POST-ACUTE COVID-19 SYNDROME (PACS)

Advisory Council to the Director

Dec 10, 2020

Walter J. Koroshetz, MD
Director, National Institute of Neurological Disorders and Stroke

TRANS-NIH POST-ACUTE COVID SEQUELAE TASK FORCE

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- Audie Atienza, NCATS
- Karin Bok, VRC
- Joseph Breen, NIAID
- Patti Brennan, NLM
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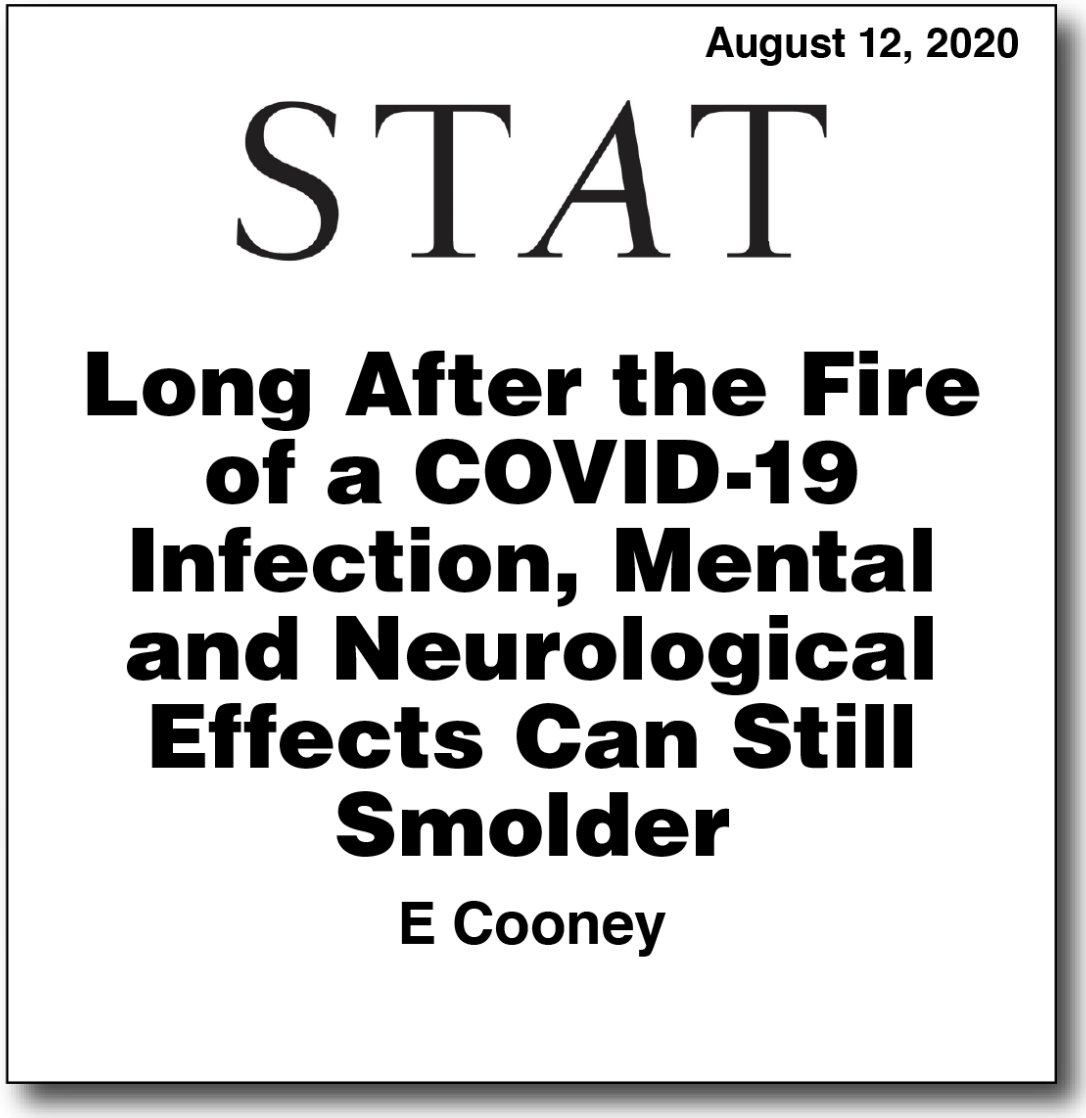
- Andrew Weitz, NIBIB
- Carolyn Williams, NIAID
- Dana Wolff-Hughes, OD
- May Wong, NINDS

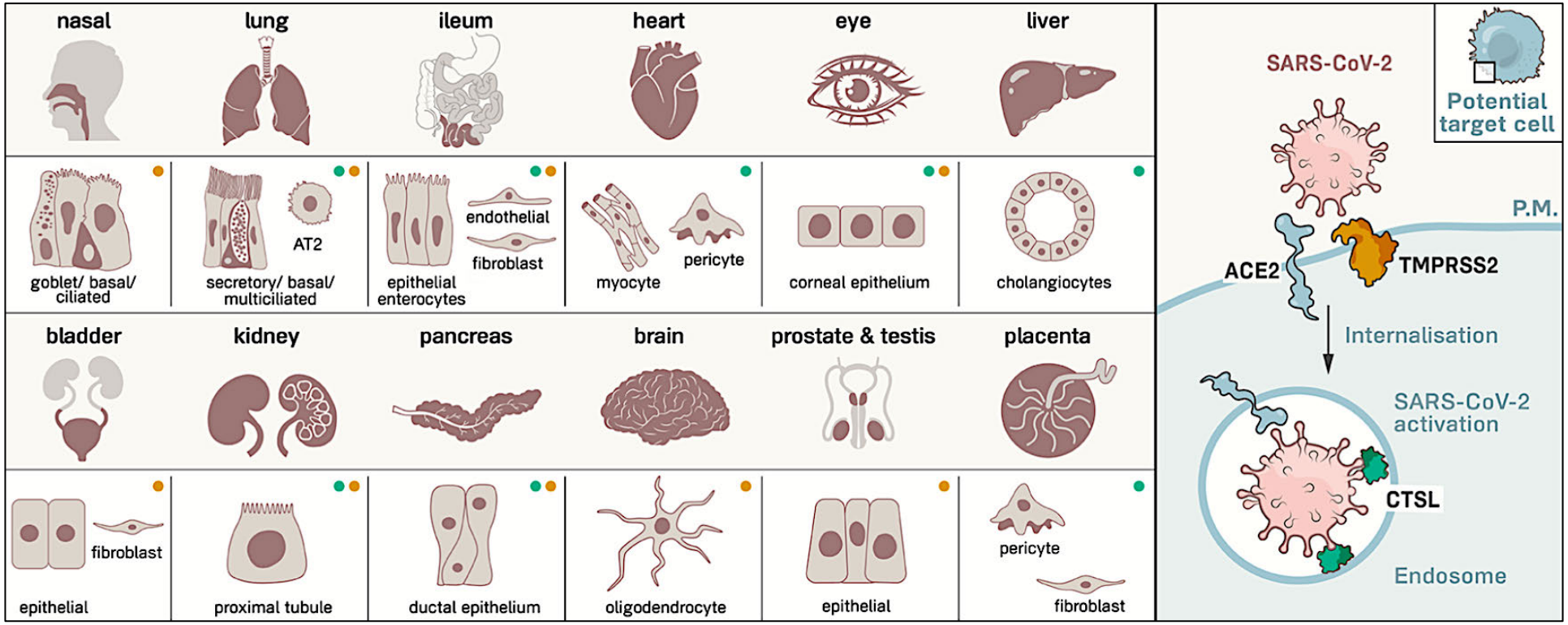
1) Problem statement
2) Clinical manifestations and knowledge gaps
3) Leveraging our assets and strengths

