

LONG COVID



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Chief Medical Officer

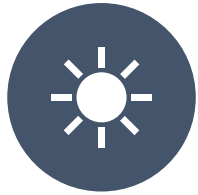
Great Plains Area Indian Health Service



The Definition

- The many names of COVID
- CDC and WHO Definitions
- Diagnosis of Exclusion

Known by Many Names...



Long COVID



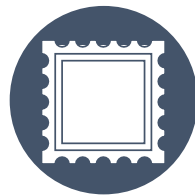
Post-COVID
Syndrome



Long-haul COVID

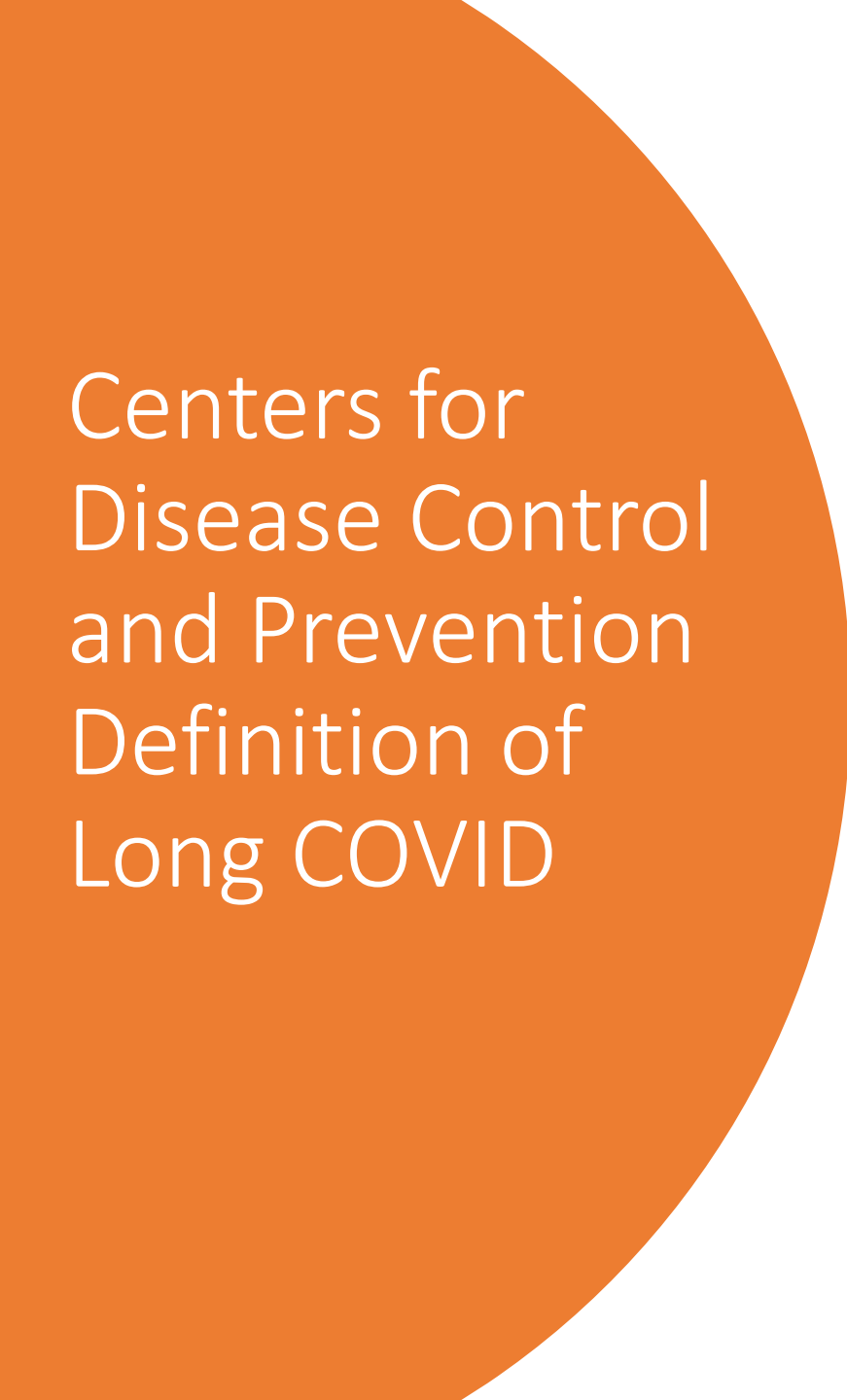


Post-acute COVID



Post-acute sequelae
of COVID (PASC)

...Still Only One Syndrome (we think)



Centers for
Disease Control
and Prevention
Definition of
Long COVID

“The occurrence of new, returning, or ongoing health problems 4 or more weeks after an initial infection with SARS-CoV-2.”

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html>



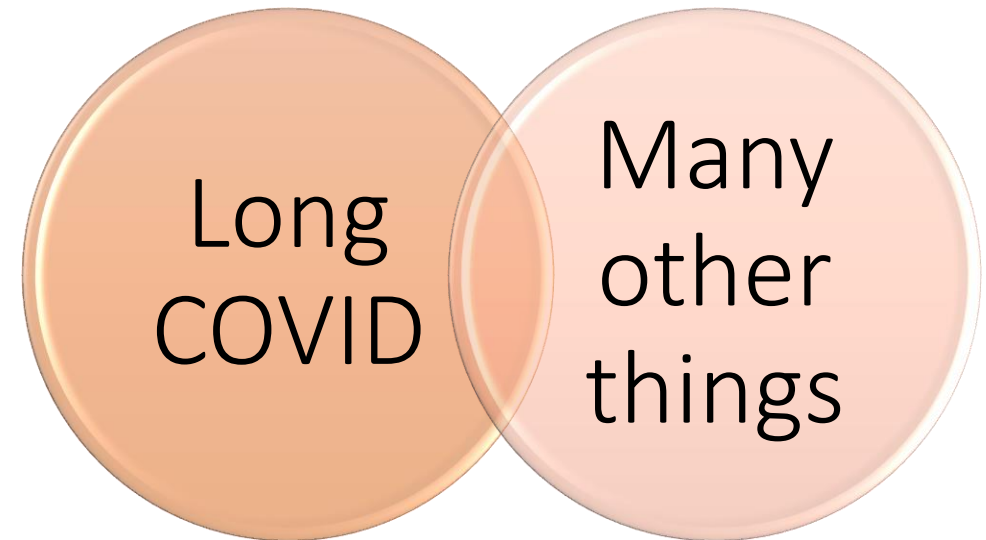
World Health Organization Definition of Long COVID

- “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 and 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 and 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.”

https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

Long COVID

- No diagnostic test
- Diagnosis of exclusion





Prevalence


Current prevalence of Long COVID is unclear...

