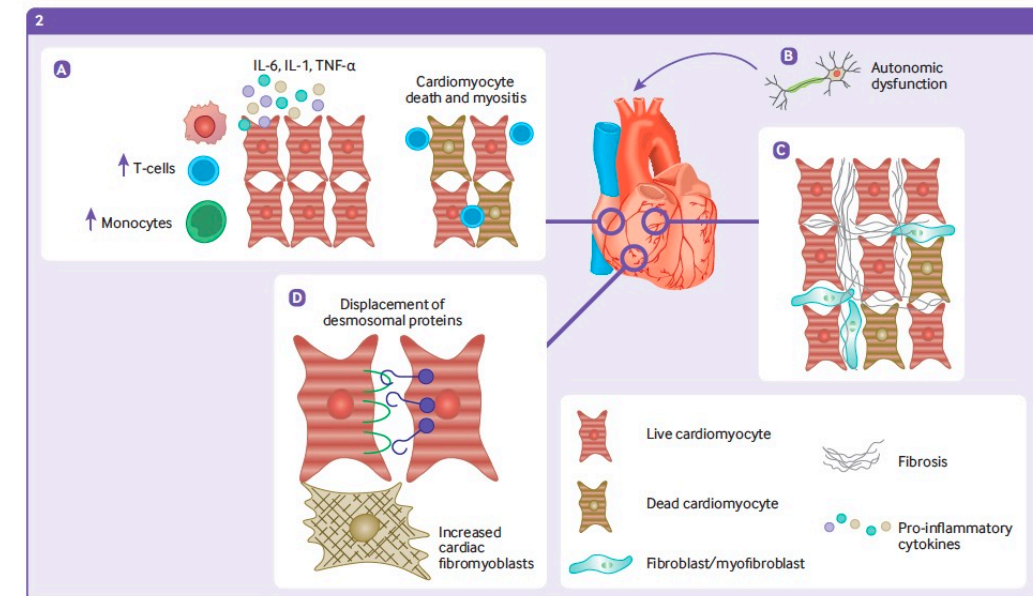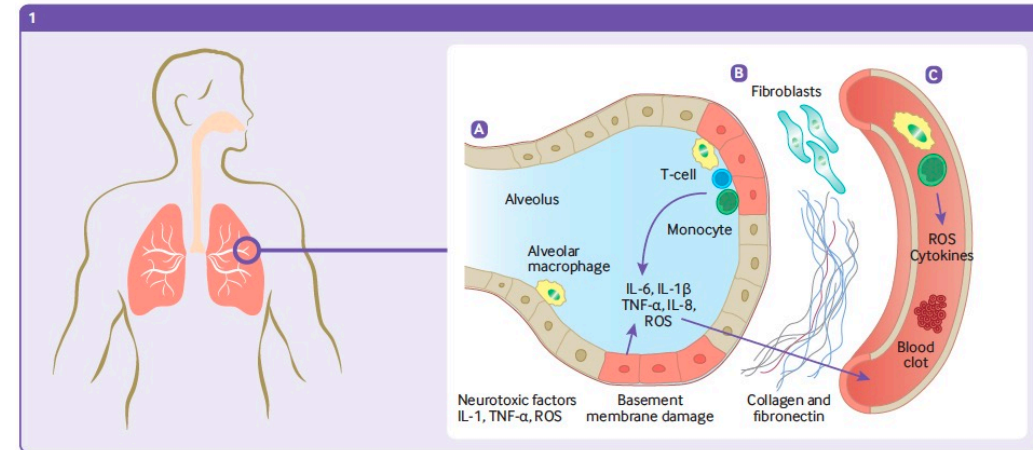
- Psychosocial stressors of illness/pandemic
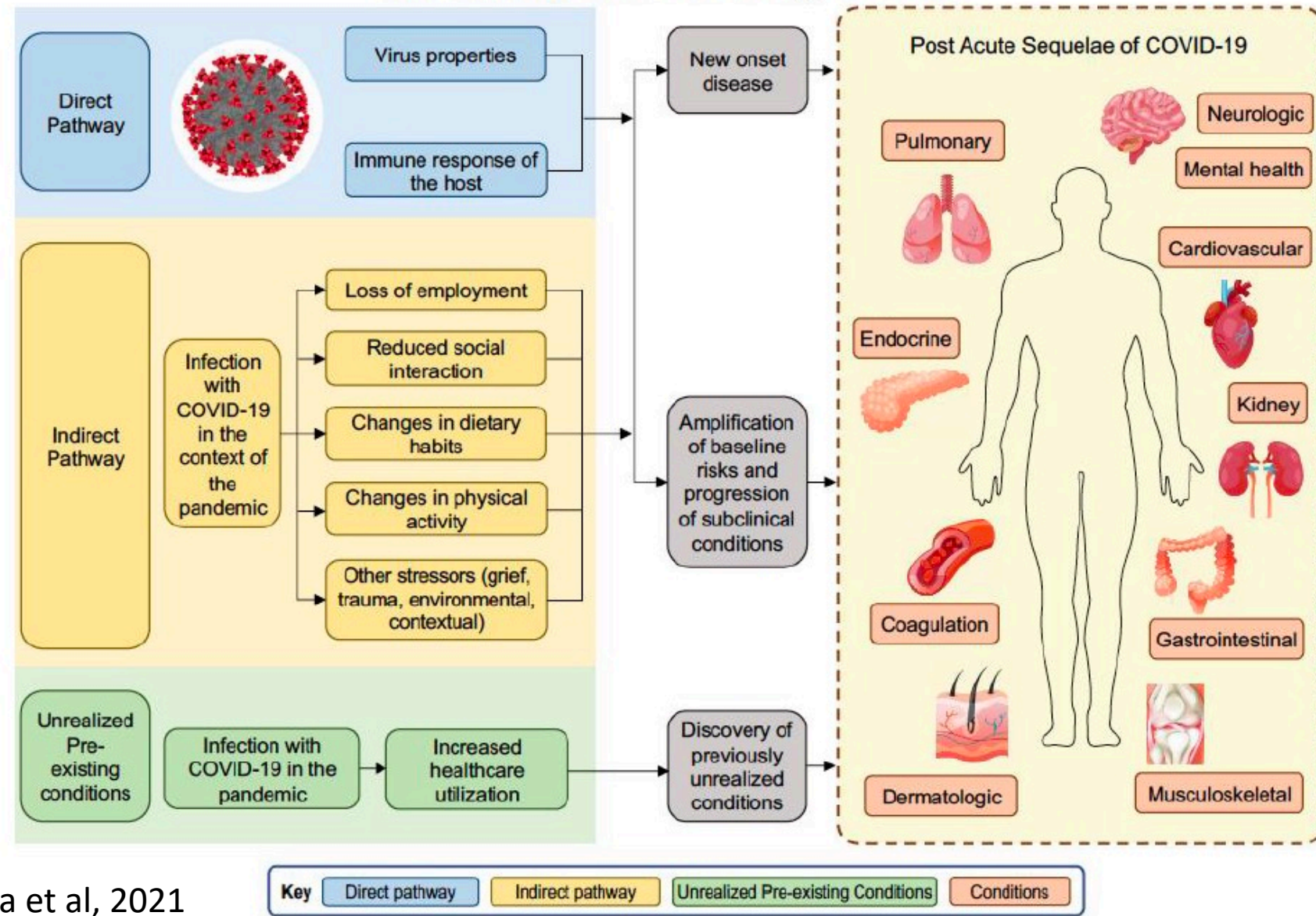
Nakamura et al, 2021
Al-Aly, 2021