Post-Acute COVID-19 Syndrome



Long-Term Effects of Covid-19 Infection

COVID-19 Affects Multiple Organs



The Scientist, April 2020

CLINICAL MANIFESTATIONS AND KNOWLEDGE GAPS

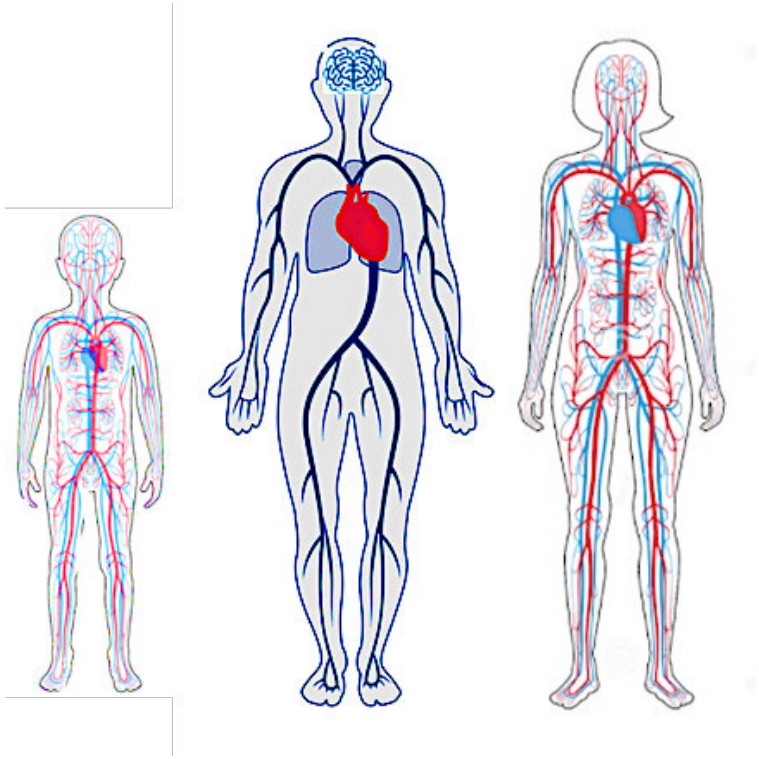
COVID-19: Persistent Symptoms in Hospitalized Patients

A Multi-Organ, Multi-System Clinical Presentation

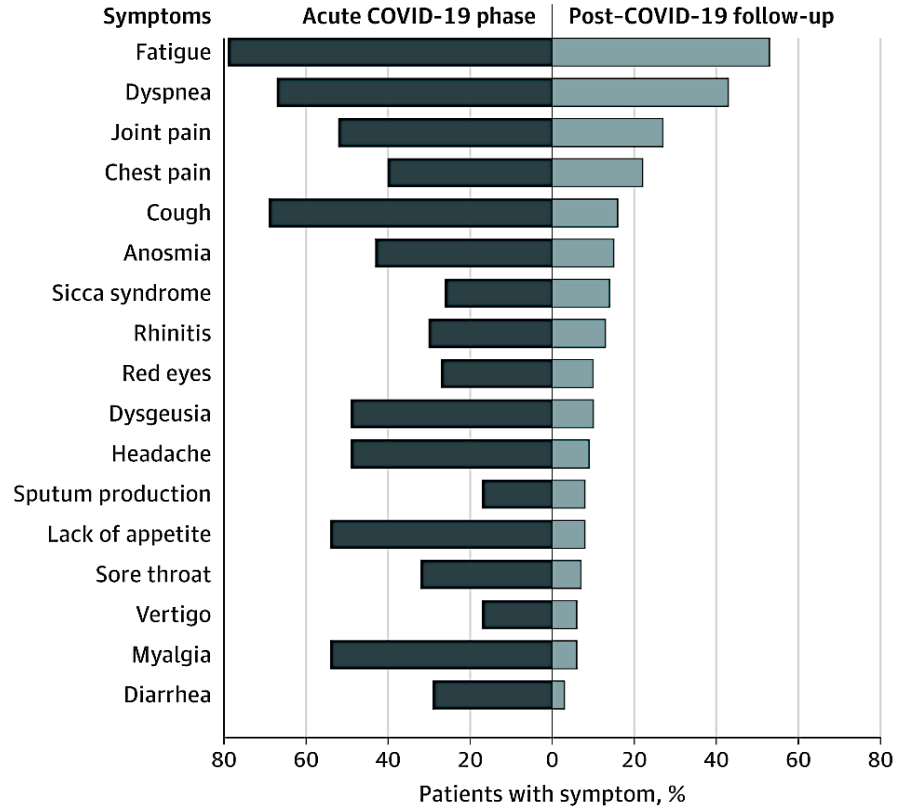
120 patients (mean = 111 days post admission)

Persistent symptoms

- Fatigue 55%
- Difficulty breathing 42%
- Memory loss 34%
- Sleep disorder 32%
- Attention disorder 27%
- Significant hair loss 20%
- Cough 17%
- Loss of smell 13%
- Chest pain 11%
- Loss of taste 11%



143 patients (mean 60 days post onset)



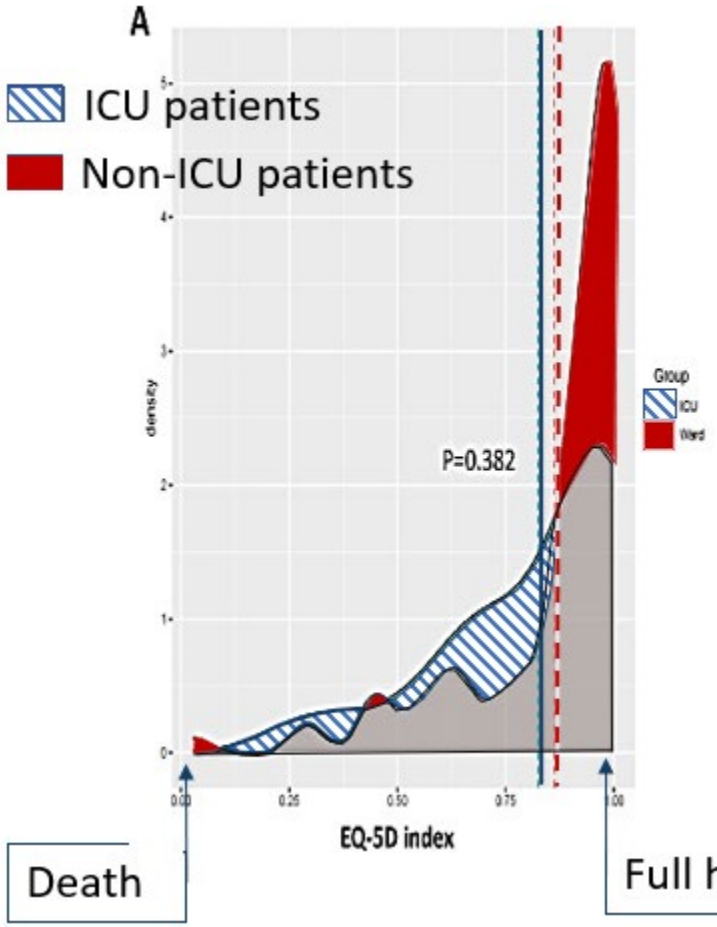
Garrigues et al. Infect. 2020 Aug 25:S0163-4453
https://doi.org/10.1016/j.jinf.2020.08.029