- Lack of clarity over case definition
- Difficult to distinguish from other post-illness conditions



Prevalence:
Difficulty in
Differentiation

Difficult to separate what is Long COVID versus what is:

- Post-sepsis syndrome
 - Post-intensive care syndrome
 - Exacerbation of pre-existing conditions
 - Complications of treatments
 - Complications of interventions that occurred while hospitalized
- 

Prevalence: Post-Intensive Care Syndrome

Symptoms remaining after critical illness from any cause:

- ICU-acquired weakness: Up to 50% of patients who stay for at least one week
- Cognitive dysfunction : 30-80% of patients
- Post-Traumatic Stress Disorder (PTSD), depression, anxiety, difficulty with sleep

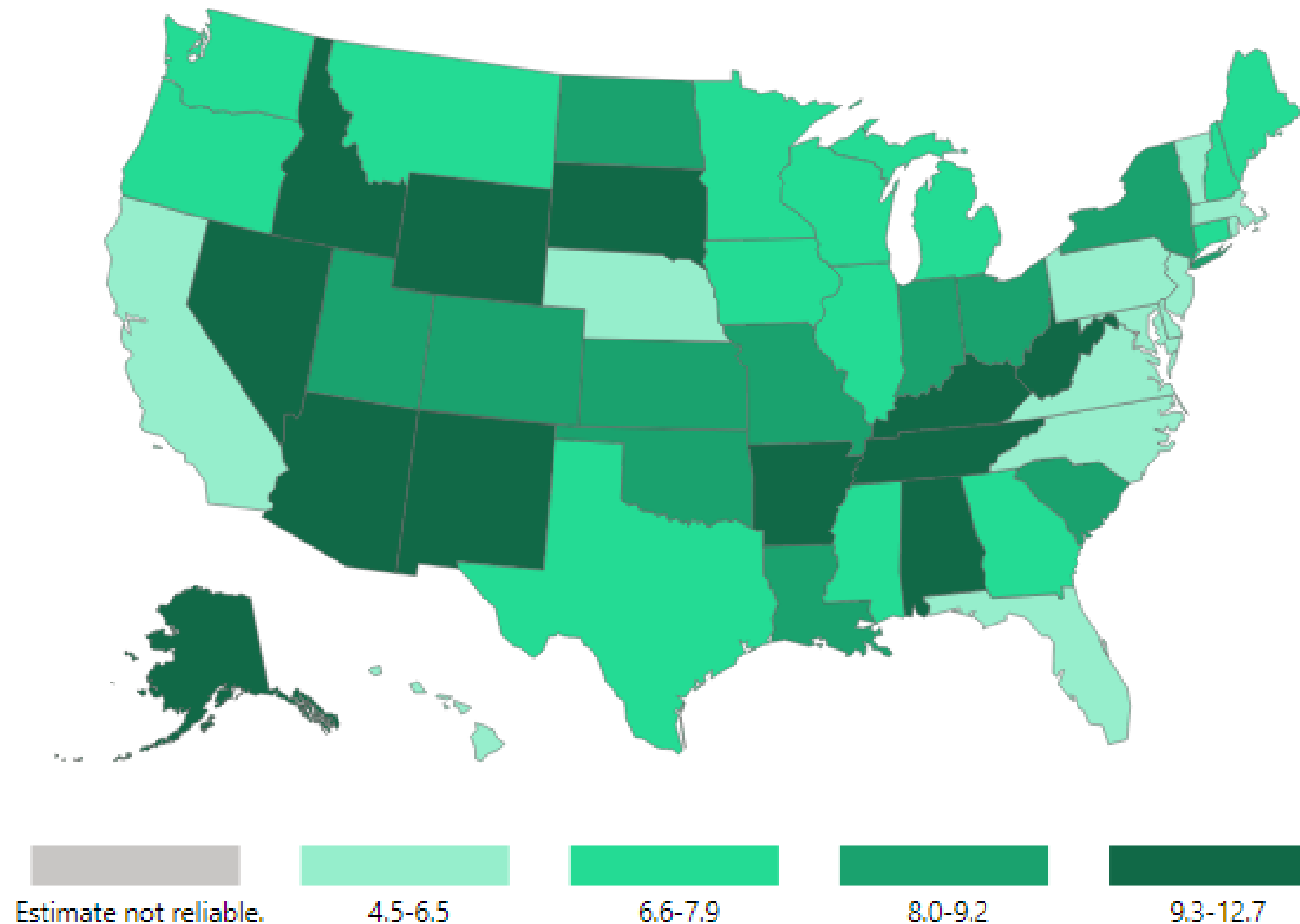


Prevalence: Post-Sepsis Syndrome

Symptoms remaining after critical illness from infection:

- Over 1 million individuals in the U.S. survive an episode of sepsis each year
- One-sixth have persistent physical disability
- Many are readmitted to the hospital
- One-third die in the year following the sepsis episode

Currently experiencing long COVID, as a percentage of all adults



Data from the U.S. Census Household Pulse Survey

- 40% U.S. adults report having had COVID
- 35% U.S. adults who had COVID report ever having long COVID symptoms
- **7.5% U.S. (1 in 13) adults report current long COVID symptoms**

<https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>



Prevalence of Long COVID may be higher

- Data from international surveys
- 35-54% of patients with mild acute COVID had persistent symptoms at 2-4 months
- 50-76% reported new symptoms not present during acute COVID or that resolved then reappeared
- 9% reported symptoms as severe

Salmon-Ceron et al. J. Infect. 2020.
Petersen et al. Clin Infect Dis. 2020
Nehme et al. Ann Intern Med. 2020.

Not well-known

Hospitalization during acute infection

Females > males

Middle-aged adults > older adults

High viral load during active infection

Unvaccinated > vaccinated

The Risk Factors for Long COVID

Currently experiencing long COVID, as a percentage of all adults

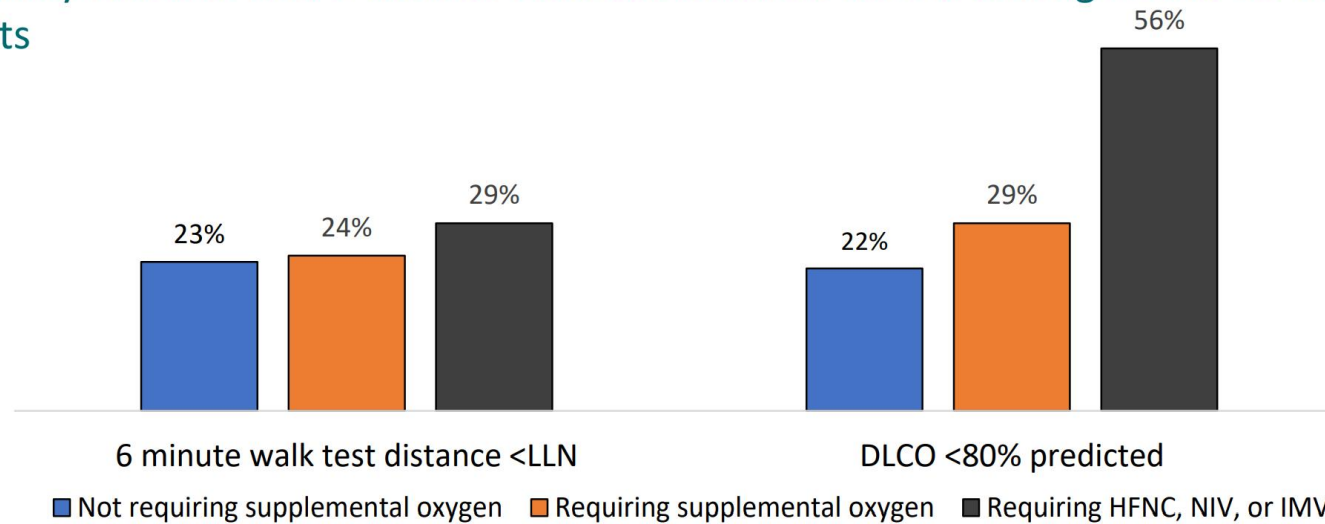
Phase	Jun 1 - Jun 13, 2022	
Time Period	Percent	95% CI
Group		
National Estimate		
United States	7.5	7.1 - 7.9
By Age		
18 - 29 years	8.4	7.0 - 9.9
30 - 39 years	7.8	7.0 - 8.6
40 - 49 years	8.8	7.9 - 9.7
50 - 59 years	8.5	7.4 - 9.7
60 - 69 years	6.6	5.8 - 7.5
70 - 79 years	5.0	4.0 - 6.2
80 years and above	2.8	2.0 - 3.8
By Sex		
Female	9.4	8.9 - 10.0
Male	5.5	5.0 - 6.0
By Gender identity		
Cis-gender male	5.3	4.8 - 5.8
Cis-gender female	9.4	8.8 - 10.0
Transgender	14.9	9.5 - 21.8
By Sexual orientation		
Gay or lesbian	6.6	4.6 - 9.1