Pathophysiology 1: End-Organ Damage

Viral invasion leads to local tissue injury in lungs, heart, and brain, with prolonged dysfunction

- Inflammation
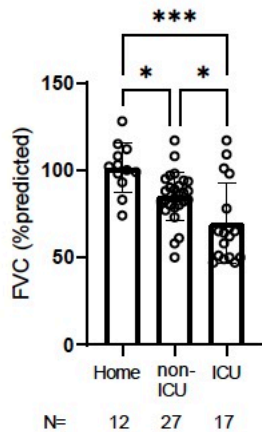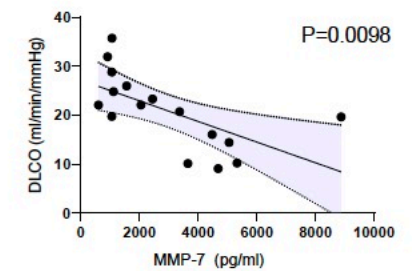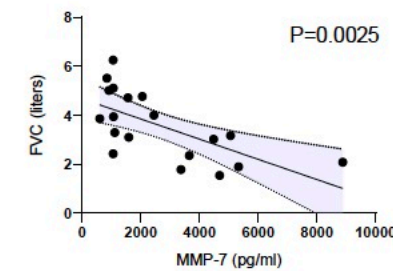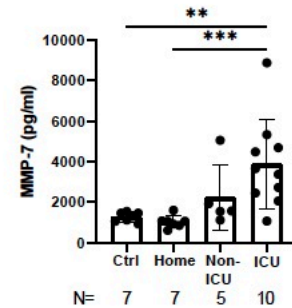- Fibrosis
- Thrombus/Embolus

Crook et al, 2021

61 subjects with COVID+, 53 with persistent symptoms

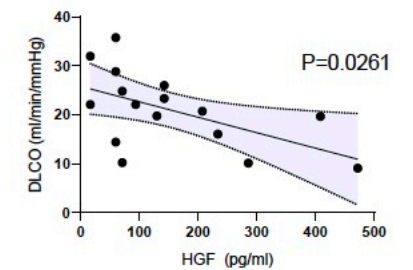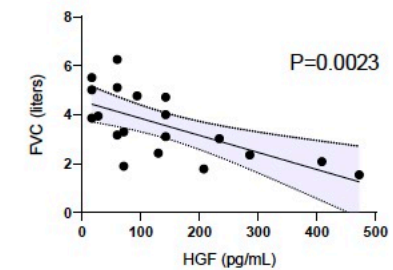FEV1, FVC, DLCO all declined more in context of greater acute illness severity
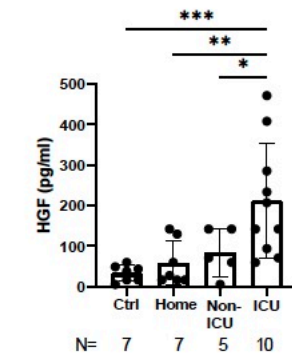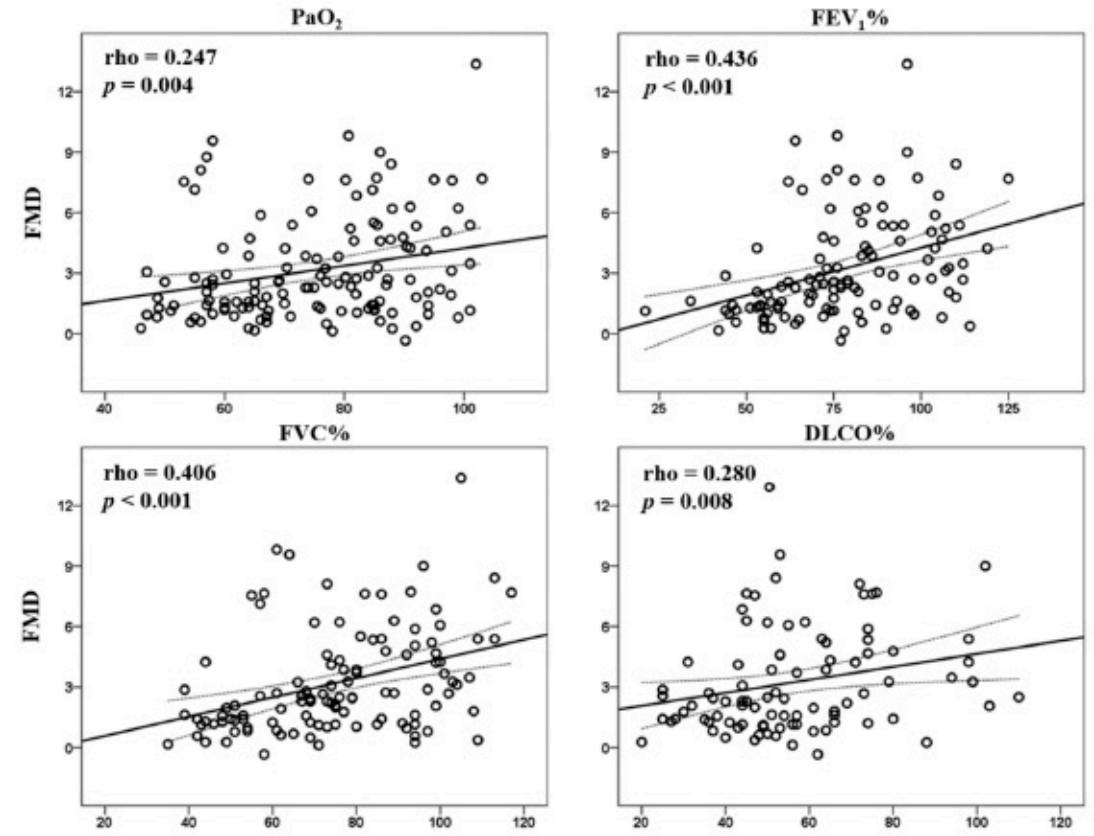Host inflammatory response profiles (MMP, LCN2, HGF) demonstrate elevated levels in more severe cases
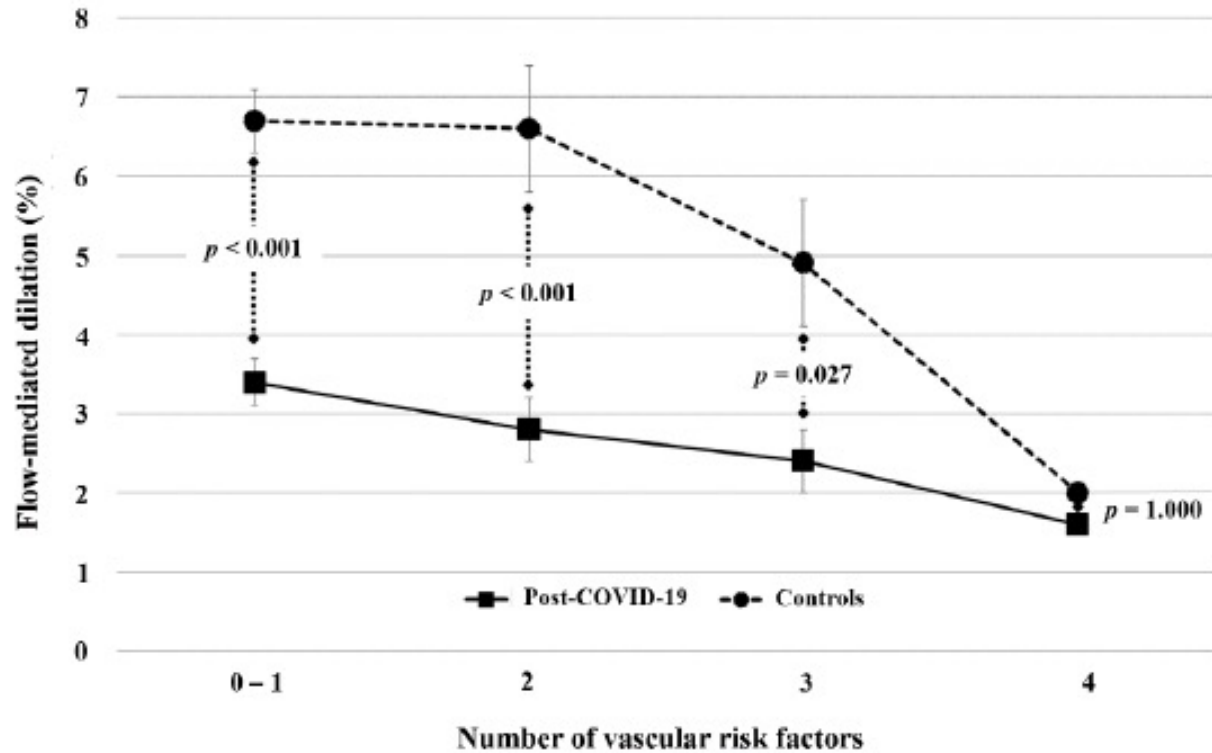

