Morbidity Challenges 2023
The Long COVID Conundrum

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Disclosures

◆ **Research Funding**

- Colton Autoimmunity Grant

- NIH 1R01HD108312-01A1: Evaluating a Comprehensive Multimodal Outpatient Rehabilitation Program to Improve the Functioning of Persons Suffering from PASC: A RCT

◆ **Long COVID Advising**

- AstraZeneca

- Moderna

- Axcella Health Inc.

- Intrivo Diagnostics

- UnitedHealth Group

Objectives

- Present data on the number of Long COVID cases to date and recent trends in diagnosis

- List known risk factors for the development of Long COVID and how to reduce these risks

- Describe current treatment protocols for the most common symptoms associated with Long COVID and in what ways treatment at a Long COVID Center of Care results in improved outcomes

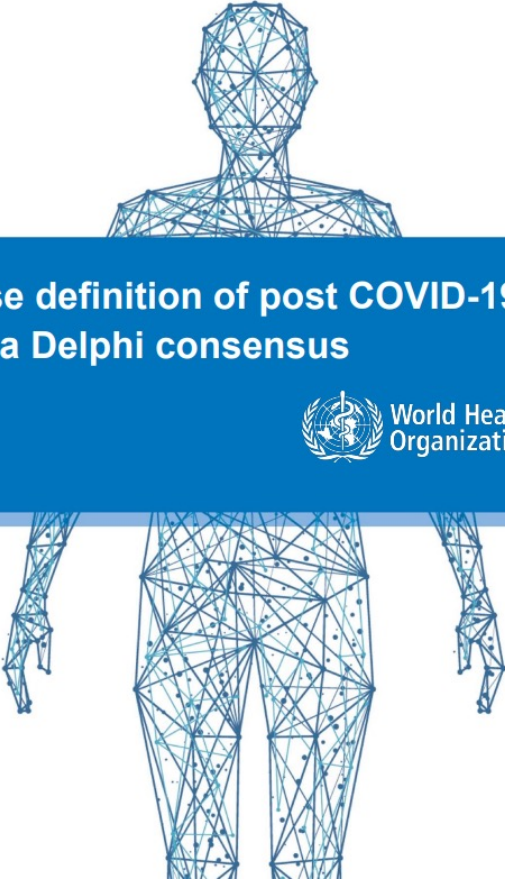- Explain the future direction of Long COVID research and specific areas that hold promising outcomes

The Case of Nurse J.

- 48 year-old female
- Past medical history of asthma and gastric reflux
- 4 months after initially feeling better
  - Extreme fatigue
  - Dyspnea with exertion
  - Arthralgia
  - "Brain fog"
  - Numbness and tingling
- Nurse at a local outpatient care center
  - 5 days off work
  - Difficulty with errands
- **Started following COVID infection**

What is Long COVID?

- History of **probable or confirmed SARS CoV-2** infection
- Usually **3 months from the onset** of COVID-19
- 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.

A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021

World Health Organization

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD; Sarah E. Jolley, MD, MS; Elizabeth W. Karlson, MD, MS; Emily B. Levitan, ScD;
Bruce Levy, MD; Grace A. McComsey, MD; Lisa McCorkell, MPP; Girish N. Nadkarni, MD, MPH;
Sairam Parthasarathy, MD; Upinder Singh, MD; Tiffany A. Walker, MD; Caitlin A. Selvaggi, MS;
Daniel J. Shinnick, MS; Carolin C. M. Schulte, PhD; Rachel Atchley-Challenner, PhD; RECOVER Consortium Authors;
Leora I. Horwitz, MD; Andrea S. Foulkes, ScD; for the RECOVER Consortium

- First published study by RECOVER Consortium

- Objective to develop a definition of PASC using self-reported symptoms

- 8646 infected, 1118 uninfected

- Fatigue=Being Very Tired

- PEM=Post-exertional malaise (Symptoms worse after even minor physical or mental effort)

B | Symptom frequencies

Frequency among PASC-positive participants, %
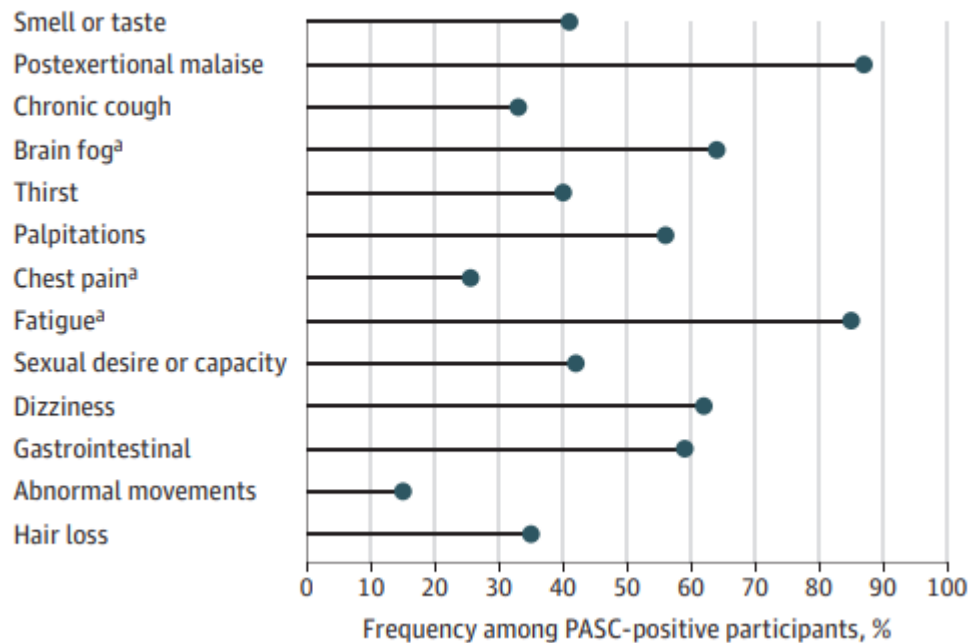
Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