Data from the U.S. Census Household Pulse Survey



<https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm>

Pulmonary function and 6-minute walk test distance results among COVID-19 hospitalized patients

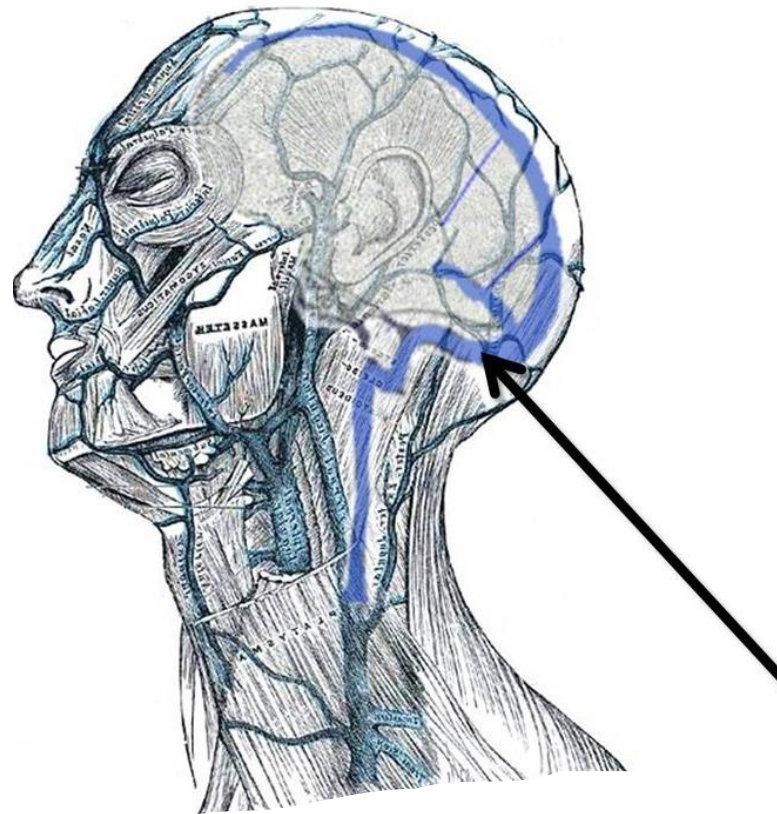


LLN = lower limit of normal; DLCO = diffusion capacity for carbon monoxide



Huang et al., Lancet. 2021

One in five patients not requiring supplemental oxygen during hospitalization had abnormal lung function after 6 months.



Long COVID

Highly variable symptoms
Pathophysiology
Evaluation/Treatment

Long COVID Symptoms

Most common:

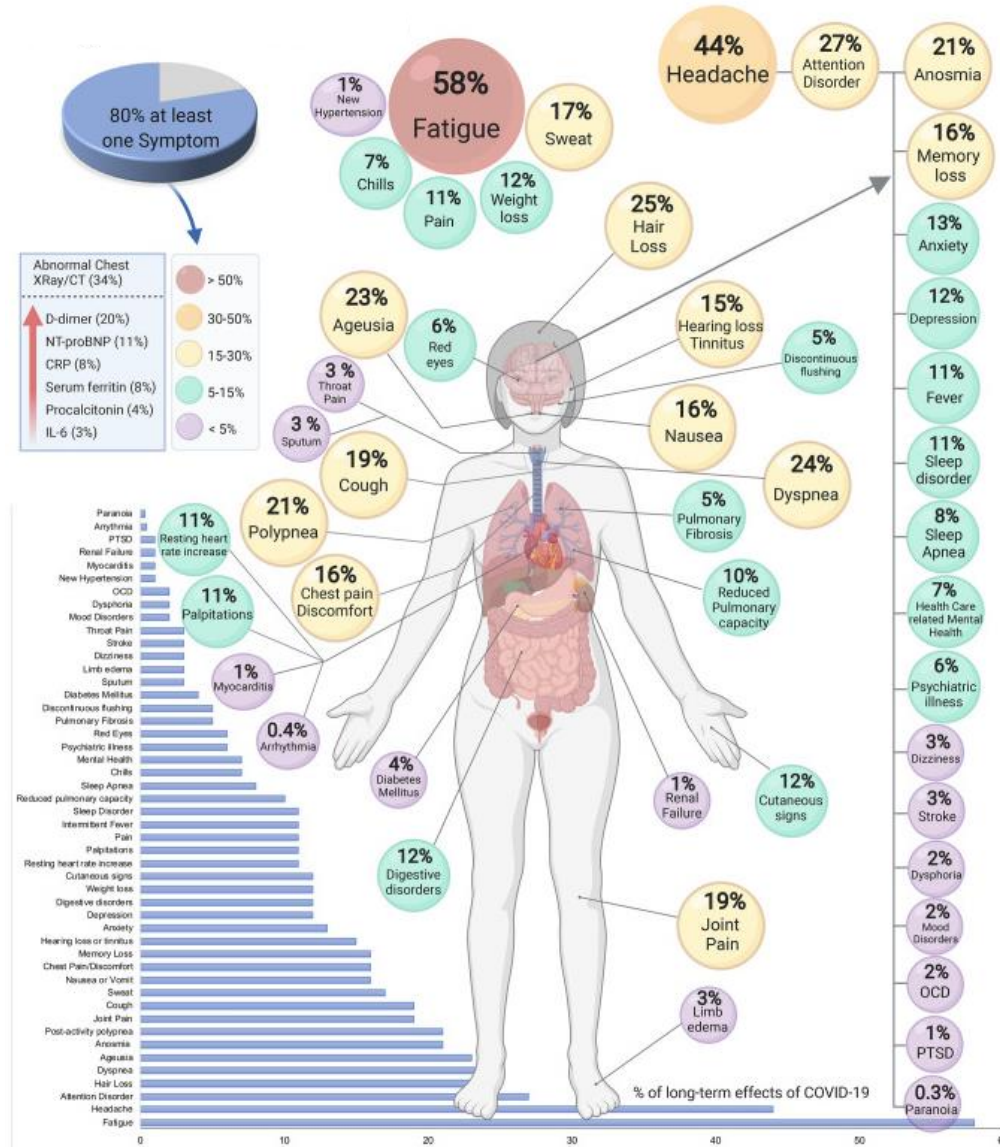
Fatigue

Headache

Attention Disorder

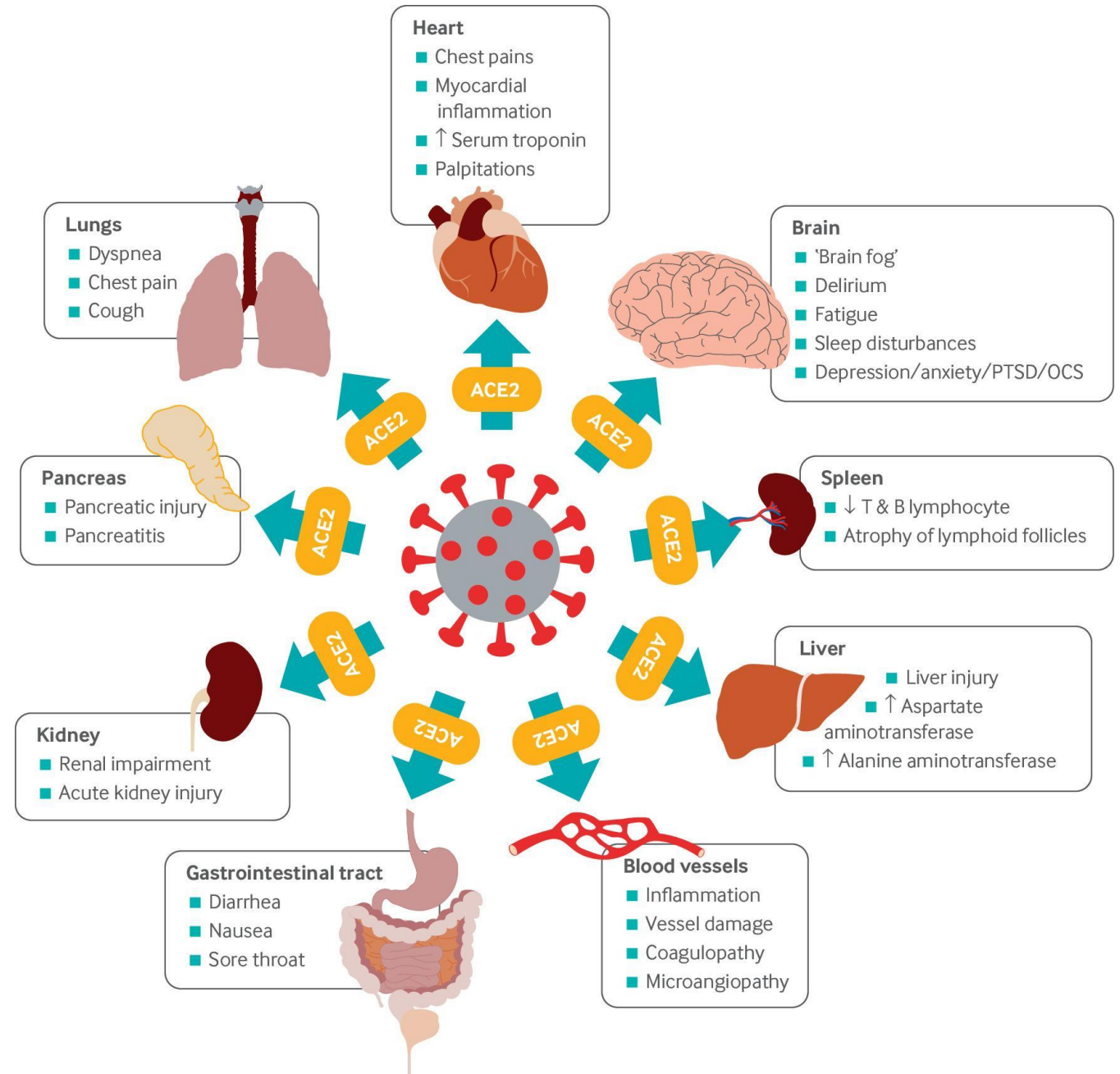
Dyspnea/Altered breathing

Depression/Anxiety

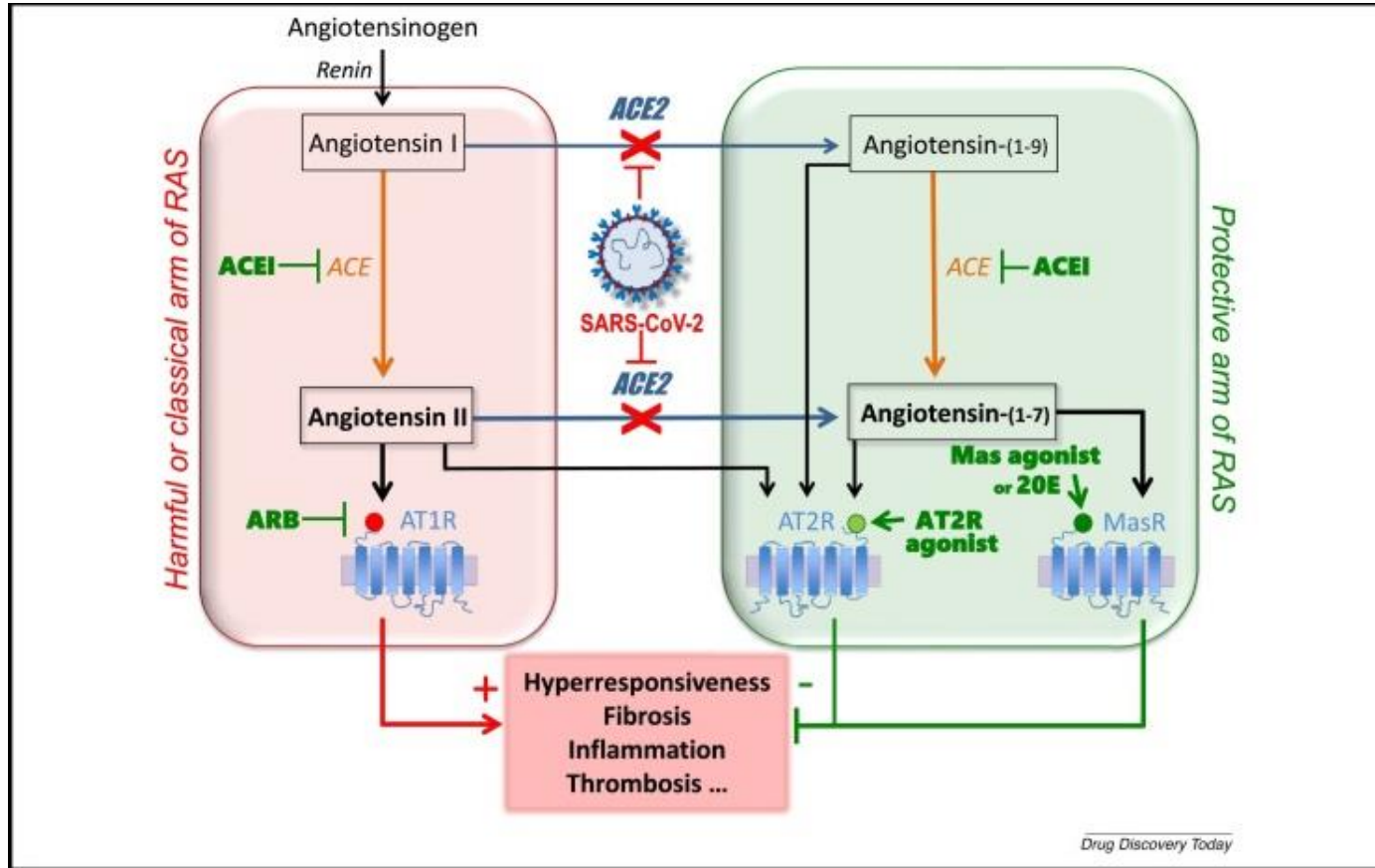


Angiotensin-converting enzyme 2 (ACE2) receptor

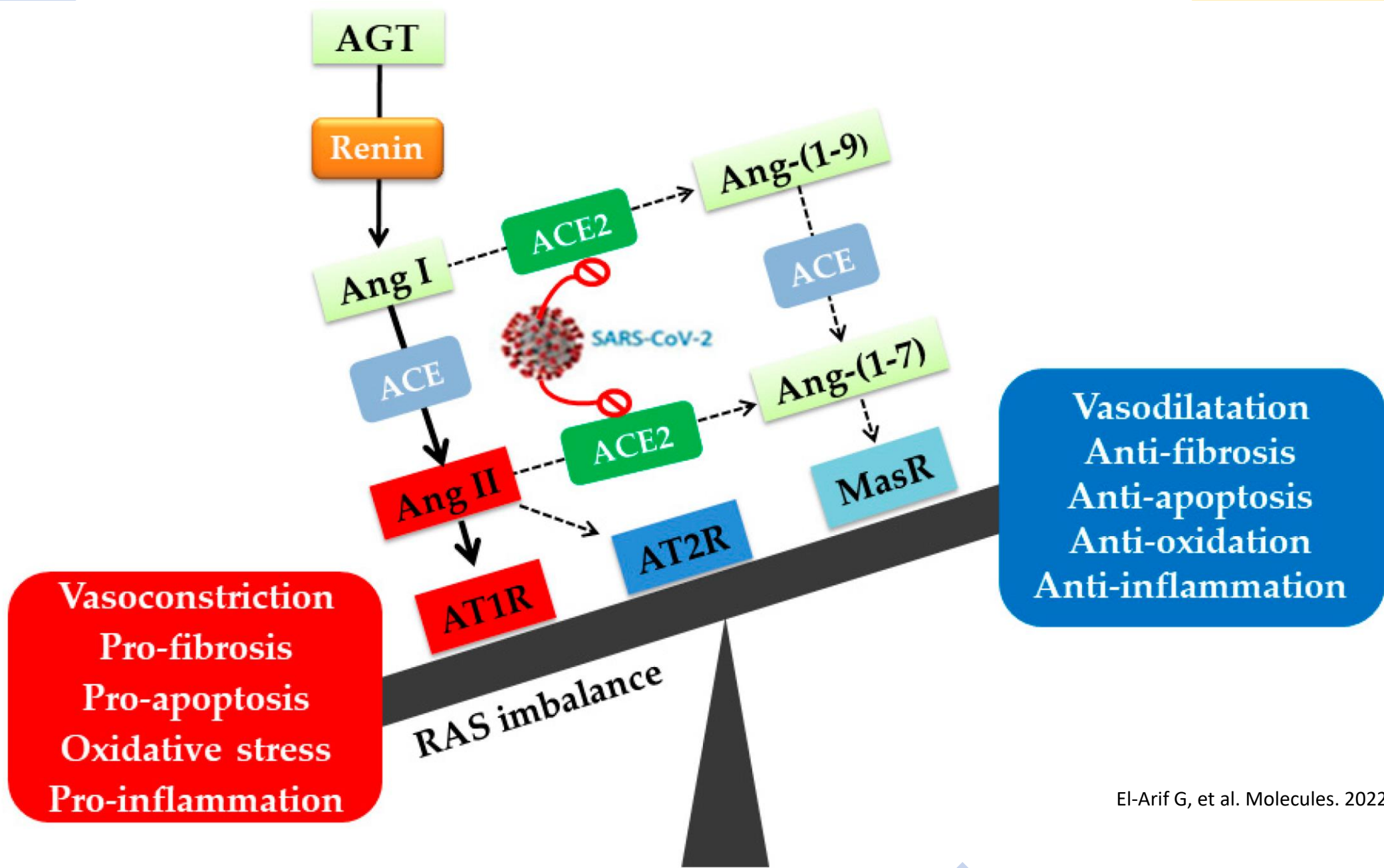
- Point of entry for SARS-CoV-2
- Elicits a downstream pro-inflammatory response, oxidative stress



SARS-Co-V-2 and the Renin Angiotensin System (RAS)



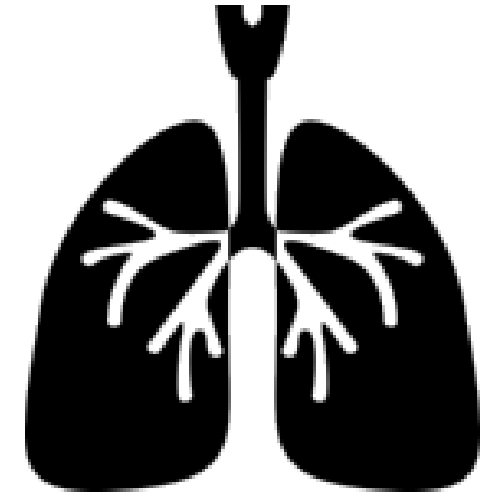
- Virus upregulates the harmful and downregulates the protective arms of RAS
- High levels of Ang II
- Low levels of Ang 1-7, Ang 1-9



Viral mediated parenchyma damage; immune mediated microvascular damage

- a) Virus binds to ACE2 → cells release DAMPs/PAMPs
 - b) Macrophages release IL1 and TNF-alpha → neutrophils attracted to site
 - c) Neutrophils release chemokines → vascular permeability increased.
differentiation of fibroblasts into myofibroblasts
 - d) Release of protein-rich exudate to interstitial space
 - e) Myofibroblasts release collagen, fibronectin, and ECM in response to TGF-beta → excess scar tissue deposition despite infection resolution