Chun et al, 2021
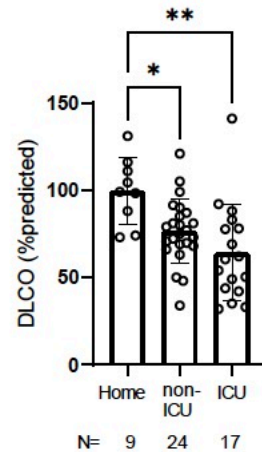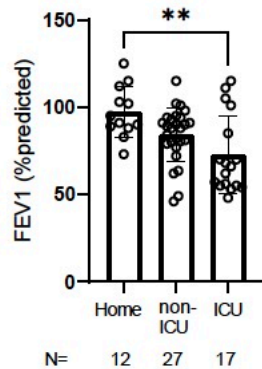
133 COVID+ patients in pulm rehab
and 133 controls

<mark>Alterations in flow-mediated dilation on ultrasound seen in COVID patients, correlating with pulmonary performance (FVC, FEV1, DLCO)</mark>

Ambrosino et al, 2021

ANNALS
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RESEARCH ARTICLE

Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers"

Edith L. Graham, Jeffrey R. Clark, Zachary S. Orban, Patrick H. Lim, April L. Szymanski, Carolyn Taylor, Rebecca M. DiBiase, Dan Tong Jia, Roumen Balabanov, Sam U. Ho, Ayush Batra, Eric M. Liotta & Igor J. Koralnik

Convenience sample of first 100 COVID clinic patients (50 +, 50 -)
No sig abnls in labs or neuro workup (incl MRI)
+ sig differences from US norms on PROMIS and NIH Toolbox

Table 3. Diagnostic testing.

|	Overall	SARS-CoV-2+	SARS-CoV-2-	p
n abnormal/n tested (%)				
Brain MRI[1]	9/48 (18.8)	5/22 (22.7)	4/26 (15.4)	0.71
MR Vessel Wall Imaging	0/4 (0)	0/2 (0)	0/2 (0)	1
Spine MRI[2]	10/16 (62.5)	5/8 (62.5)	5/8 (62.5)	1
EMG[3]	3/9 (33)	1/3 (33)	2/6 (33)	1
EEG	0/4 (0)	0/3 (0)	0/1 (0)	1
CSF analysis [4]	3/5 (60)	0/1 (0)	3/4 (75)	0.40
Tilt table test	3/4 (75)	0 (0)	3/4 (75)	1
Antinuclear antibody ≥ 1:160	11/33 (33.3)	3/6 (50)	8/27 (29.6)	0.38
Erythrocyte sedimentation rate				
Median [IQR], Reference: Males: <15 (0-50 years)	8/47 (17)	2/15 (13.3)	6/32 (18.8)	1
or < 20 mm/h (51-85 years). Females: <20 (0-50 years)	9 [3-19]	11 [2-19]	8.5 [3.75-19.5]	
or < 30 mm/h, (51-85 years).				
C-reactive protein				
Median [IQR], Reference: 0.0-0.5 mg/dL	10/52 (19.2)	5/19 (26.3)	5/33 (15.2)	0.47
	0.5 [0.29-0.57]	0.5 [0.5-1.2]	0.4 [0.24-0.5]	
D-dimer				
Median [IQR], Reference: 0-230 ng/mL	8/27 (29.6)	3/10 (30)	5/17 (29.4)	1
	174.5 [150-329]	150 [150-289]	215 [163-327]	
Ferritin				
Median [IQR], Reference: 24-336 ng/mL	2/11 (18.2)	2/5 (40)	0/6 (0)	0.18
	75 [42-120]	105 [42-120]	65.2 [50.7-88.5]	

Pathophysiology 2: Systemic Inflammation

- Infection may not fully clear
- Continued viral antigenic presence
- Leads to ongoing cytokine release, systemic inflammation