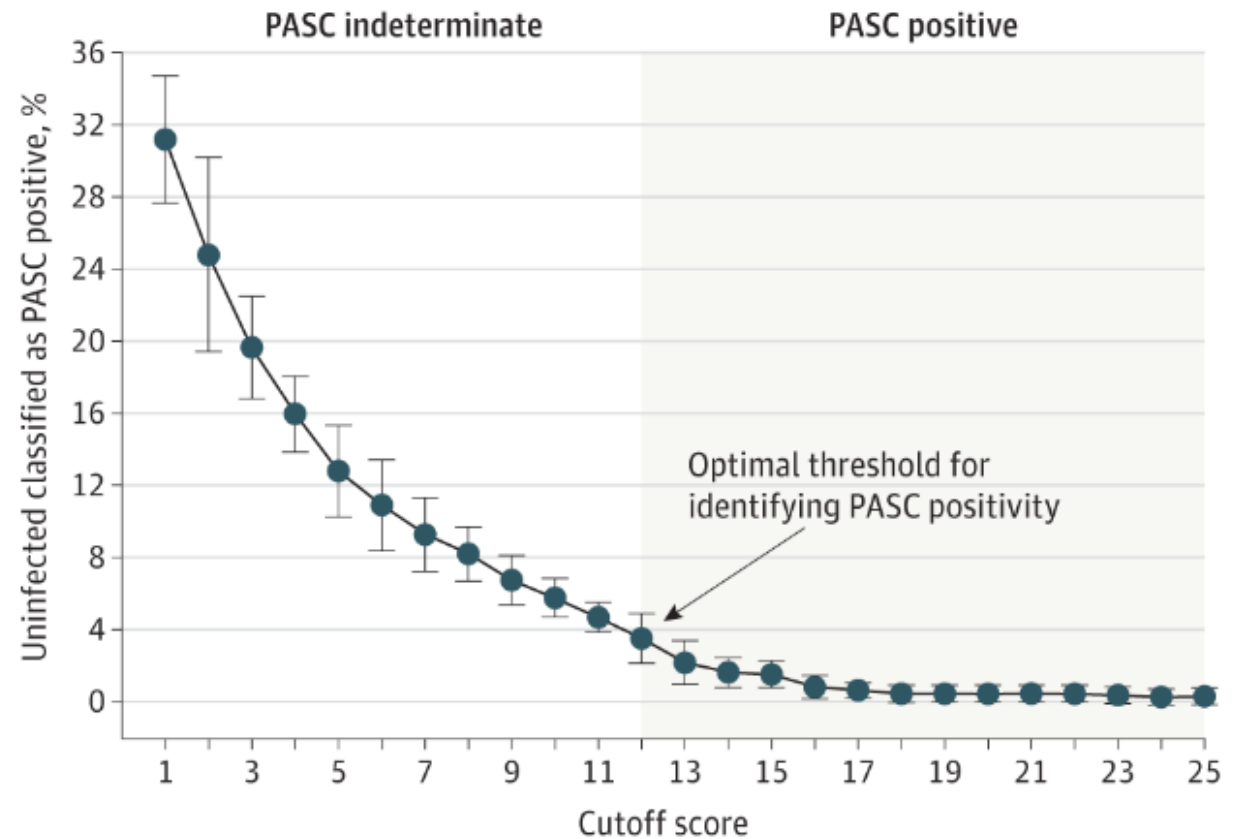| Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

[a] Least absolute shrinkage and selection operator was used to identify which symptoms defined PASC. A symptom score was assigned by dividing the estimated log odds ratio by 0.10 and rounding to the nearest integer. For each person, the total score was defined as the sum of the scores for each symptom a person reported.

- PEM- 28% infected, 7% uninfected, OR=5.2

- Fatigue- 38% infected vs. 17% uninfected. OR=2.9

- Optimal threshold score of 12 to diagnose Long COVID

- 10% who enrolled within 30 days would be classified as having PASC at 6 months

- Higher scores associated with worse functioning

- Other symptoms that did not contribute to score may also be important to QOL

- 4% of those without history of COVID met PASC criteria

- *Insurers, disability agencies, and/or doctors should not use findings from this study to clinically define or rule out Long COVID.*

A | Optimal threshold for identifying PASC positivity

PASC indeterminate   PASC positive

Uninfected classified as PASC positive, %

Optimal threshold for identifying PASC positivity
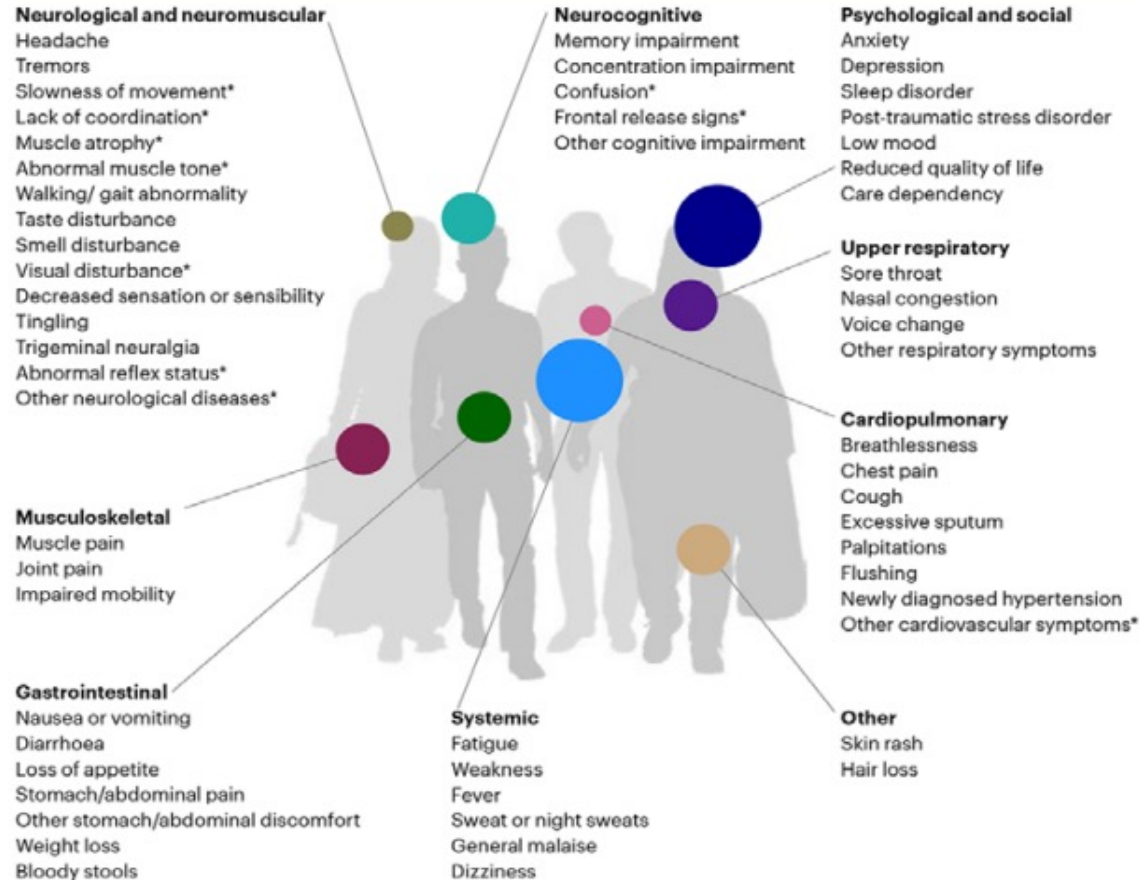
Cutoff score