-

Dyspnea, hypoxia, fatigue, ground glass opacities and pulmonary fibrosis



Pathophysiology: Pulmonary

*DAMP = Damage Associated Molecular Patterns

*TNF = Tumor Necrosis Factor *ACE2 = Angiotensin-Converting Enzyme 2

*PAMP = Pathogen-Associated Molecular Pattern *ECM = Extracellular Matrix

Long COVID Symptoms: Pulmonary

Presentation

- Cough, shortness of breath, fatigue, chest pain, decreased exercise tolerance
- Secondary symptoms of palpitations, dizziness, anxiety can be exacerbated by shortness of breath
- Chest myopathy from COVID-19 skeletal muscle injury and viral airway hyperresponsiveness contribute
- Vagal nerve inflammatory mediators and vocal cord dysfunction may be implicated

Evaluation/Treatment

- 6-minute walk test, Timed Up and Go (TUG) Test
- Pulmonary function tests
- CT scan – ground glass opacities or fibrotic changes
- Evaluate for sleep apnea – especially those with fatigue
- Pulmonary rehabilitation
- Drugs used to treat idiopathic fibrosis (pirfenidone, nintedanib, prednisolone)

Pathophysiology: Cardiovascular

*IL = Interleukin

Immune-mediated myocardial and microvascular destruction.