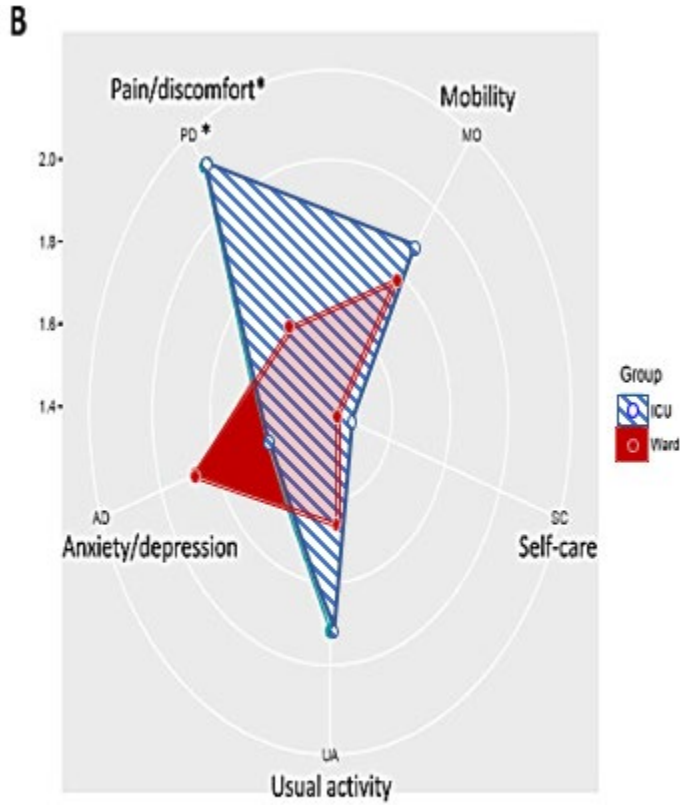
Carifi, et. al. JAMA. 2020;324(6):603-605.
doi:10.1001/jama.2020.12603

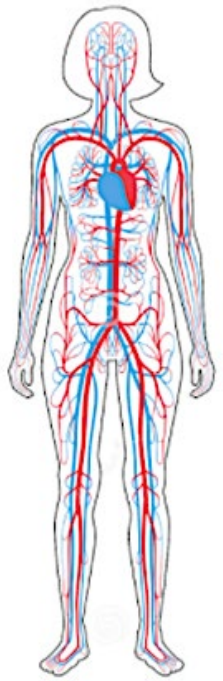
COVID-19: Persistent Symptoms and Health-related Quality of Life[1]

A Multi-Organ, Multi-System Clinical Presentation

120 patients (mean = 111 days after admission for COVID-19)







Professional and physical activities

- Not yet resumed to sports (engaged regularly pre-COVID) 28%
- Slower walking 29%
- Not yet returned to work (worked pre-COVID) 32%

[1]Letter to the Editor, Journal of Infection, **Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19,** Eve Garrigues et al. https://doi.org/10.1016/j.jinf.2020.08.029

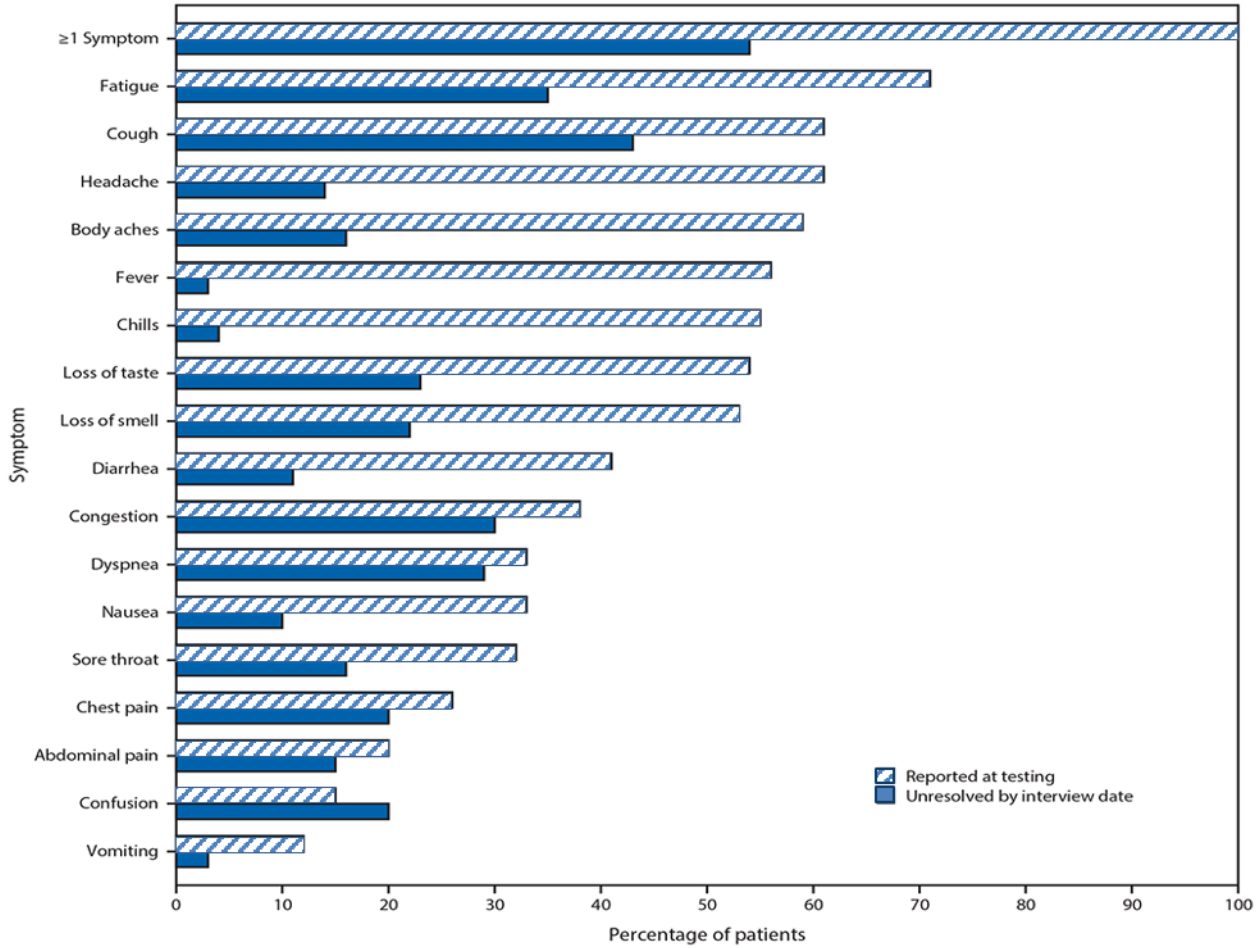
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