Long Covid symptoms and signs

Frequency: ● Very common ● Common ● Less common

People hospitalised during acute phase of Covid-19
Based on 26 studies with 7147 people*

Neurological and neuromuscular
Headache
Tremors
Slowness of movement*
Lack of coordination*
Muscle atrophy*
Abnormal muscle tone*
Walking/ gait abnormality
Taste disturbance
Smell disturbance
Visual disturbance*
Decreased sensation or sensibility
Tingling
Trigeminal neuralgia
Abnormal reflex status*
Other neurological diseases*

Neurocognitive
Memory impairment
Concentration impairment
Confusion*
Frontal release signs*
Other cognitive impairment

Psychological and social
Anxiety
Depression
Sleep disorder
Post-traumatic stress disorder
Low mood
Reduced quality of life
Care dependency

Upper respiratory
Sore throat
Nasal congestion
Voice change
Other respiratory symptoms

Cardiopulmonary
Breathlessness
Chest pain
Cough
Excessive sputum
Palpitations
Flushing
Newly diagnosed hypertension
Other cardiovascular symptoms*

Musculoskeletal
Muscle pain
Joint pain
Impaired mobility

Gastrointestinal
Nausea or vomiting
Diarrhoea
Loss of appetite
Stomach/abdominal pain
Other stomach/abdominal discomfort
Weight loss
Bloody stools

Systemic
Fatigue
Weakness
Fever
Sweat or night sweats
General malaise
Dizziness

Other
Skin rash
Hair loss

People non-hospitalised during acute phase of Covid-19
Based on 4 studies with 1168 people*

Neurological and neuromuscular
Headache
Tremors
Seizures/ cramps
Slowness of movement*
Lack of coordination*
Muscle atrophy*
Abnormal muscle tone*
Walking/ gait abnormality*
Taste disturbance
Smell disturbance
Ear/ hearing conditions
Visual disturbance
Decreased sensation or sensibility*
Tingling*
Abnormal reflex status*
Other neurological diseases*

Neurocognitive
Memory impairment
Concentration impairment
Confusion
Frontal release signs*
Other cognitive impairment*

Psychological and social
Anxiety*
Depression*
Sleep disorder*
Post-traumatic stress disorder
Low mood*
Reduced quality of life*
Care dependency*

Upper respiratory
Sore throat
Nasal congestion
Other respiratory symptoms

Cardiopulmonary
Breathlessness
Chest pain
Cough
Excessive sputum
Palpitations
Other cardiovascular symptoms*

Musculoskeletal
Muscle pain
Joint pain
Impaired mobility*

Gastrointestinal
Nausea or vomiting
Diarrhoea
Stomach/abdominal pain
Weight loss

Systemic
Fatigue
Weakness*
Fever
Sweat or night sweats*
Enlarged lymph nodes
Dizziness

Other
Skin rash
Hair loss
Conjunctivitis

* Identified only in studies including both hospitalised and non-hospitalised people (9 studies including 2636 people)

Last updated 17 Mar 202*

Greater than 200 individual symptoms have been attributed to Long COVID
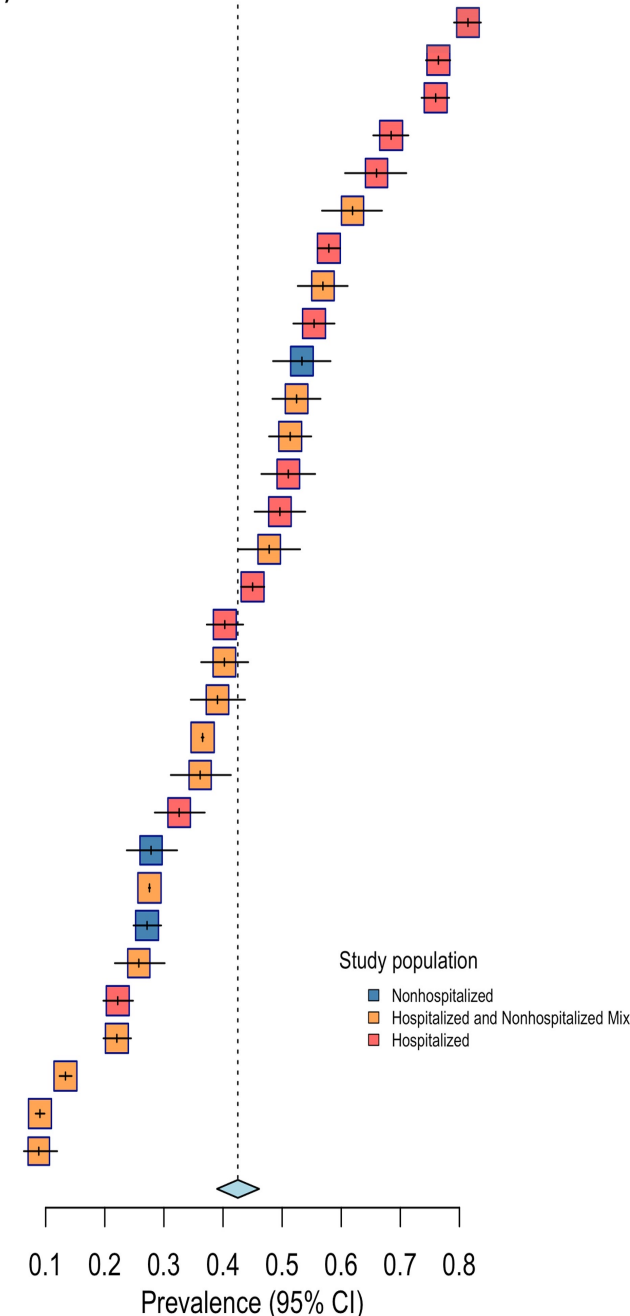
Prevalence

◆ Varies Widely in Studies

- 3-80%

- Hospitalized (50-70%) > Non-hospitalized (10-30) > Vaccinated/Breakthrough (10-12%)

- Limitations: Observational, Premorbid Data, Control Group, Standard Assessments, Selection/Reporting Bias, Early Strains, Vaccination Status.