- a) Endothelial cell disruption similar to pulmonary
- b) Increased cardiometabolic demand → myocardial injury via hypoxia and overuse
- c) Chronic myocarditis and IL6 → fibrofatty replacement
- d) Fibrofatty replacement → reentrant arrhythmias and sudden cardiac arrest and death
- e) Medications also induce cardiotoxicity and electrolyte imbalances

**Chest pain, palpitations, pericarditis, myocarditis, fibrosis,
arrhythmias/death**

Joshee S, et al. Mayo Clin Proc. 2022.



Long COVID Symptoms: Cardiovascular

Presentation

- Chest discomfort and palpitations, exercise Intolerance
- Dysautonomia (tachycardia and orthostasis)
- Postural Orthostatic Tachycardia Syndrome (POTS); occurs typically in females of childbearing age
- Increased troponin, myocarditis, cardiac fibrosis
- Important to evaluate for hypertrophic cardiomyopathy, particularly in young athletes
- Resolution of symptoms generally a very slow process

Evaluation/Treatment

- EKG may show tachycardia or PVCs
- Echocardiogram typically normal
- Orthostatic vital signs and, if needed, tilt-table testing
- Continue ACE-inhibitors, ARBs
- For POTS: propranolol, ivabradine being studied

Pathophysiology: Neurological

*BBB = Blood Brain Barrier *PNS = Peripheral Nervous System *HIF-1 = Hypoxia-Inducible Factor 1



Immune-mediated damage to BBB & thromboembolism; viral mediated hypoxia and damage to PNS

- a) inflammatory markers increase leakage and allow leukocyte infiltration and basement membrane modification
 - b) Megakaryocytes in the parenchyma of alveolar tissue which may travel into the brain tissue due to endothelial disruption
 - c) Hypoxia due to hypercoagulable state → HIF-1 increase → increase in BBB permeability and prolonged cytokine release
-

Neuropsychiatric, cognitive and peripheral nerve pathologies

Long COVID Symptoms: Neuropsychiatric

Presentation

- Symptoms often disabling but poorly defined
- Headache, poor cognitive performance, attention deficit, memory deficit, abnormal sensation, ataxia, chronic fatigue
- Anosmia, olfactory symptoms
- Females at greater risk

Evaluation/Treatment

- Standard noninvasive screening tools
- Several drugs in trial
- Vaccine may be protective against neurologic sequelae
- For anosmia: nasal steroids
- Many improve in 6 to 12 months

Long COVID Symptoms: Rheumatology

Presentation

- Fatigue and pain: joint pain, localized pain - especially back and neck
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: post exertion worsening of symptoms, unrefreshing sleep, cognitive impairment
- Fibromyalgia: pain generalized, fatigued, unrefreshing sleep (female & prior use of corticosteroids increases risk)
- Relapse Triggers: physical activity, stress, exercise, mental activity, menstruation
- Exclude autoimmune disorders that mimic Long COVID

Evaluation/Treatment

- Acupuncture, graduated exercise program
- Electrotherapy - TENS for localized pain
- Replace low vit D, Mg (may help with HA and pain)
- Amitriptyline (good w/poor sleep), duloxetine
- For neuropathic symptoms:
 - gabapentin, pregabalin

Long COVID Symptoms: Emotional & Mental Health

Presentation

- Traumatized with memories of illness, PTSD
- Disturbed by cognitive symptoms – brain fog
- Frustrated, angry, sleep-deprived and frightened
- May feel that symptoms will never resolve
- Anxiety and depression may occur or be triggered in patients with previous history
- Important to address cognitive impairments

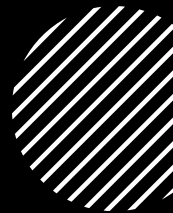
Evaluation/Treatment

- Cognitive Behavioral Therapy
- Breath retraining and relaxation
- Physical activity
- Natural sunlight helps regulate mood and sleep
- Address sleep hygiene
- Compensatory cognitive training for brain fog

Long COVID in children
is less well-studied but
can occur



Long COVID in Children and Teens



Post-viral airway hyperresponsiveness – exacerbated in those with history of asthma, atopia, smoking parent

Increased anxiety and depression

Cognitive changes most challenging

May unmask diabetes

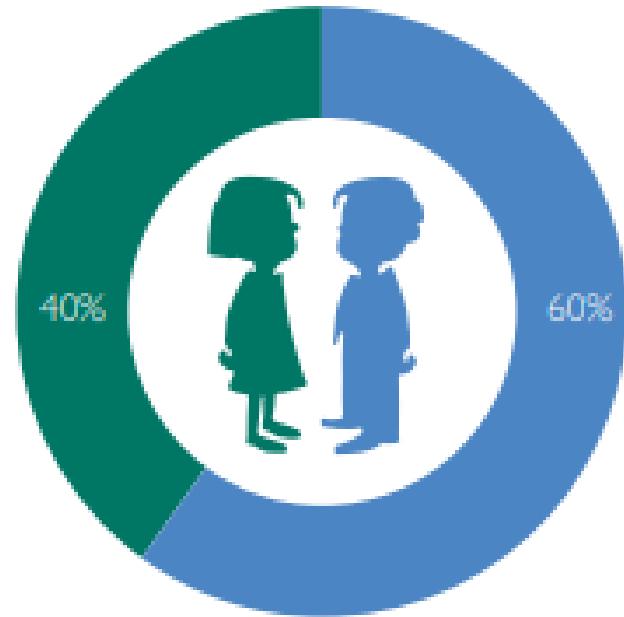
Multisystem Inflammatory Syndrome in Children (MIS-C)

- Presents 2-6 weeks after initial infection
- Diagnostic Criteria – age ≤ 21 years, fever $\geq 38^{\circ}\text{C}$ or ≥ 24 hours, lab evidence of inflammation, multiorgan system dysfunction
- Fever, rash, GI symptoms, shock
- Increase in inflammatory mediators, "cytokine storm"
- Frequent cardiac involvement

American Academy of Pediatrics. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance.