Crook et al, 2021
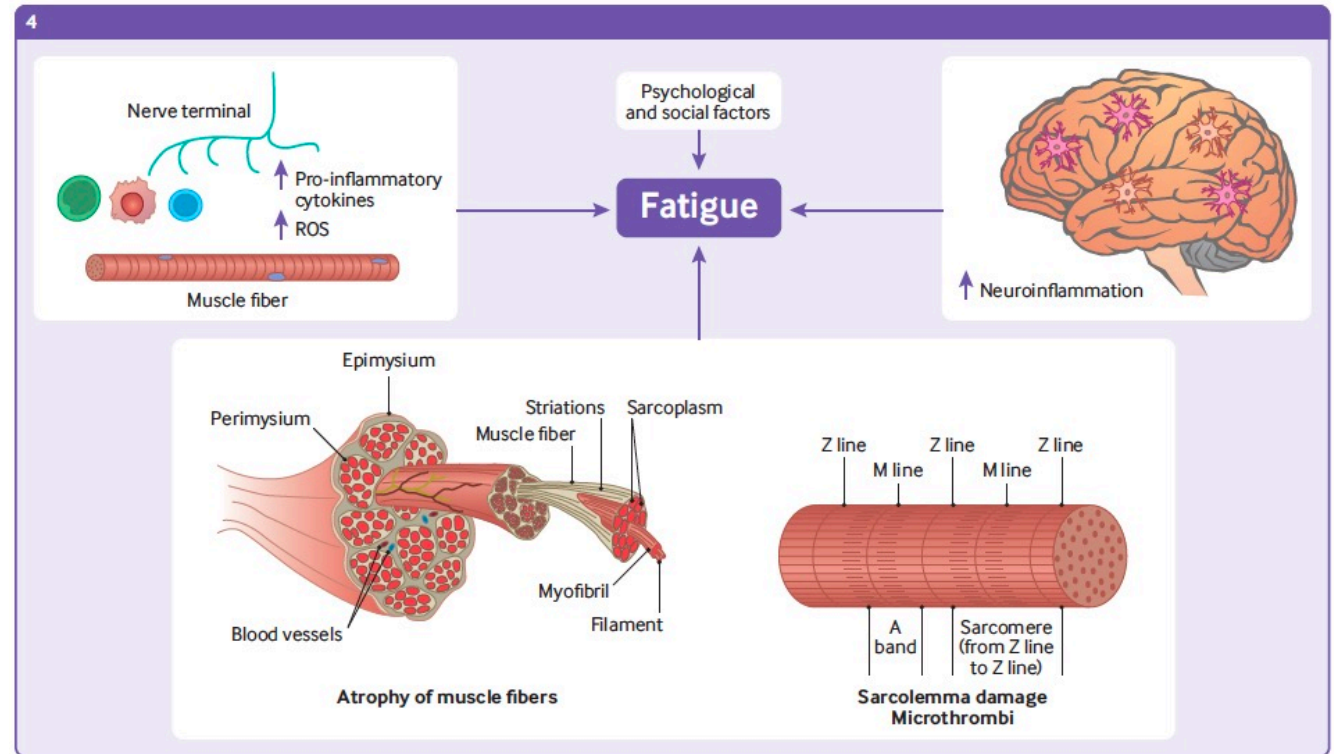
75 patients with confirmed COVID+ and PASC

100% demonstrated elevations in ferritin, d-dimer

70% demonstrated elevations in ESR, CRP

70-90% demonstrated low Hgb, albumin

Pasini et al, 2021
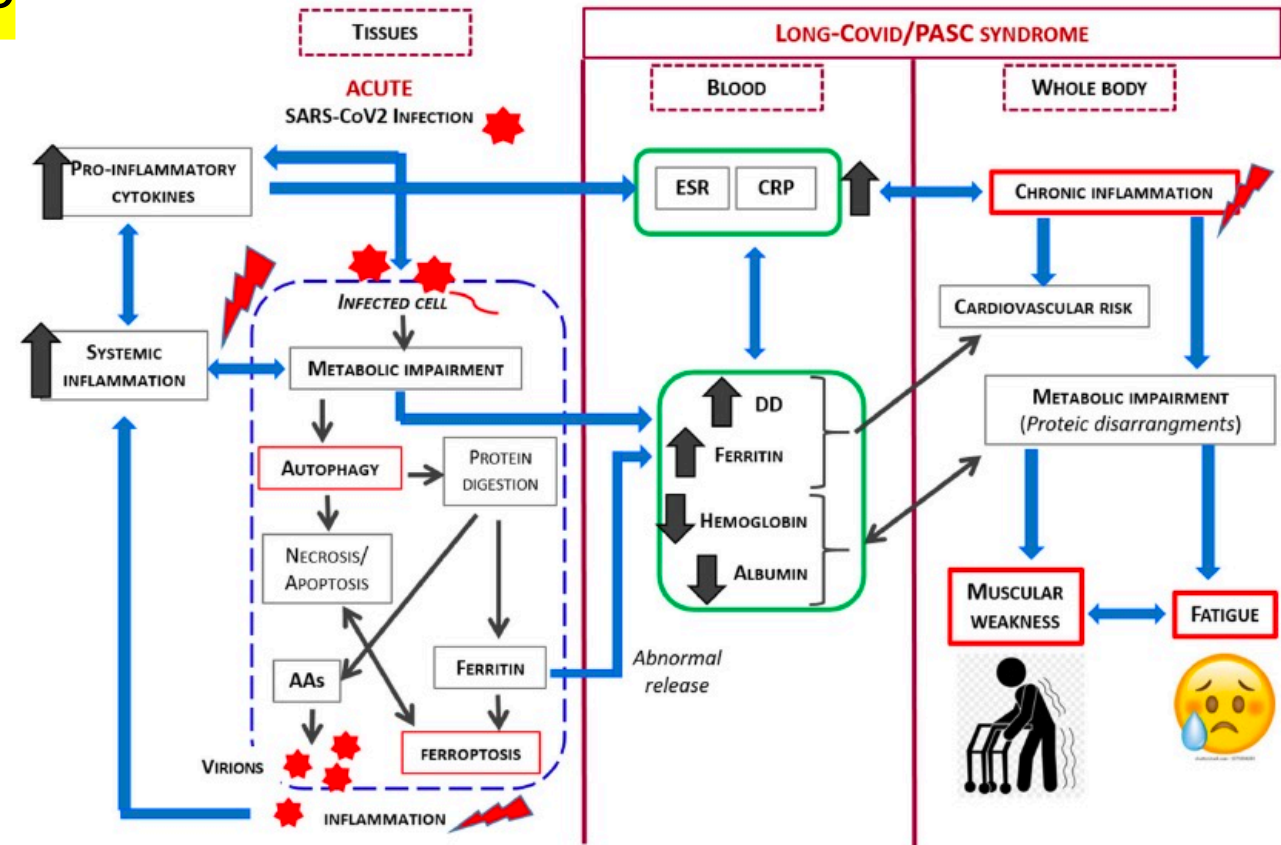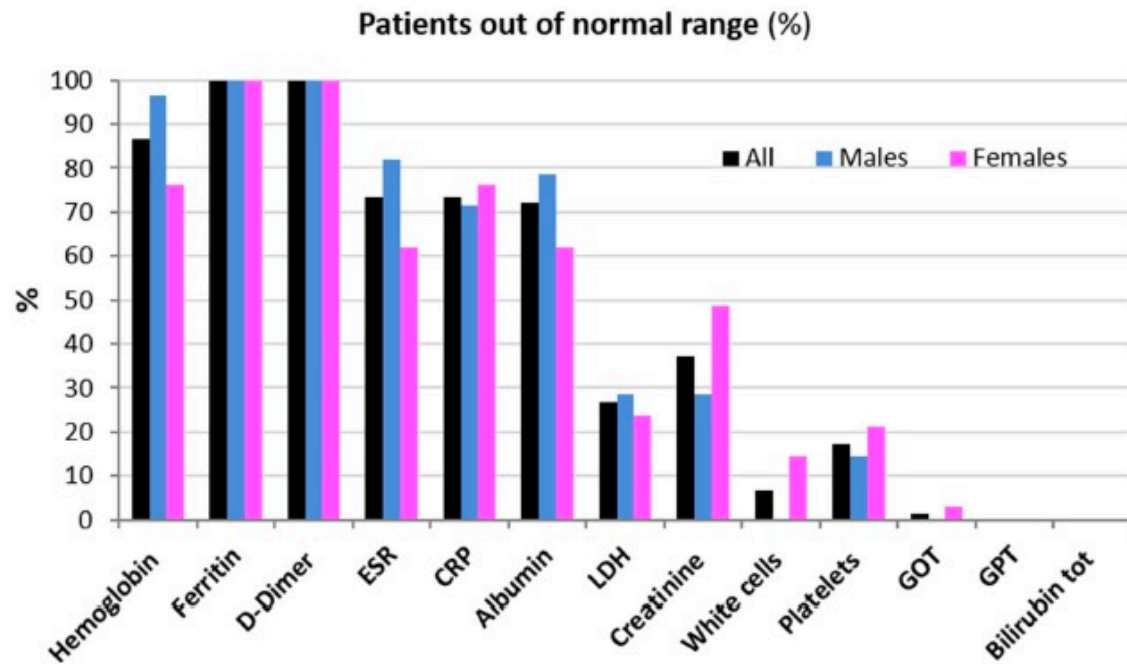
27 COVID+ followup patients, 53% with persisting symptoms,
41 healthy controls, and 18 acutely hospitalized patients
Certain metabolic parameters did not normalize (taurine, glu/gln)
Followup group showed intermediate metabolic variance between acute pts and controls