Studies	Prevalence (95% CI)
Fernández-de-Las-Peñas et al Spain	0.81 [0.79; 0.84]
Huang et al China	0.76 [0.74; 0.78]
Wong-Chew et al Mexico	0.76 [0.74; 0.78]
Ghosn et al France	0.68 [0.65; 0.71]
Areekal et al India	0.66 [0.61; 0.71]
Lemhofer et al Germany	0.62 [0.57; 0.67]
Munblit et al Russia	0.58 [0.56; 0.60]
Maestre-Muñiz et al Spain	0.57 [0.53; 0.61]
Shang et al China	0.55 [0.52; 0.59]
Desgranges et al Switzerland	0.53 [0.48; 0.58]
Hirschtick et al USA	0.52 [0.48; 0.57]
Venturelli et al Italy	0.51 [0.48; 0.55]
Morin et al France	0.51 [0.46; 0.56]
Xiong et al China	0.50 [0.45; 0.54]
Yomogida et al USA	0.48 [0.43; 0.53]
Zhang et al China	0.45 [0.43; 0.47]
Budhiraja et al India	0.40 [0.37; 0.43]
Peghin et al Europe	0.40 [0.36; 0.44]
Righi et al Europe	0.39 [0.35; 0.44]
Taquet et al USA+others	0.37 [0.36; 0.37]
Cirulli et al USA	0.36 [0.31; 0.41]
Chopra et al USA	0.33 [0.28; 0.37]
Augustin et al Europe	0.28 [0.24; 0.32]
Spotnitz et al USA	0.28 [0.27; 0.28]
Huang et al California	0.27 [0.25; 0.30]
Menges et al Switzerland	0.26 [0.22; 0.30]
Evans et al UK	0.22 [0.20; 0.25]
Naik et al India	0.22 [0.20; 0.24]
Sudre et al UK/SE/US	0.13 [0.12; 0.14]
Perlis et al USA	0.09 [0.08; 0.10]
Lampl et al Germany	0.09 [0.06; 0.12]
Total	0.43 [0.39; 0.46]

Heterogeneity: χ^2_{30} = 13875.94 (P < .001), I^2 = 100%

Study population
- Nonhospitalized
- Hospitalized and Nonhospitalized Mix
- Hospitalized

Prevalence (95% CI)

Prevalence

- **U.S. National Center for Health Statistics**
  - 6% currently reporting long COVID symptoms. 15% had at some point.
- **Ballering et al. (2022)**
  - 76,422 participants
  - Prospective
  - Pre- and Post-
  - Control Group
  - Non-hospitalized
  - **12.7% of individuals had increase in symptoms following COVID-19 of at least moderate severity attributable to COVID**
    - One out of eight patients with COVID
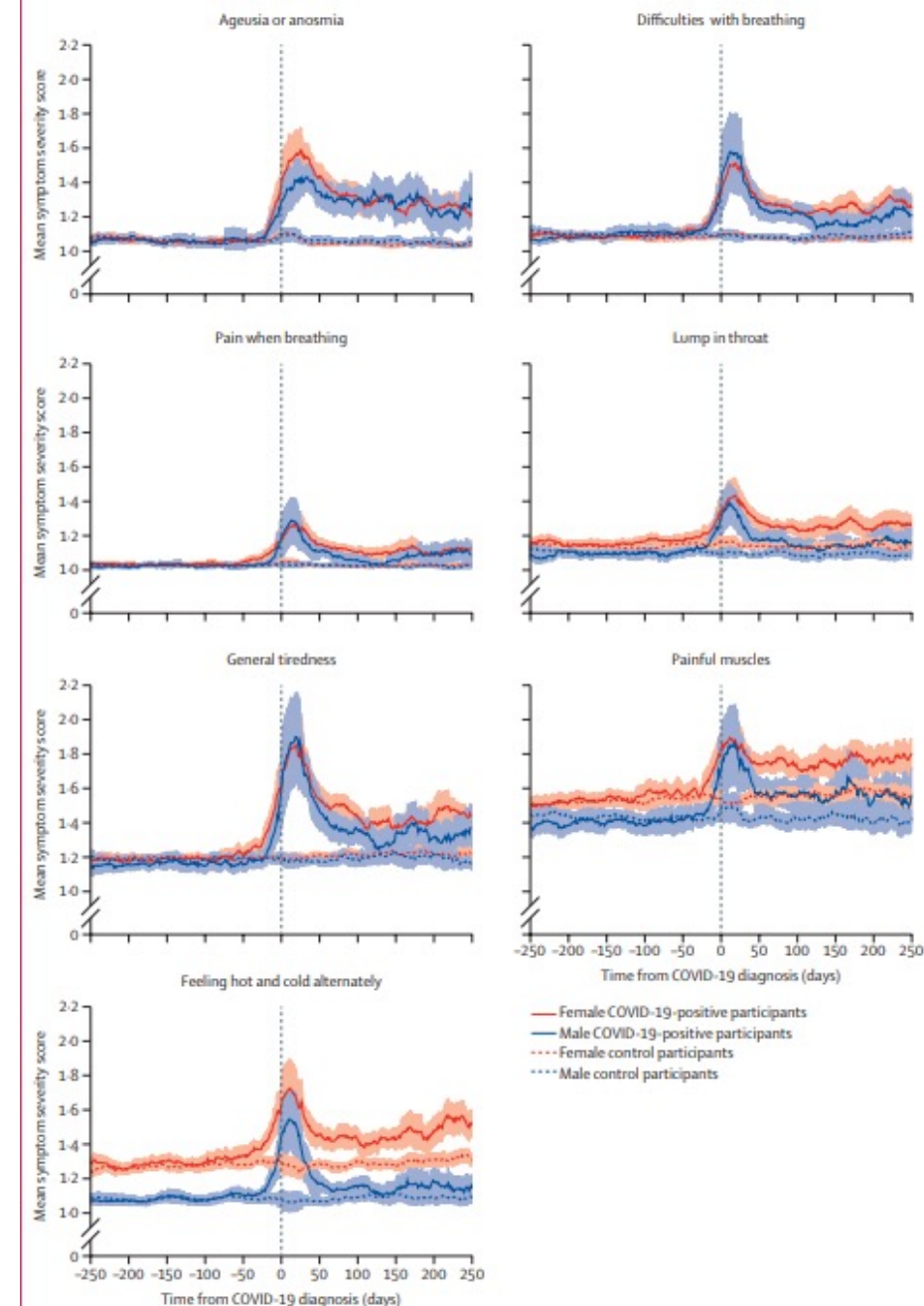
Prevalence