July 31, 2020

Morbidity and Mortality Weekly Report (*MMWR*)

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

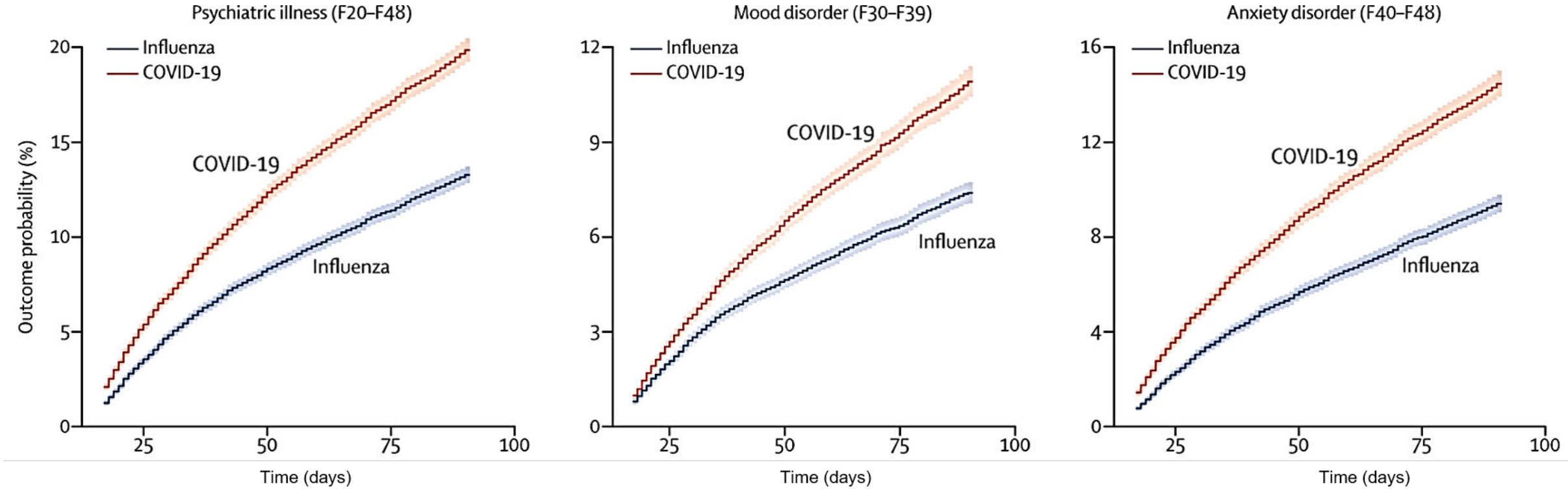
MW Tenforde, LR Feldstein et al. for the IVY Network Investigators and CDC COVID-19 Response Team



Among symptomatic <u>non hospitalized</u> patients with positive test for SARS-CoV-2, 35% not returned to baseline health <u>2-3 weeks</u> after testing

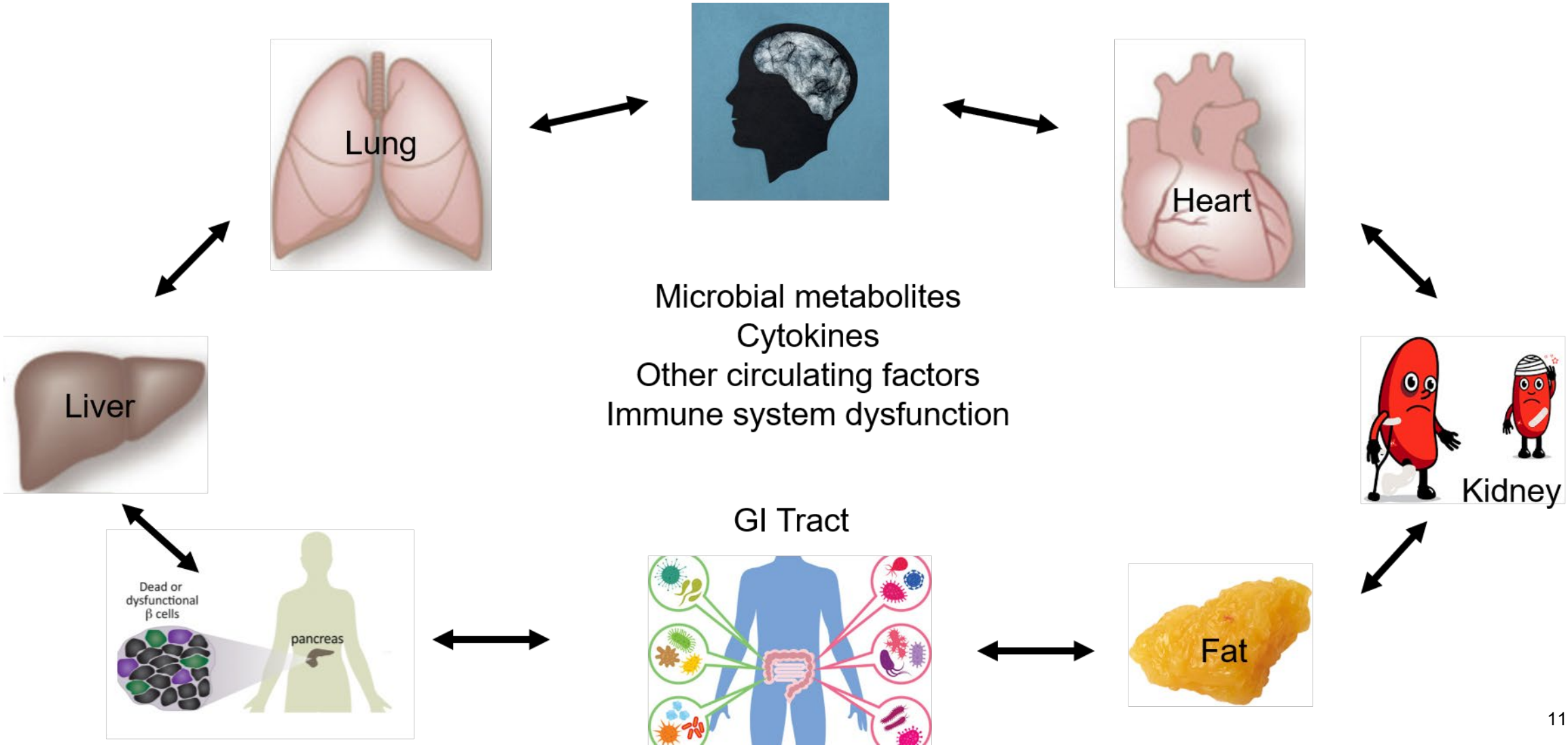
- Older age and comorbidities associated with lack of return to baseline health
- 19% of young adults (18-34) with no comorbidities had not returned to baseline health
- In contrast 90% of influenza outpatients recover within 2 weeks