Holmes et al, 2021
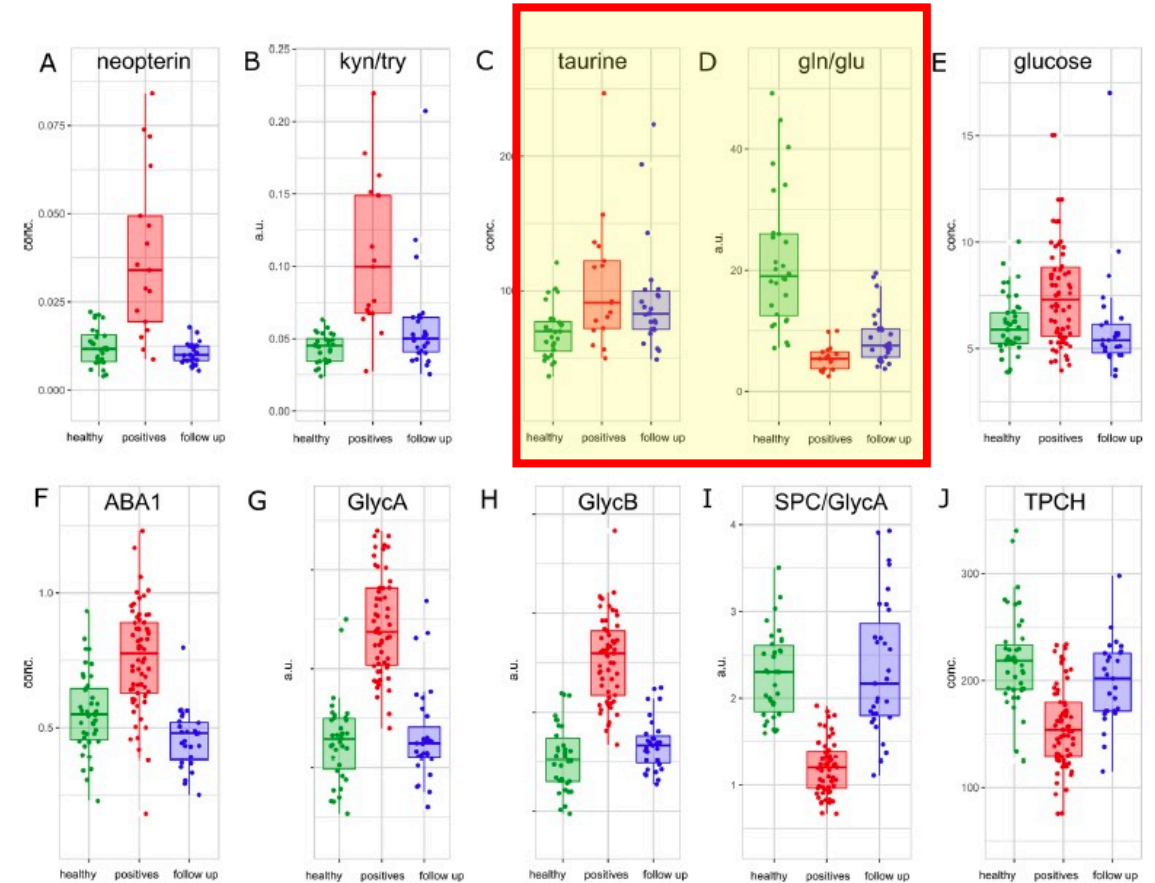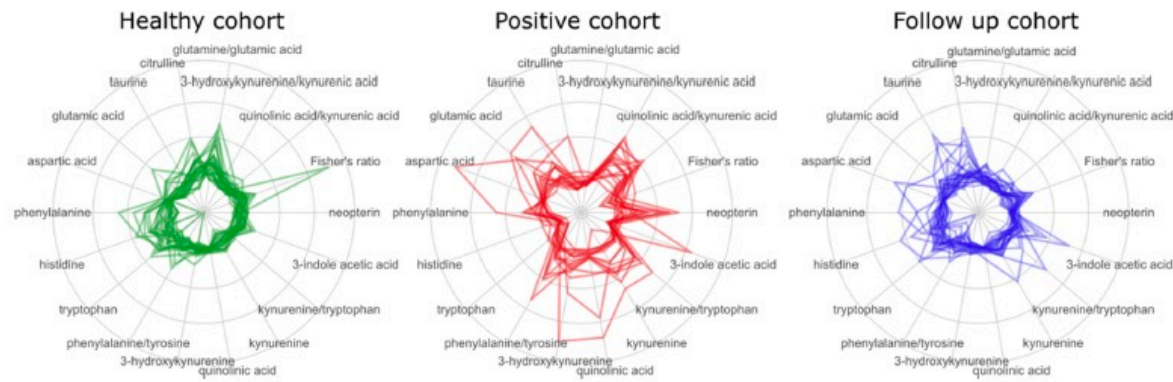
Pathophysiology 3: Immune Dysfunction

- Failure of immune system to fully control infection
- Development of autoimmunity leads to attack of host tissue
- May account for delayed onset particularly in milder cases