- **Global Burden of Disease Long COVID Collaborators (2022)**
  - Meta-analysis of 54 studies and two medical record databases from 22 countries
  - 6.2% with symptomatic COVID-19 at 3 months
    - Fatigue with body pain or mood swings (3.2%)
    - Cognitive problems (2.2%)
    - Respiratory problems (3.7%)

aapm&r

View Dashboard Assumptions, Methodology, and Sources

SUMMARY	BY STATE

FILTERS
(reset to default)
Select Est. PASC %

| 12% | ⌄ |

Select a State

| All | ⌄ |

Select a County

| All | ⌄ |

MODEL ASSUMPTIONS AND SOURCES
(see all)

1. Model assumes 30% of COVID-19 surviving cases in the U.S. result in PASC.

2. COVID-19 surviving cases are confirmed cases less deaths.

3. U.S. case data is pulled nightly from JHU CSSE COVID-19 Data. U.S. Census data uses 2019 1-year estimates.

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ASSOCIATION ANALYTICS

COVID-19 SURVIVING CASES (TOTAL)
PASC CASES (ESTIMATED)

100,554,103   12,066,492

ESTIMATED PASC CASES PER STATE

State	PASC Cases (Estimated) ▼
California	1,419,104
Texas	973,742
Florida	876,753
New York	788,994
Illinois	473,362
Pennsylvania	407,830
North Carolina	402,541
Ohio	394,862
New Jersey	351,620
Michigan	349,933
Georgia	343,391
Arizona	283,127
Tennessee	278,365
Virginia	263,925
Indiana	239,100
Wisconsin	234,973
Massachusetts	234,551

CUMULATIVE AND DAILY CASES

Select Display
- ● Cumulative
- ○ Daily

PASC CASES (ESTIMATED)
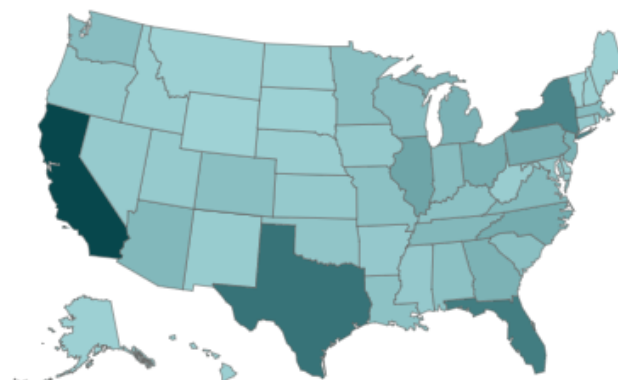
Employment Effects

- 15308 US Adults
  - 14.6% reported PASC
  - 9.3% reported being unemployed
    - 12.3% PASC
    - 8.7% with PASC
  - Odds ratio (adjusted) 0.84 (0.74-0.96)

Employment Effects

◆ **Brookings Metro Report- January 2022**

- Conservative 1.6 million workers out due to Long COVID
- 15% of labor shortage

◆ **Census Bureau Household Pulse Survey, June-July 2022**

- 2-4 million workers out due to Long COVID
- Lost wages alone $170 billion

Number of Americans out of the labor force due to long Covid

16.3M — Working age Americans who have long Covid today

12.2M — Working age Americans with long Covid who were likely in the labor force pre-illness

Full-time equivalent workers out of the labor force due to long Covid:
- 4.1M — Using Lancet report
- 2.9M — Using TUC report
- 1.8M — Using Fed report
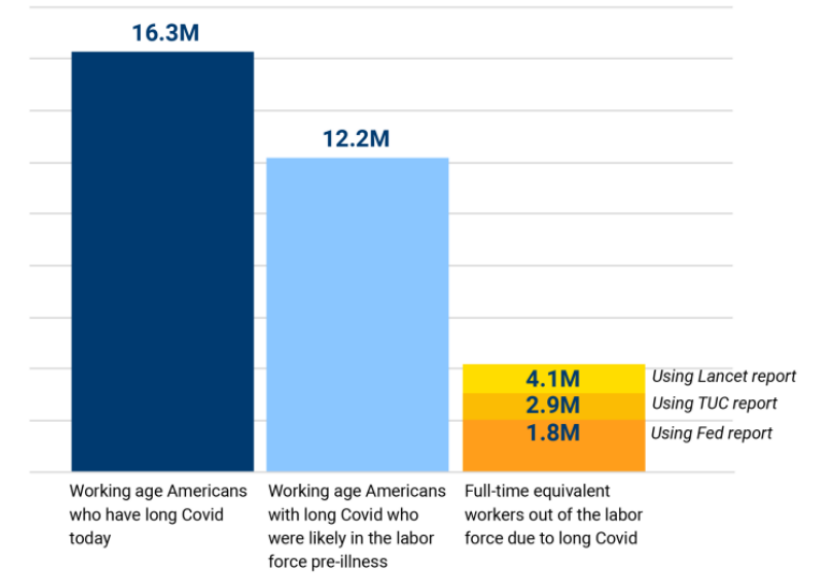
Annual lost wages due to long Covid

Legend:
- Using Fed analysis
- Using TUC data
- Using Lancet report

- 1.8M — $105B
- 2.9M — $168B
- 4.1M — $235B

In millions

Number of people out of work due to long Covid
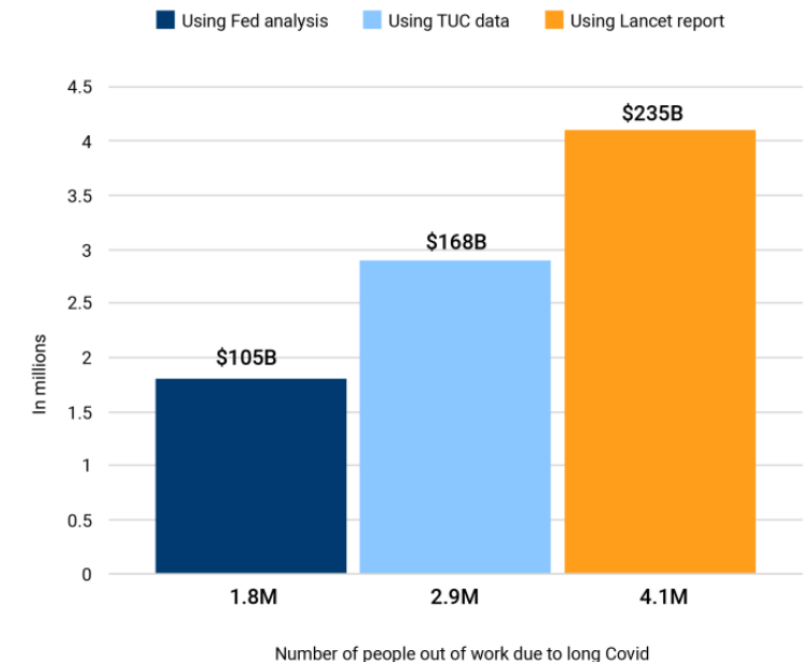
Risk Factors

- Female
- Age (36-50 yo)
- Single
- Time since infection
- More symptoms during acute COVID
- Hispanic/Latino
- Lower income/inability to rest?