New diagnoses of anxiety, insomnia, dementia, and mood disorders, as well as psychiatric disorders in general, were increased after COVID-19 illness



www.thelancet.com/psychiatry Published online November 9, 2020 https://doi.org/10.1016/S2215-0366(20)30462-4

Cross-talk among injured organs might explain post-acute COVID syndrome



JAMA Cardiology

Published online July 27, 2020

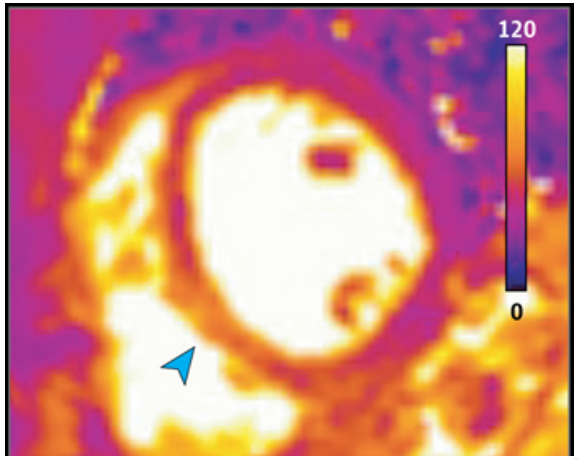
JAMA Cardiology | Original Investigation

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jedrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

cMRI revealed cardiac abnormalities in 78%, and gadolinium enhancement in 60%, (N-100), median 72d p dx.

- Independent of preexisting conditions, severity, and overall course of acute illness, and time from original diagnosis
- Lower EF, Higher LV volume, Higher hsTroponin
- 3 patients biopsied, demonstrate inflammatory infiltrates, no virus



Research Letter

September 11, 2020

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Saurabh Rajpal, MBBS, MD[1]; Matthew S. Tong, DO[1]; James Borchers, MD, MPH[1]; et al

15% of Ohio State University athletes had myocarditis after mild COVID-19, and fully half had CMR abnormalities

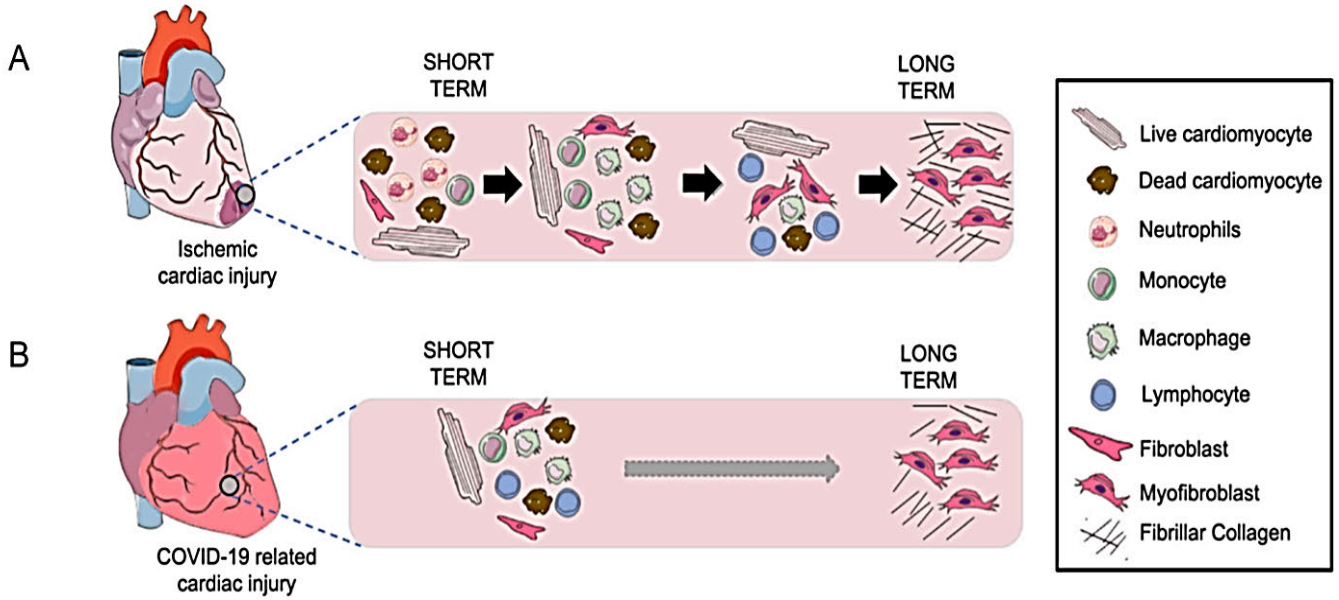
Cardiac Involvement in COVID-19

EDITORIAL

Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter?

Clyde W. Yancy, MD, MSc; Gregg C. Fonarow, MD

Published Online: July 27,2020 doi:10.1001/jamacardio.2020.3575



Inflammation and potential remodeling mechanisms in COVID-19 heart.

Potential common mechanisms between ischemic injury and COVID-19 induced cardiac remodeling; Unudurthi S. Life Sciences 2020; 260: 118482

- Autopsy reports suggest direct cardiac involvement
  - Lindner showed virus in myocardium in majority of 39 autopsy cases with evidence of viral replication:
    - **Direct viral infection leading to myocardial injury??**
  - Other reports have also shown myocardium infiltration of both innate and adaptive immune cells:
    - **Potential for cardiac fibrosis and decrease cardiac function in the long term??**
- Conclusion: Long-term follow-up of recovered COVID-19 patients is necessary to assess risk of heart failure and other chronic CV complications