Crook et al, 2021
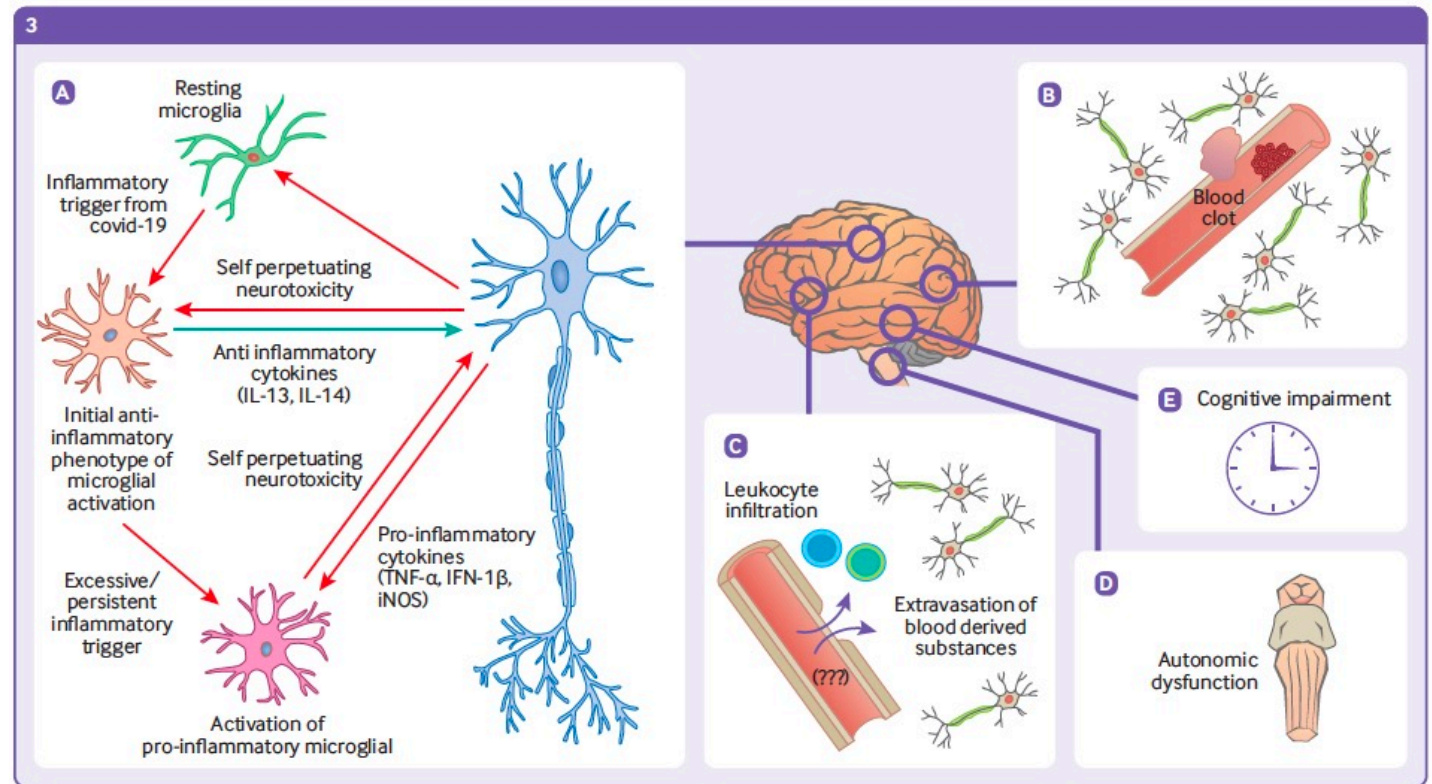
70 patients with PCR-confirmed COVID-19 infection, 32 with persistent symptoms

PASC is associated with decline in IFN-producing CD8+ T cells

Peluso et al, 2021
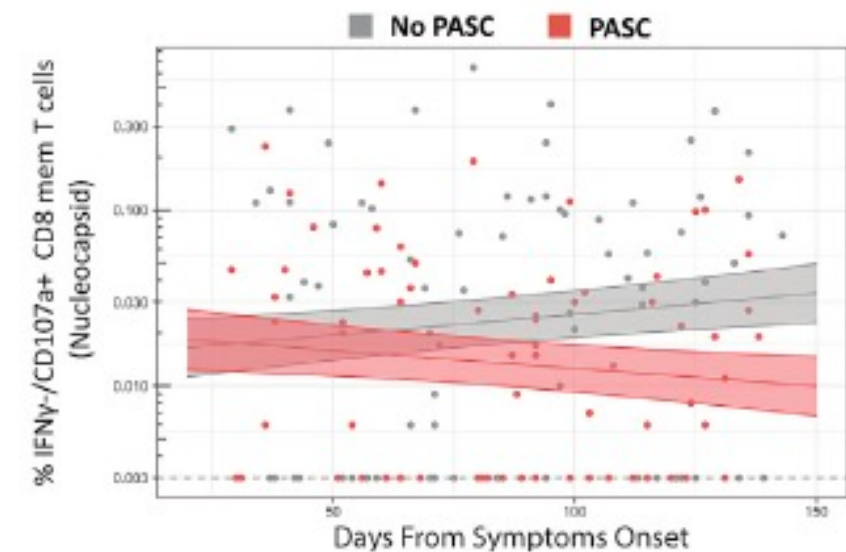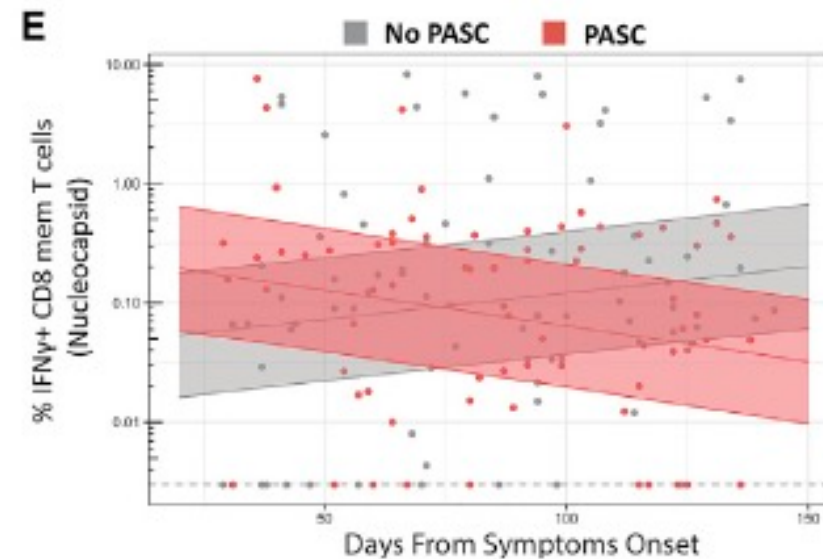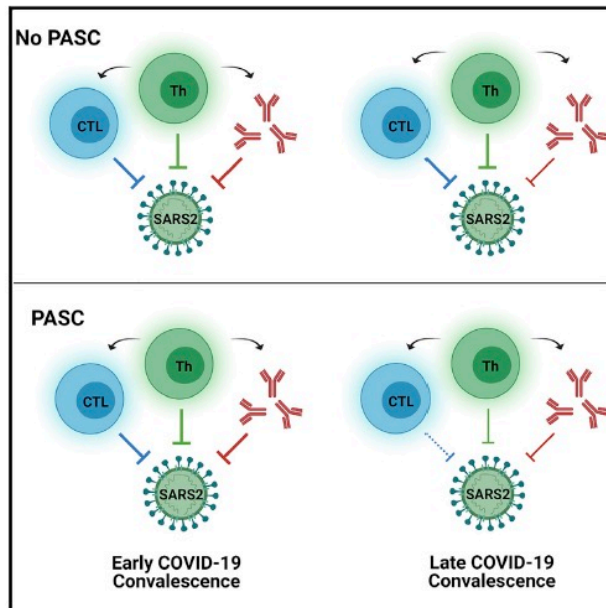
56 Neuro-PASC patients; 24 COVID recovered; 31 healthy controls

Neuro-PASC patients demonstrated worse QOL, attention, increased CD4+, decreased CD8+ T cell activity, increased vaccine-related IFN levels compared to recovered and HC