5 Major Risk Factors for PASC

1 Vaccination status   2 Hospitalization   3 Age

4 Being female   5 Obesity, heart disease and other comorbid conditions
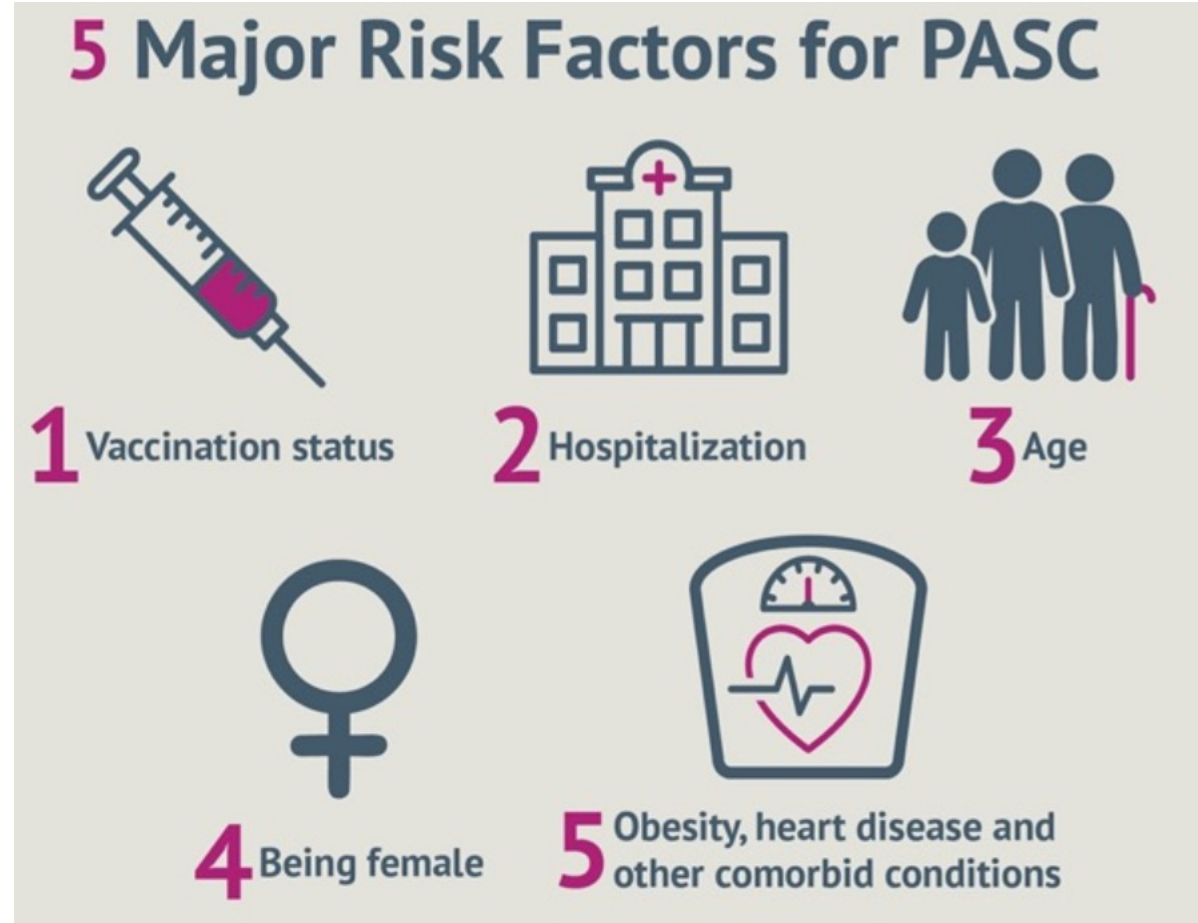
Risk Factors

- Pre-existing
  - Type 2 Diabetes
  - ADHD
  - Connective Tissue Disorders
  - Chronic urticarial/allergic rhinitis
- Presence of
  - Confusion
  - Depression
  - Dyspnea
  - Heart disease (hospitalized)

5 Major Risk Factors for PASC

1 Vaccination status 2 Hospitalization 3 Age 4 Being female 5 Obesity, heart disease and other comorbid conditions
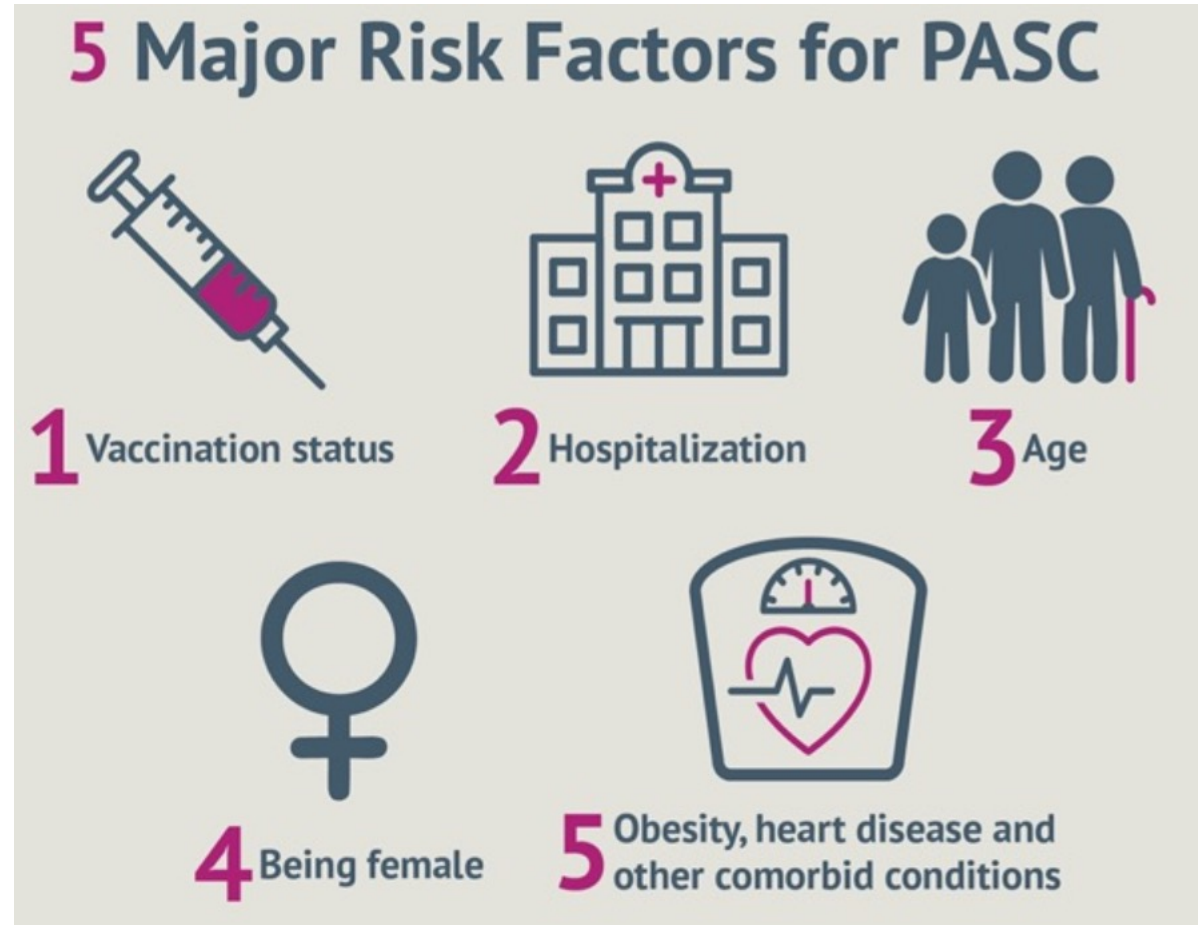
Risk Factors