<https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/>

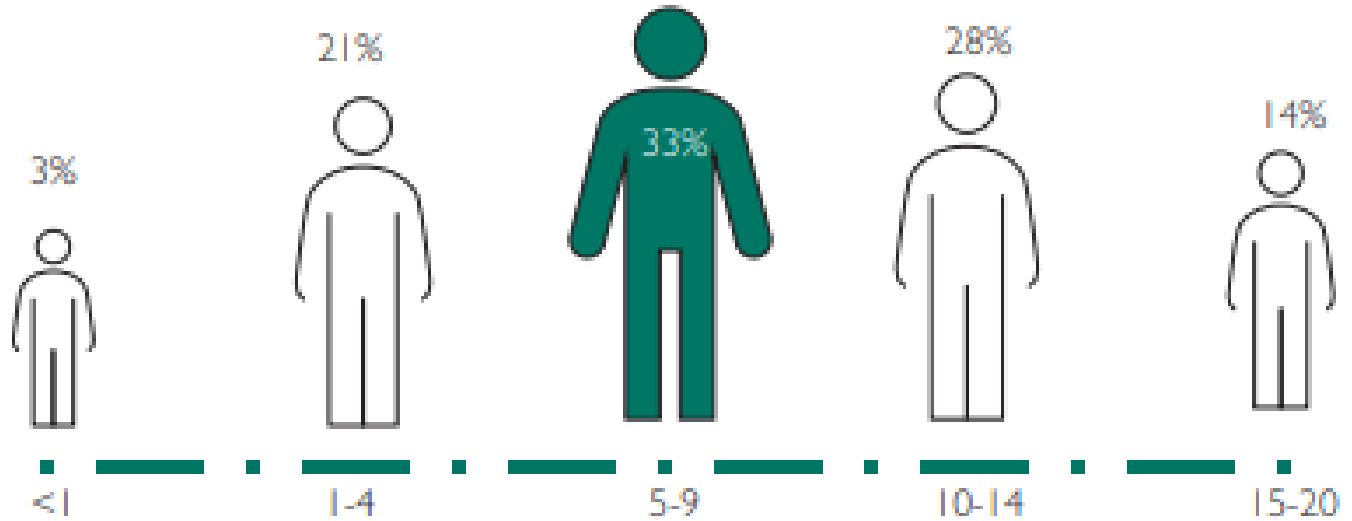
Gender distribution



Female v. male

MIS-C by the numbers

Age of affected individuals-years



Percentage by race and ethnicity

Hispanic or latino



32%

BLACK, non-hispanic



30%

WHITE, non-hispanic



28%

Asian, NH/OPI, AI/NA



4%

Other



4%

Multiple



3%

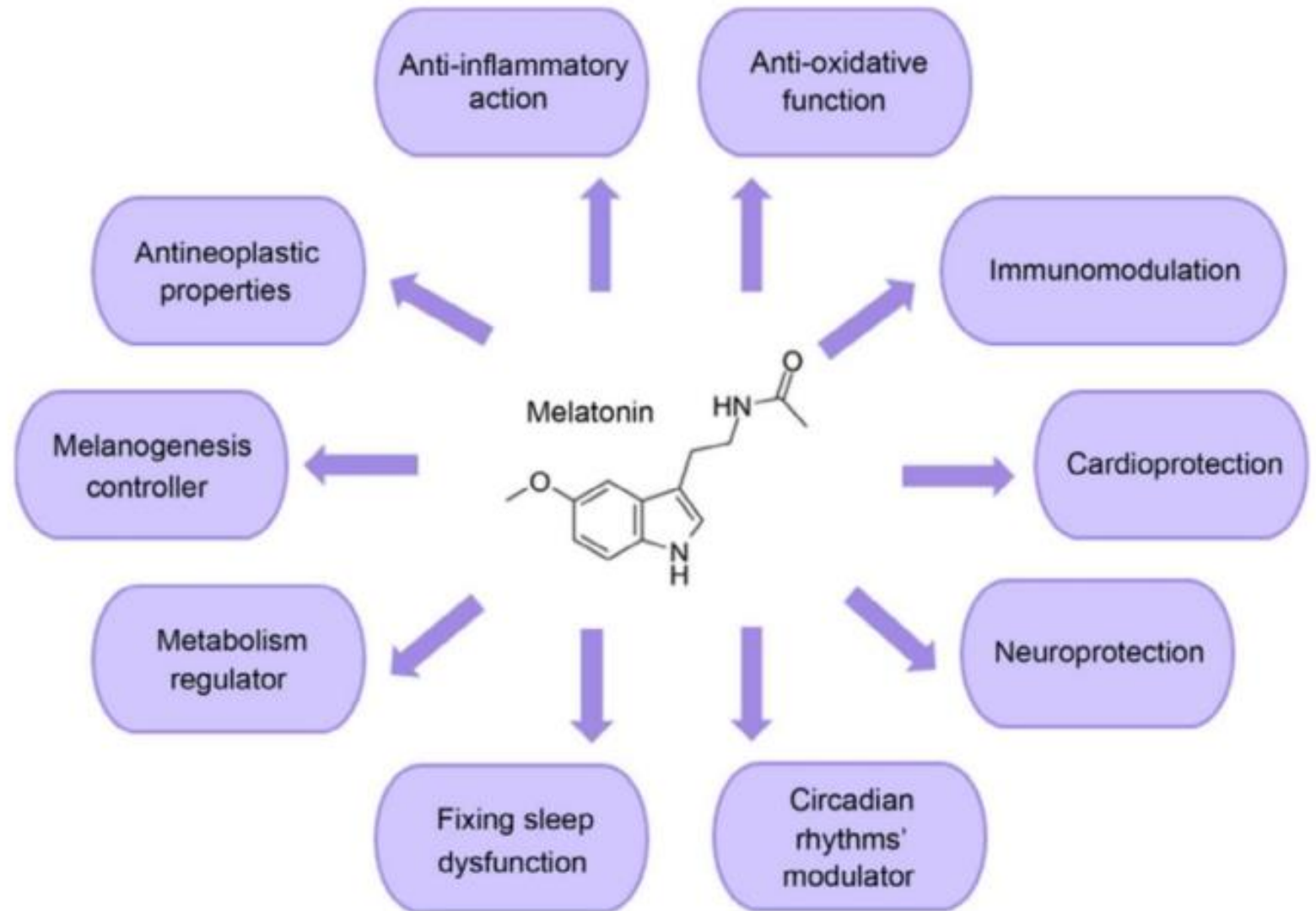


Long COVID Treatments

- Supportive/rehabilitative services most useful at this point
- Medications - many ongoing trials, nothing with strong evidence
- Most aimed at re-balancing RAS – antioxidant and anti-inflammatory properties

Melatonin

- Hormone released by pineal gland and other organs
- Good safety profile
- Activator of nuclear factor erythroid 2-related factor (NRF2)
- Promotes production of intracellular antioxidants such as glutathione



Other Drugs under Review

- Statins
- Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)
- Monoclonal antibodies that block inflammatory mediators (TNF, IL-6)
- Antivirals used to treat mild-moderate COVID-19 (nirmatrelvir/ritonavir)
- COVID-19 vaccine

Ayoubkhani D, et al. BMJ. 2022.

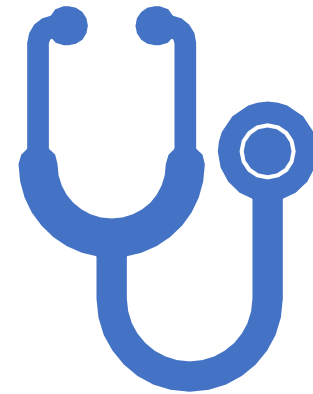
Carson E, et al. American J Therapeutics. 2022.

Crook H, et al. BMJ. 2021.

Jarrott B, et al. Pharmacol Res Perspect. 2022.



Prognosis



Longitudinal Study of hospitalized COVID-19 patients from Wuhan, China

At 6 months:

- 68% had at least one persistent symptom
 - Fatigue, muscle weakness (52%)
- 30% reported dyspnea
- 23% reported anxiety or depression

At 1 year:

- 49% had at least one persistent symptom
 - Fatigue, muscle weakness (20%)
- 26% reported dyspnea
- 26% reported anxiety or depression
- 88% of those formerly working had returned to work



Much that we
don't know

Lessons from prior pandemics:

- H1N1 Pandemic of 1918-1919
 - Individuals born during the pandemic had increased cardiovascular disease in adulthood compared to other birth cohorts
 - They also achieved a lower mean height in young adulthood compared to surrounding birth cohorts
- Influenza A2 outbreak in Helsinki, Finland of 1952
 - Maternal viral infection during the 2nd and 3rd trimester may have increased the risk of adult schizophrenia
- Mouse studies – viral infections affect brain cell development

• Mazumder B, et al. J Developmental Origins of Health and Disease. 2010.