Visvabharathy et al, 2021
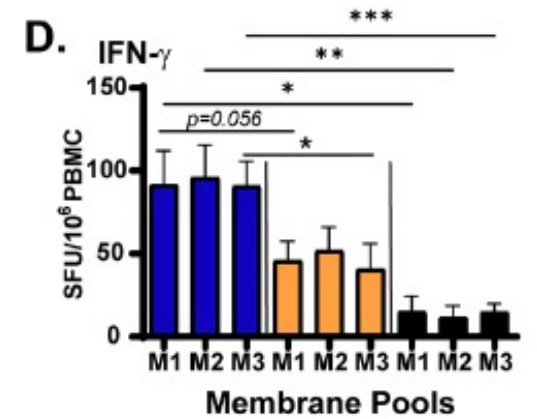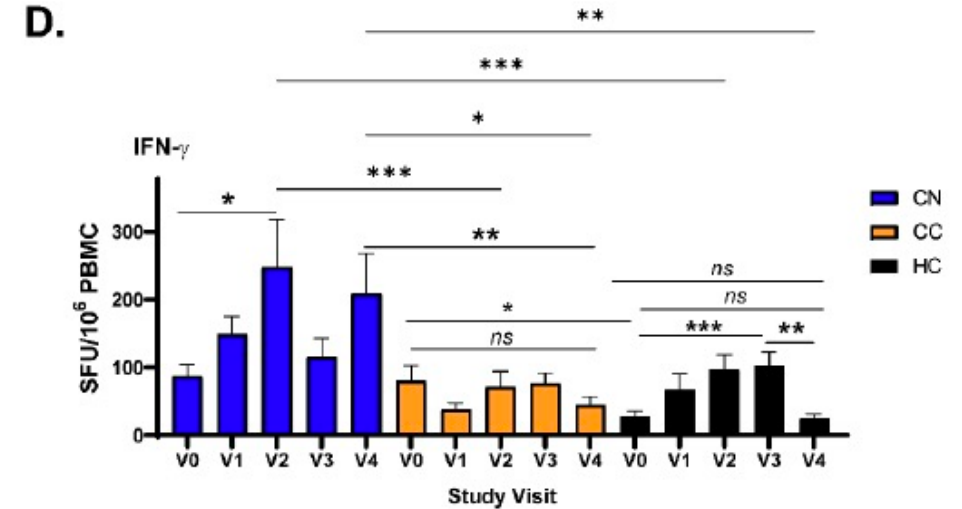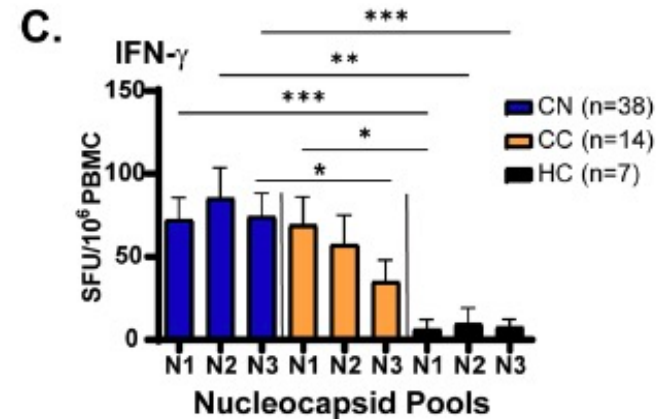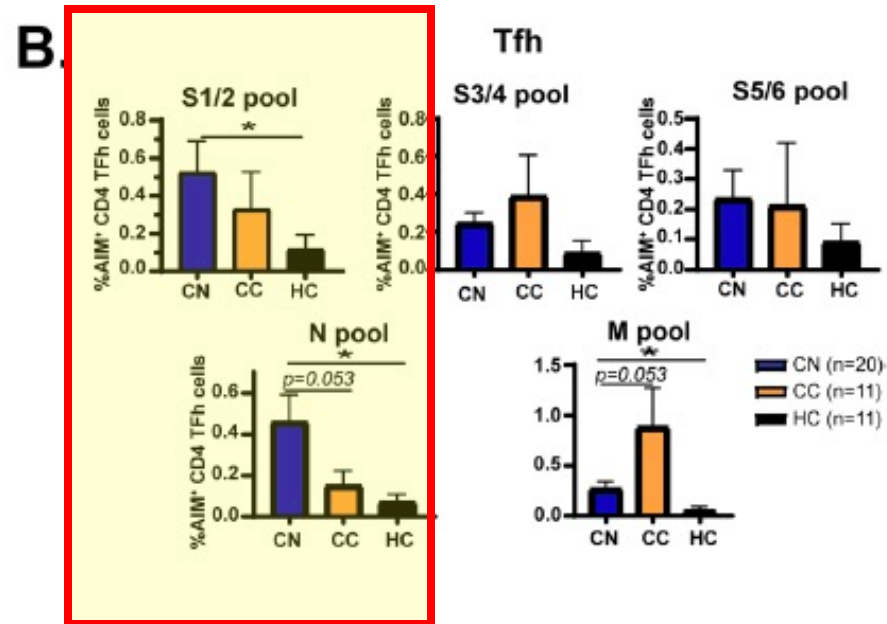
Pathophysiology 4: Dysautonomia

Associated with lightheadedness, fatigue, brain fog, shortness of breath, exercise intolerance, palpitations, chest pain
Overlap with chronic fatigue, fibromyalgia