- Mitigate the Risk
  - Vaccination (OR= 0.68)
  - Paxlovid (RR= 0.74)
  - Metformin (HR= 0.41)
  - Graduated return?

Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition

Yan Xie, PhD; Taeyoung Choi, MPH; Ziyad Al-Aly, MD

The effectiveness of COVID-19 vaccine in the prevention of post-COVID conditions: a systematic literature review and meta-analysis of the latest research

Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial

What is Missing?
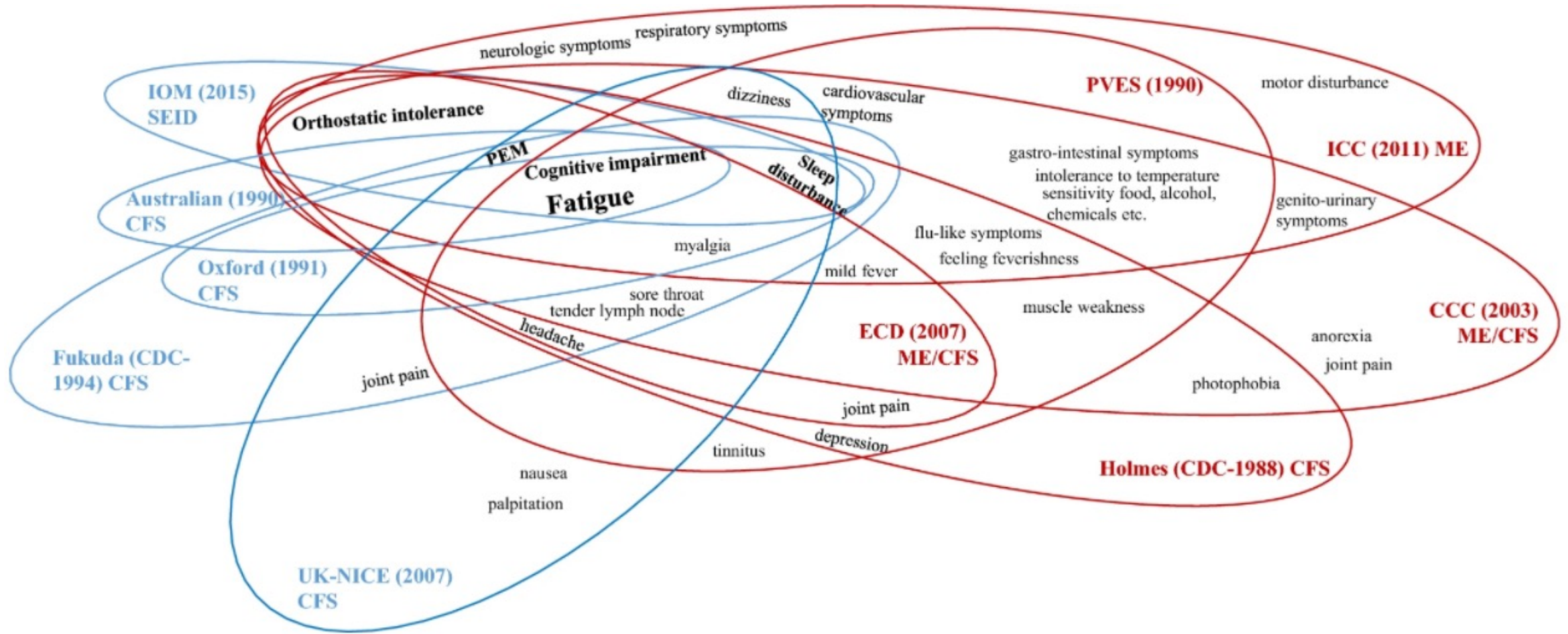
Pathophysiology

- Dozens, if not hundreds of proposed mechanisms
- Varying quality, little reproduced
- Cause and effects
- Overlapping or multiple