JAMA Cardiol. doi:10.1001/jamacardio.2020.3557

JAMA Cardiol. doi:10.1001/jamacardio.2020.3551

COVID-19: Long-term lung sequelae

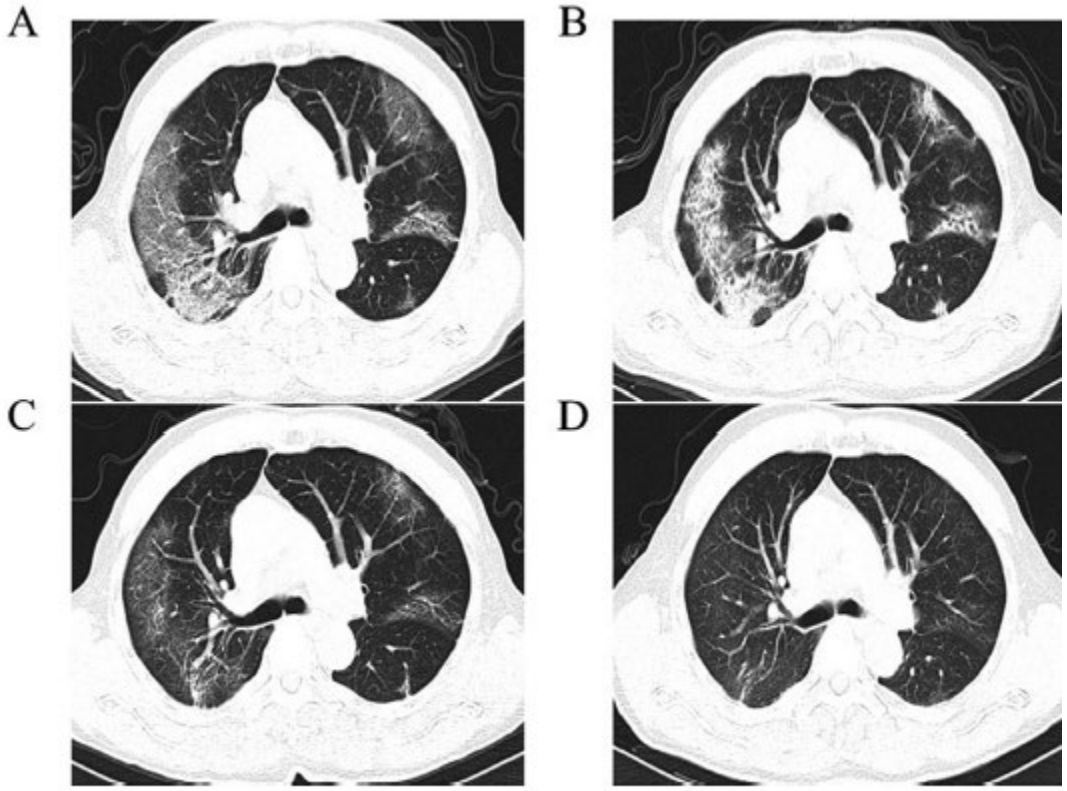


Fig. 2. Follow-up thin-section CT imaging of 63-year-old man with confirmed COVID-

- Carvalho-Schneider et al. followed 150 patients with non-critical COVID-19 for 2 months after symptoms onset
  - **Persistent dyspnea: 36.7% pts at 30d, 30% pts at 60d**
- Conclusion: A prolonged medical follow-up of patients with COVID-19 seems essential, whatever the initial clinical presentation (never admitted patients in this case)

  ***https://pubmed.ncbi.nlm.nih.gov/33031948/* Oct 2020**
- Zhao et al. analyzed 55 COVID-19 survivors (non-critical cases) 3 months after hospital discharge
  - **Radiological abnormalities: 71% pts**
  - **Lung function abnormalities: 25% pts**
  - Elevated D-dimer on admission predictive of **impaired DLCO** at 3 months post-d/c (in some pts, only abnormality)
- Conclusion: It is necessary to follow up COVID-19 patients to appropriately manage persistent or emerging long-term sequelae

  ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361108/* July 2020**

Nervous System and COVID-19

Manifestations during infection

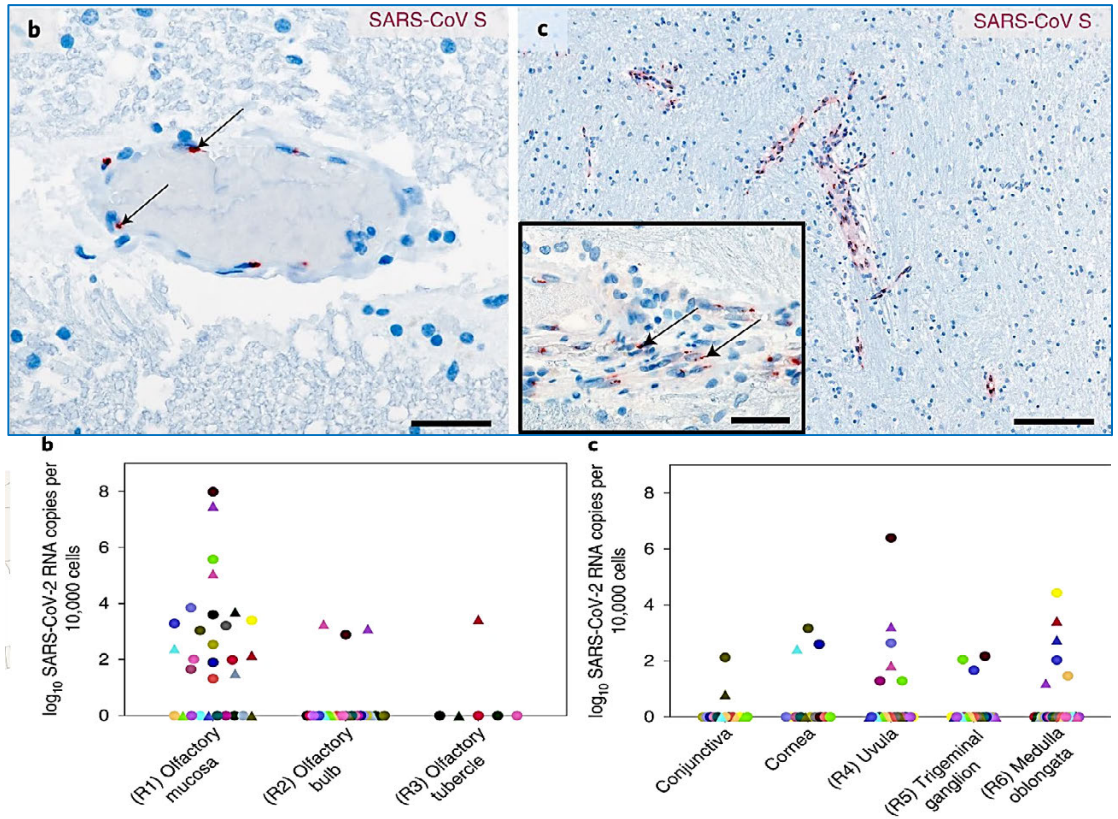
- Stroke- large & small vessel occlusion, micro-bleeds
- Confusion and depressed level of consciousness
- Loss of smell
- Muscle/Nerve pain and weakness
- Meningitis/encephalitis
- Seizures
- Asymptomatic hypoxia

Rare Post-viral syndromes

- Delayed injury to brain and spinal cord (multiple sclerosis- like).
- Delayed injury to nerves (ie. Guillain Barre Syndrome)
- Parkinsonism

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-020-00758-5
Check for updates

Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19



The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Volume 383 July 23, 2020 Number 4