Becker 2021; Dani et al, 2021
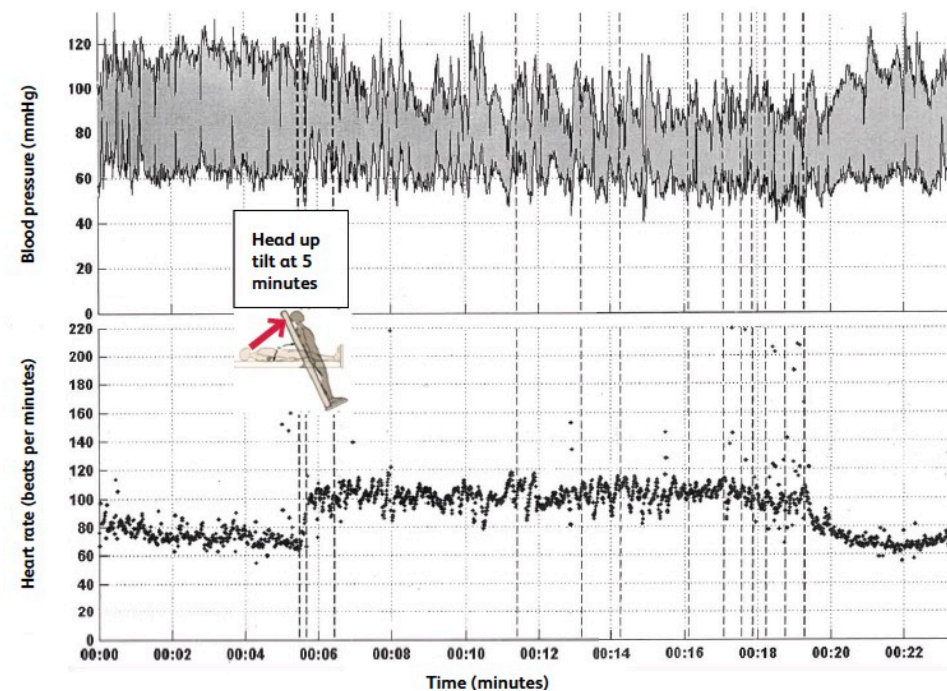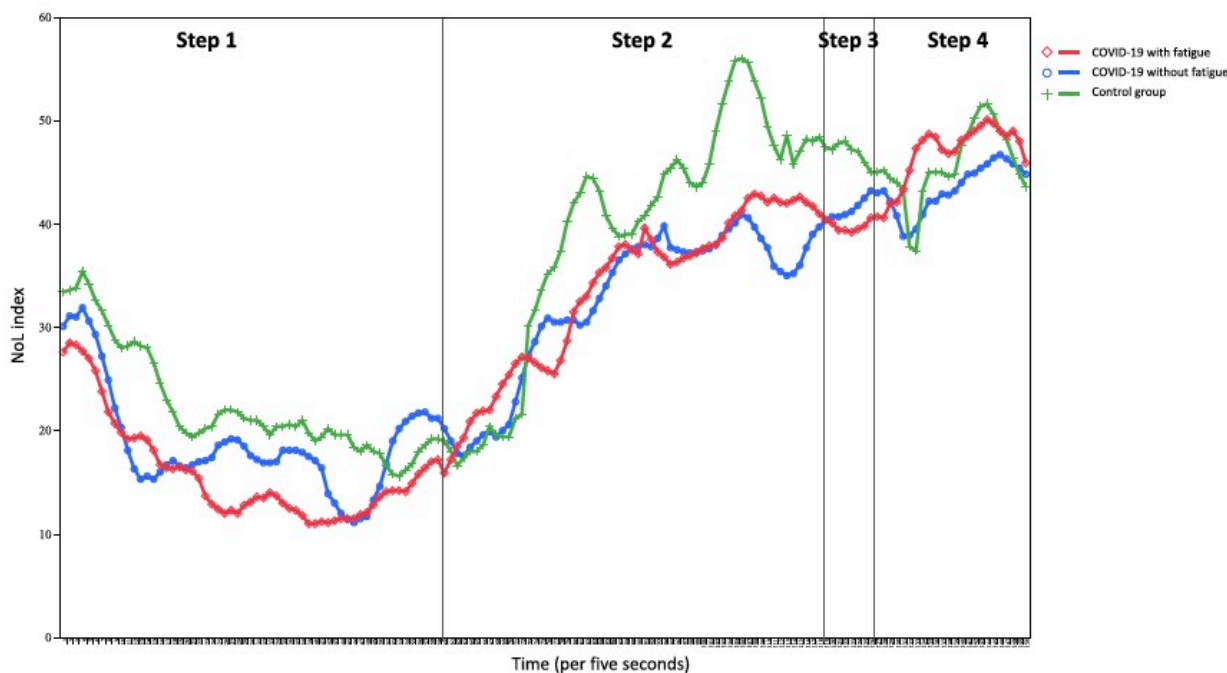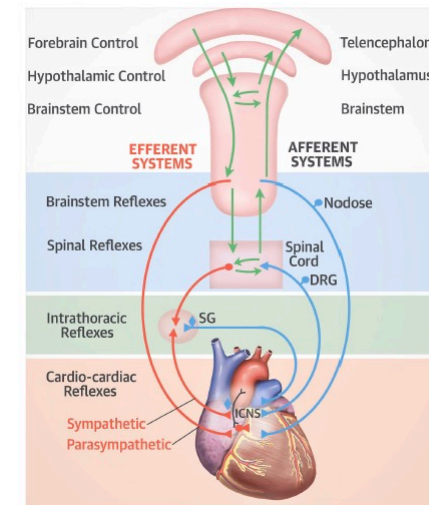
Approach to Workup

Surveys/Batteries

- Symptoms: Long COVID Symptom Tool
- QOL: PROMIS, NeuroQOL
- Mood: PHQ-9
- Anxiety: GAD-7
- PTSD: PCL-C
- Dysautonomia: COMPASS-3
- Cognition: MOCA, NIH Toolbox
- Function: Post-COVID Functional Status Tool

- https://www.phenxtoolkit.org/covid19/
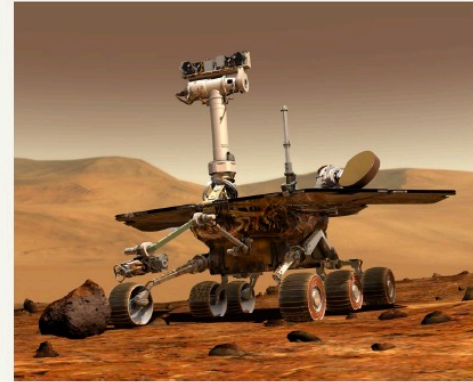
Diagnostics

- Hematologic: CBC
- Metabolic: chem 10, BUN/Cr, LFTs, albumin
- Inflammatory: CRP, ESR, Ferritin, D-dimer
- Pulmonary: O_2 sat, 6-min walk, CXR, Chest CT
- Cardiac: EKG, troponins
- Autonomic: Orthostatics, head up tilt
- Neurologic: MRI

RECOVER
Researching COVID to Enhance Recovery
An Initiative Funded by the National Institutes of Health

PASC Investigator Consortium: A Moment of Opportunity To Bring Scientists and Patients Together

- A looming public health crisis
- A novel virus with limited characterization of pathobiology
- Very few PASC studies in the medical literature
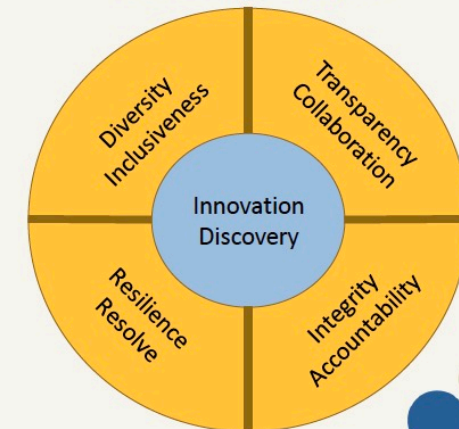- Widespread support for PASC efforts among public and scientific communities

NASA/JPL/Cornell University, Maas Digital LLC - http://photojournal.jpl.nasa.gov/catalog/PIA04413

RECOVER
Researching COVID to Enhance Recovery

PASC Investigator Consortium: Not Business as Usual

Mission of the PASC Consortium

"Through the PASC Initiative, we now ask the patient, medical, and scientific communities to come together to help us understand the long-term effects of SARS-CoV-2 infection, and how we may be able to prevent and treat these effects moving forward."

-Dr. Francis Collins

CSC Guiding Principles

- Diversity Inclusiveness
- Transparency Collaboration
- Innovation Discovery
- Resilience Resolve
- Integrity Accountability

RECOVER
Researching COVID to Enhance Recovery

https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid

Conclusions

- PASC is a likely heterogeneous clinical entity
- We are still determining and characterizing the relevant pathophysiologies of PASC symptoms
- The clinical trajectory to PASC may have influence on the relevant pathophysiologies involved