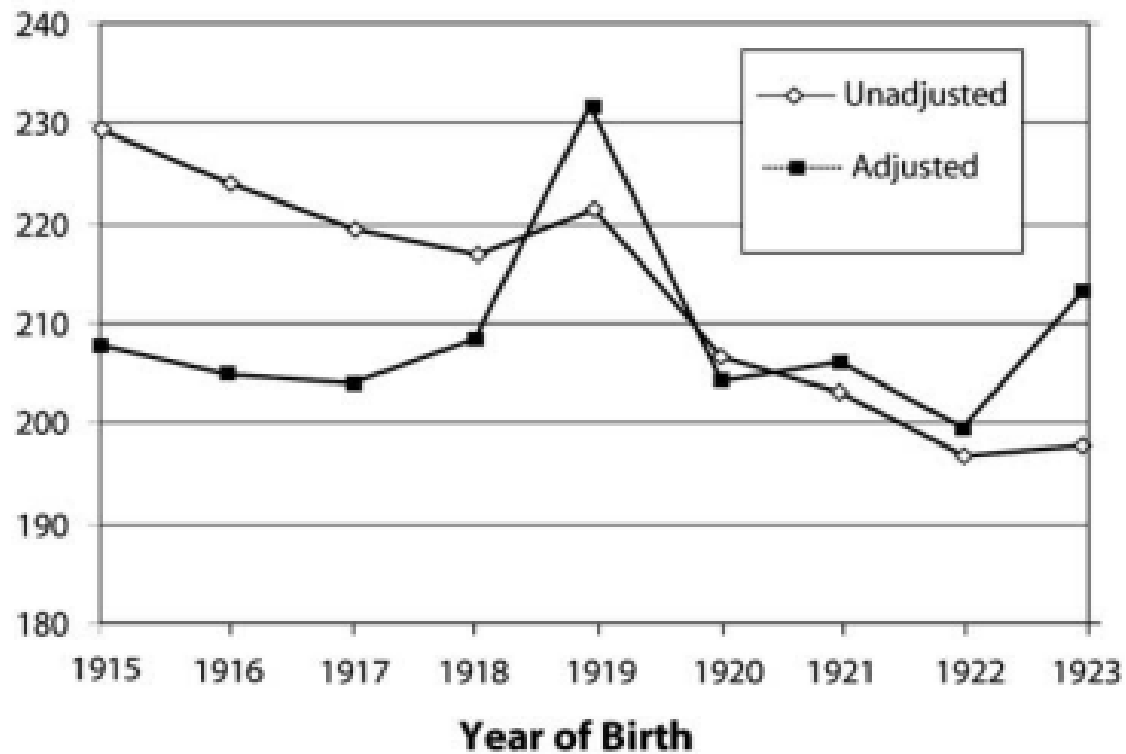
• Mednick SA, et al. Arch Gen Psychiatry. 1988.

Influenza Pandemic 1918-1919

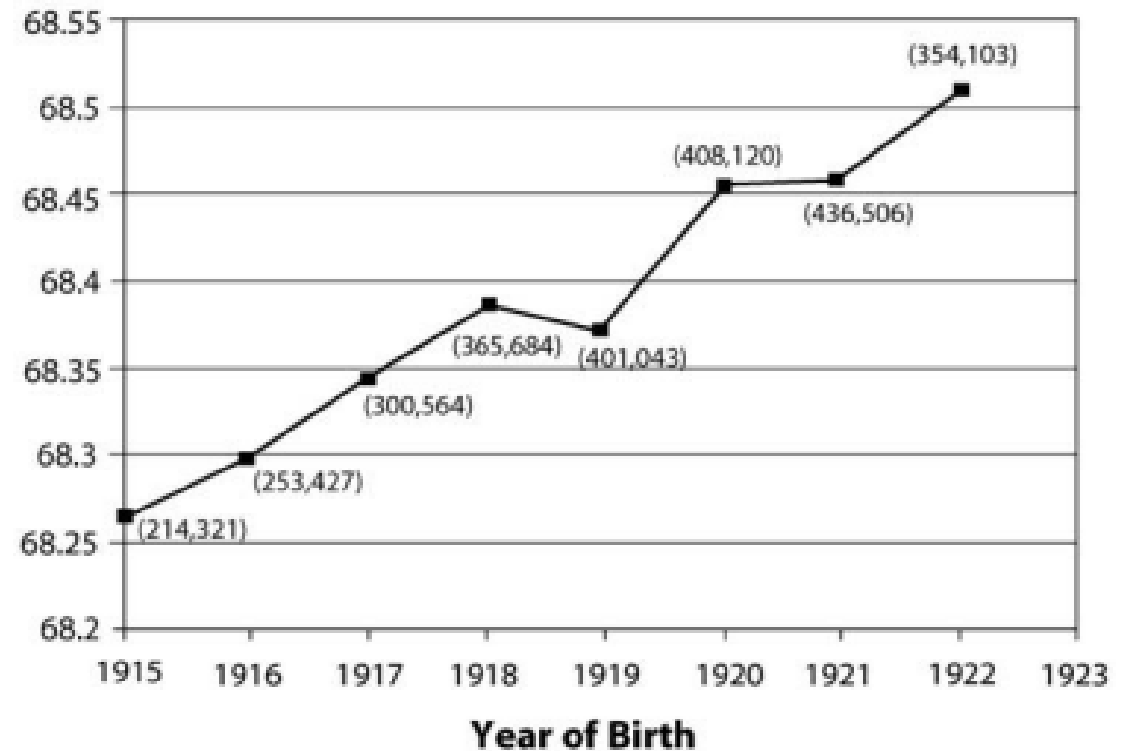
Cardiovascular Disease at 60-82
Years of Age By Birth Cohort

Mean Height at 19-27 Years by Birth
Cohort at Enlistment 1941-1942

(a) Rate/1000



(b) Mean height (in.)



What is being done to help?

\$1.15 Billion in NIH grants for Long COVID research – Researching COVID to Enhance Recovery (RECOVER)

Coverage for affected patients under American Disabilities Act 1990

Some may qualify for Social Security Disability Insurance

COVID-19 Vaccine is the Best Prevention against Long COVID

- CDC recommends COVID-19 primary series vaccines for everyone ages 6 months and older, and COVID-19 boosters for everyone ages 5 years and older, if eligible

<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/expect.html>
https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html?s_cid=11747:covid%20vaccine%20schedule:sem.ga:p:RG:GM:gen:PTN:FY22



Key Points

Many patients who experience acute COVID-19 have lingering symptoms weeks to months after recovery from initial illness



Risk of Long COVID is not directly linked to severity of acute COVID infection

Inflammation appears to play a key role in the etiology of long COVID symptoms

Multidisciplinary approach to treatment is important, emphasizing nonpharmacologic therapies

Research is ongoing on possible drug treatments