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

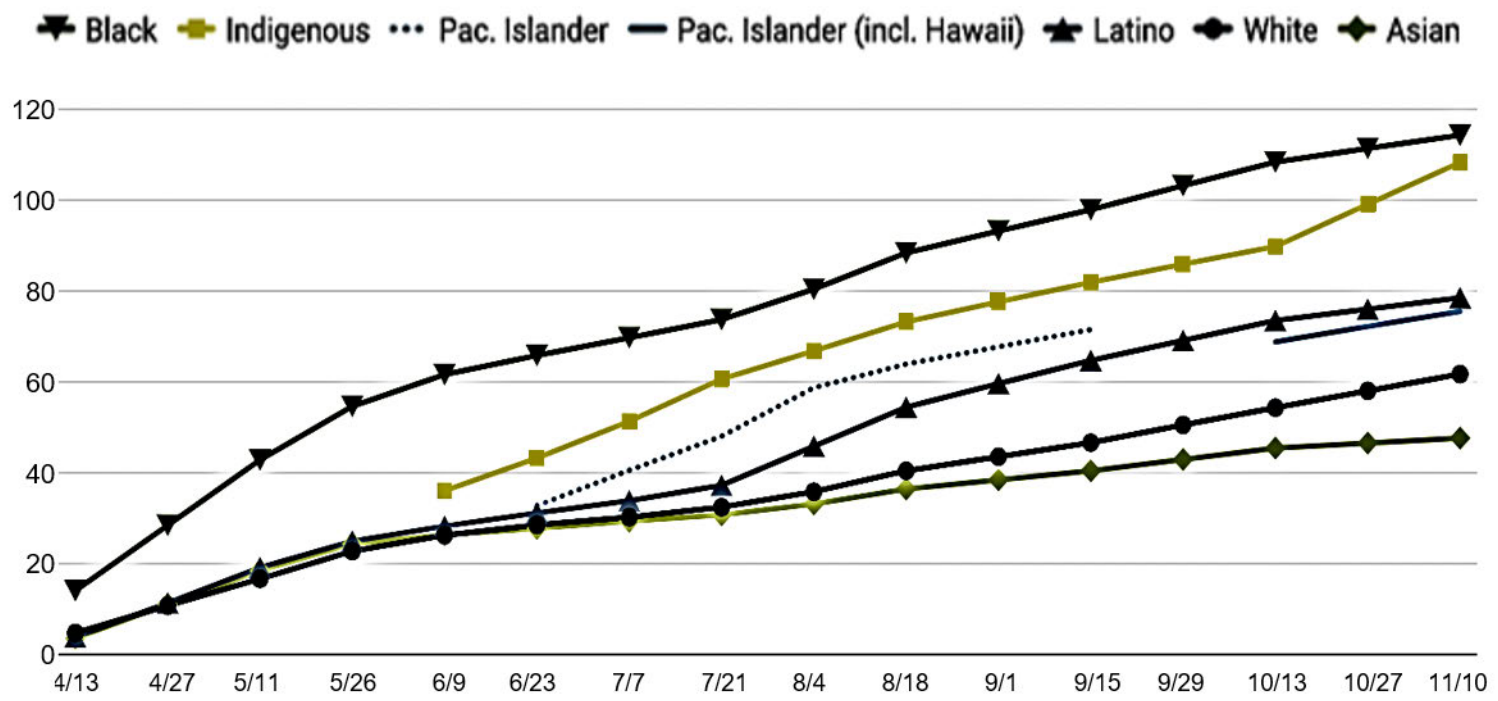
LR Feldstein, S Li et al., for the Overcoming COVID-19 Investigators, and the CDC COVID-19 Response Team

- 186 patients in 26 states, median age 8.3 years
- 80% required ICU care, 20% required mechanical ventilation
- 71% with involvement of at least 4 organ systems
- 73% with no underlying conditions

Health Disparities in COVID-19 Risk and Mortality

Black & Indigenous Americans experience highest death tolls from Covid-19

Cumulative actual Covid-19 mortality rates per 100,000, by race and ethnicity, April 13-Nov. 10, 2020



Note: All intervals are 14 days apart, except for 5/11-5/26, which is a 15-day period. 9/1, 9/29 and 10/27 data has been interpolated. Pacific Islander data prior to 10/13 did not include Hawaii, as it was not releasing data; its inclusion resulted in an overall drop in the Pacific Islander rate, which begins a new series at 10/13.

Source: APM Research Lab. Get the data. Created with Datawrapper.

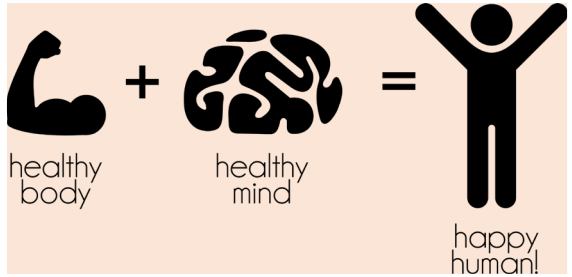
Predisposing Conditions

- Cancer
- Chronic Kidney Disease
- COPD
- Heart Conditions
- Obesity
- Pregnancy
- Sickle Cell Disease
- Smoking
- Type 2 Diabetes

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html

What we need to understand about recovery

- **What is the spectrum of clinical “recovery” from COVID-19 infection?**
  - Of those with symptoms 2-3 weeks post infection the rate of improvement is not yet known.
- **What interventions might enhance or hasten recovery?**
  - In the immediate post infection phase as well as in the more chronic phase
- **What is the spectrum of tissue injury due to COVID-19 infection?**
  - Are the various tissue injuries reversible, static, or contribute to progressive organ dysfunction
  - How to identify those with tissue injury in heart, lung, nervous system, kidney
- **Will unabated symptoms lead to chronic illness(s) in a subset of people?**
  - If so, what is its pathophysiology (s).
  - Is so, what are the drivers of special vulnerability or resilience across the lifespan and in special populations
- **Will COVID-19 infection predispose people to other diseases in the future?**



Preparing for the Possibility of a Post-COVID Storm

- Current expectation is that up to tens of thousands could suffer from sequelae of acute infection with COVID-19

- Time is of the essence - interventions are expected to have a greater effect the earlier they are employed

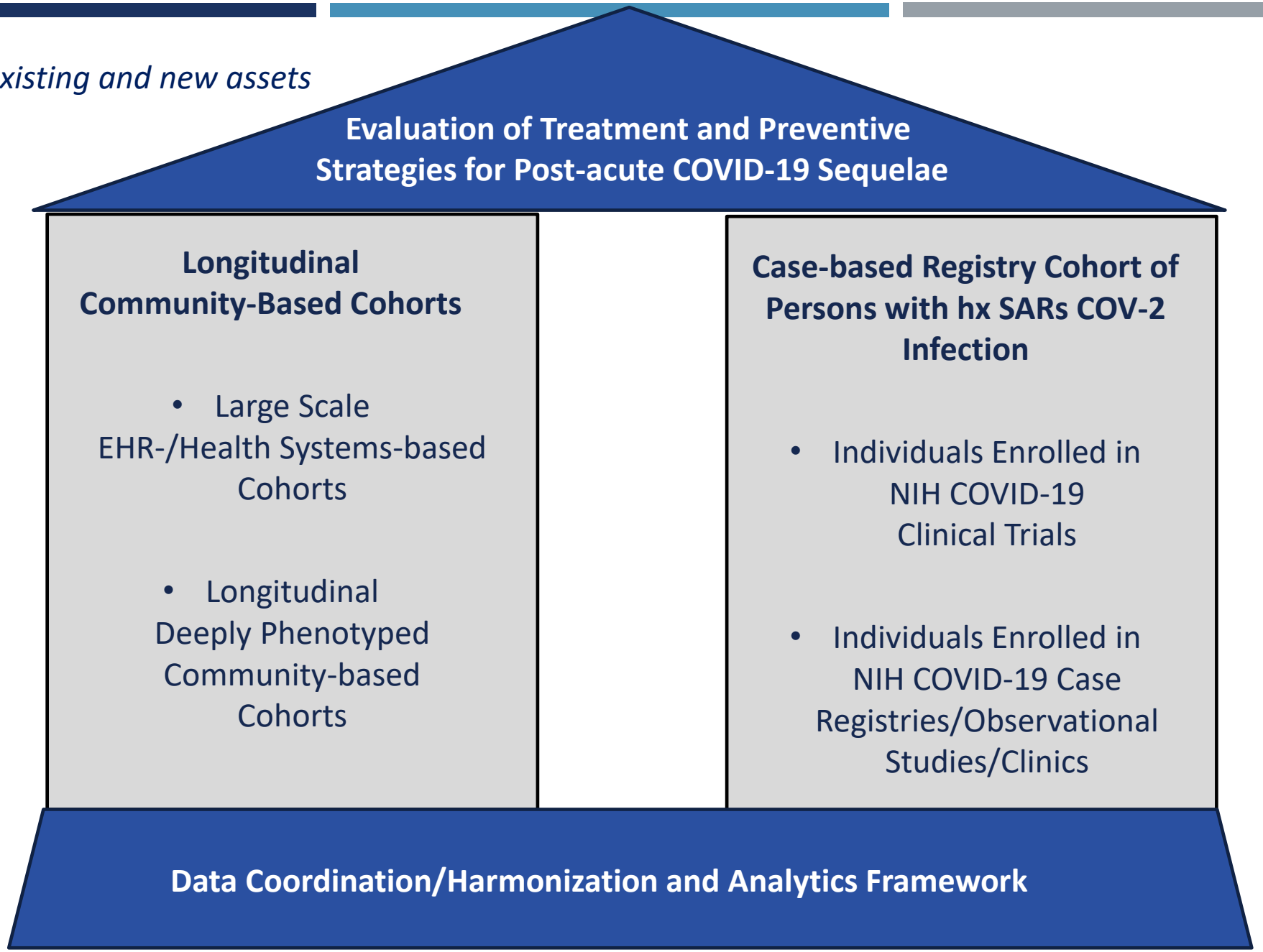
- The multi-organ involvement calls for a coordinated research program drawing on the expertise in multiple NIH Institutes and Centers

LEVERAGING OUR ASSESTS AND STRENGTHS

A Few Examples

NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

Note: Includes existing and new assets



NIAID: Observational Cohorts

- International Observational Study of Outpatients With SARS-CoV-2 Infection
- PREVAIL-XI: PREVAIL COVID-19 Observational Study
- Chasing COVID Cohort
- Immunophenotyping in a COVID-19 Cohort (IMPACC)
- Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM)
- Observational study at San Antonio VA

- EHR based
  - Corona infectious virus epidemiology team (CIVETs)
  - Big Data Driven Clinical Informatics & Surveillance (BDD-CIS) project

Collaborative Cohort of Cohorts for COVID-19 Research (C4R)

- **70,000+ participants from 14+ longstanding longitudinal population- and disease-based cohorts**
  - Highly diverse with multi-racial, multi-ethnic populations
  - Broad age range, national span of geographic reach
  - Enriched for at-risk populations (e.g., pre-existing lung disease)
  - Genotyped and deep phenotyping across multiple domains
    - Imaging, biomarkers, social determinants, lung function, anthropometry, vascular function, cognition, genetics and other -omics
- **Leverage existing infrastructure, processes, data, and biospecimens from available cohorts/existing patient populations**
  - Embed systematic protocolized assessment in existing cohorts
  - Include multiple nested sub-studies
- **Collaboration with NHLBI, NINDS, and NIA**

NHLBI platforms leveraged for development of COVID-19 long-term follow-up cohorts

Registry and observational cohort study (CORAL) follow-up of COVID-19 inpatients (n = 3,000) leveraging critical care network

- Clinical characteristics, Rx, biology, and outcomes using retro/prospective methods
- Deidentified repository of clinical, imaging, and biologic data and biospecimens

Serves as a pilot for:

Larger Scale Multicenter Prospective COVID-19 Registry Cohort

- Leveraging the diagnosis, screening, and referral cores and clinical centers
- COVID-19 enriched and diverse cohort spanning pre-hospital, hospital, and post-discharge enrollment
- Systematic and protocolized collection of health data, biospecimens, and imaging on post-COVID pts for long-term, post-infection follow-up studies; utilizing full spectrum of data (EHR mining to IPLD)
- Fully consented for data sharing and follow-up

NIAID: A Longitudinal Study of COVID-19 Sequelae and Immunity

- Adults who have recovered from COVID-19 or were in close contact with someone with COVID-19 but did not become infected
- Evaluation includes history, physical exam, mental health exam, imaging and functional tests, laboratory draws
- Study visits at NIH Clinical Center every 6 months for 3 years
- Goal enrollment: 900

Funded programs to assess long-term neurological effects of COVID-19

- **Natural History of Post-Coronavirus Disease 19 Convalescence** Avi Nath (NINDS), Brian Walitt (NINR)
  - To observe and describe the range of medical syndromes that occur following an acute COVID-19 infection in1000 adults within six months of their convalescence from an acute COVID-19 infection
- **Observational Study of Neurologic Function after COVID-19 Infection** Avi Nath, Bryan Smith (NINDS)
  - To investigate brain MRI and components of neurologic function in those with prior SARS-CoV-2 infection and persistent neurologic symptoms
- **NIH COVID-19 NeuroDataBank and NeuroBioBank** (at NYU Langone)
  - Building a national (**NeuroDatabank and BioBank**) to document and study neurological complications of COVID
- **Projects (through supplements)**
  - 2 studies examining **cognitive sequelae** of the biological effects of COVID-19 on the nervous system-cognitive batteries every 3 months for one year via phone to determine cognitive trajectories over time
  - **Neurofilament light chain (NfL) protein in** predicting long term cognitive, behavioural and functional prognosis for ICU COVID patients
  - Add-on study to college student cohort (followed for post EBV **chronic fatigue** syndrome) to assess long-term health post COVID-19

GOAL	**To improve understanding of and develop strategies to treat and prevent post-acute manifestations of SARS-CoV-2 infection through a multi-pronged research framework**
Understand	**COVID-19 clinical sequelae, risk factors for illness, severity, outcomes**
Recognize	**SARS-CoV-2 infected individuals at risk for post-acute manifestations**
Identify	**Pathogenic mechanisms and therapeutic targets**
Develop	**Therapeutic strategies for people with post-acute sequelae**

DISCUSSION