Proposed contributing mechanisms
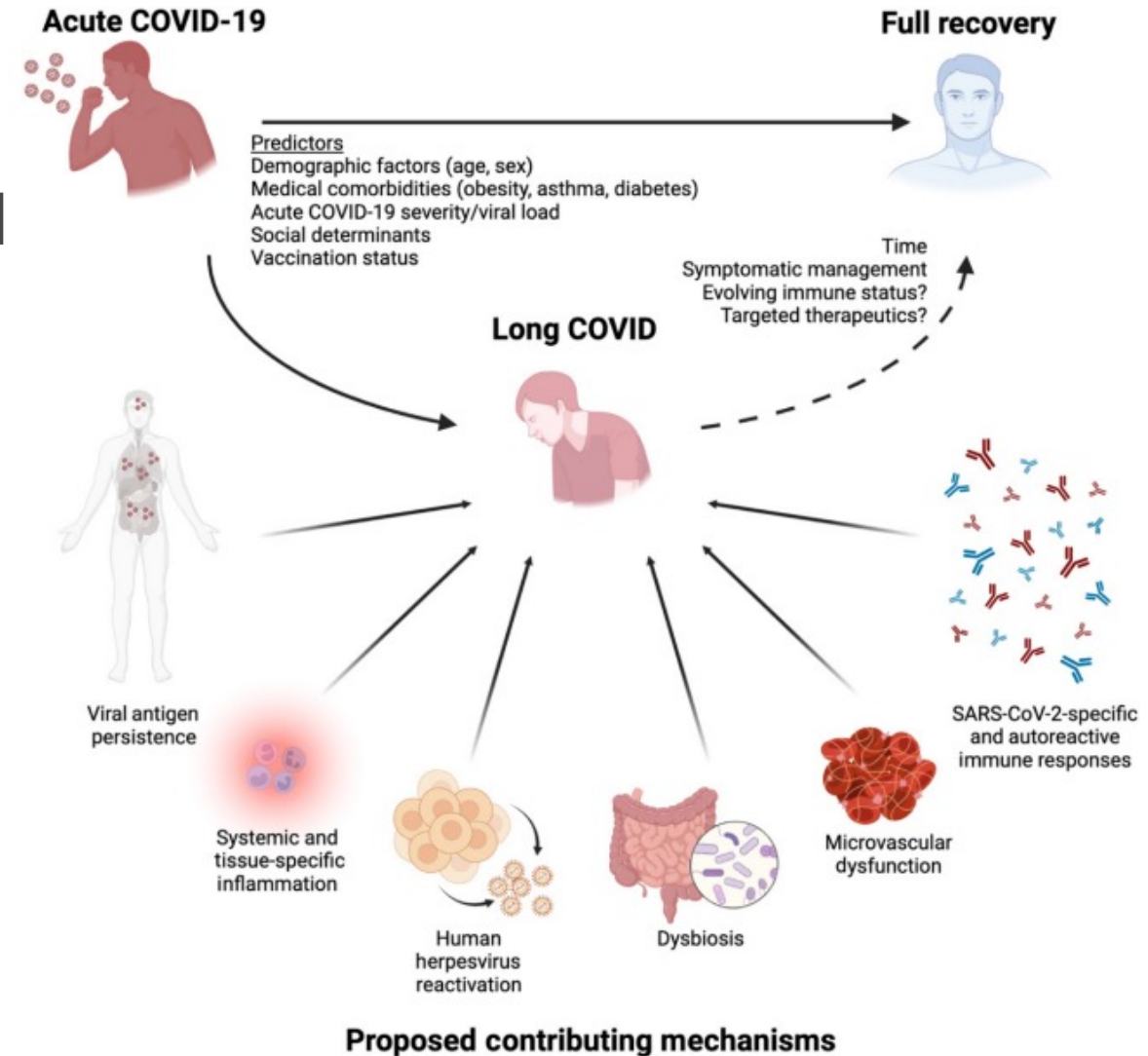
Immune Dysregulation

- Increased exhausted T Cells
- Increase in IL-4 and IL-6 secreting T cells
- Elevated PD1 expression
- Highly activated innate immune cells
- Increase type I and type III interferons
- Increase in activated B cells, non-classical monocytes
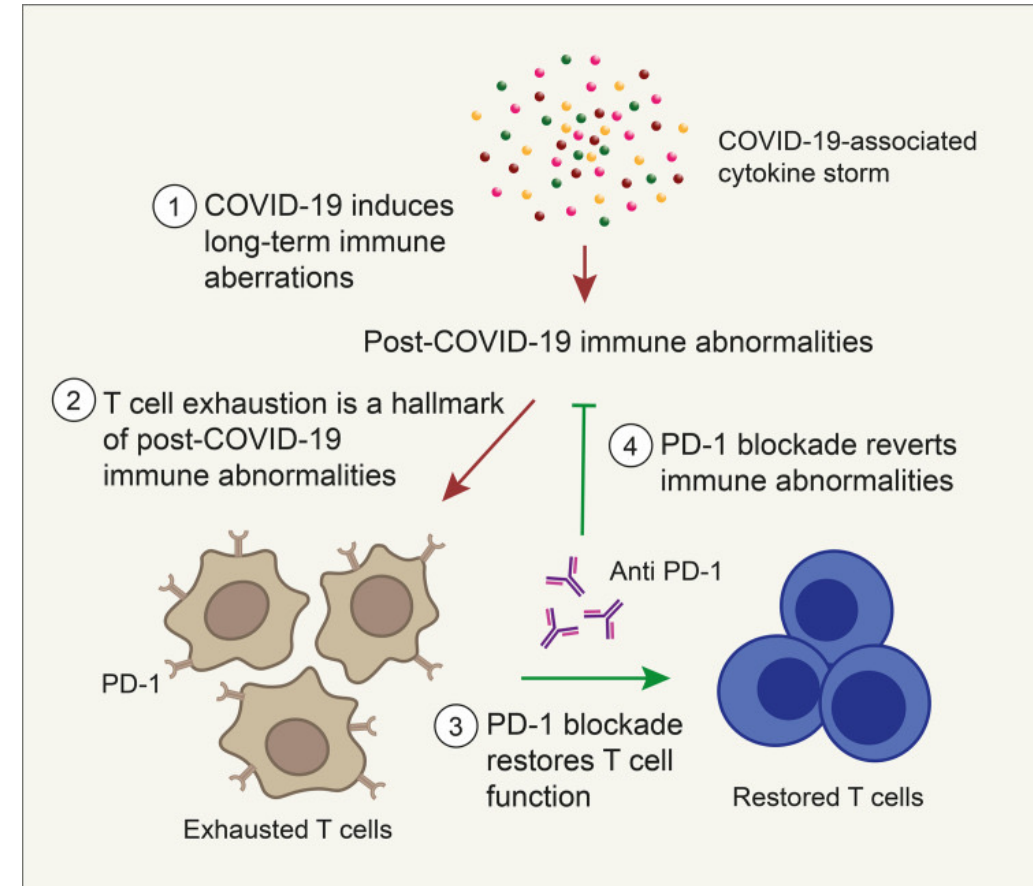
Immune Dysregulation

- Autoantibodies
  - ACE-2
  - B2-Adrenoceptor
  - Muscarinic M2 receptor
  - Angiotensin receptors
- Autoantibodies inversely correlated with protective SARS-CoV-2 antibodies
- Sex differences

Autoimmunity and immune priming

Autoimmunity and primed immune cells from molecular mimicry
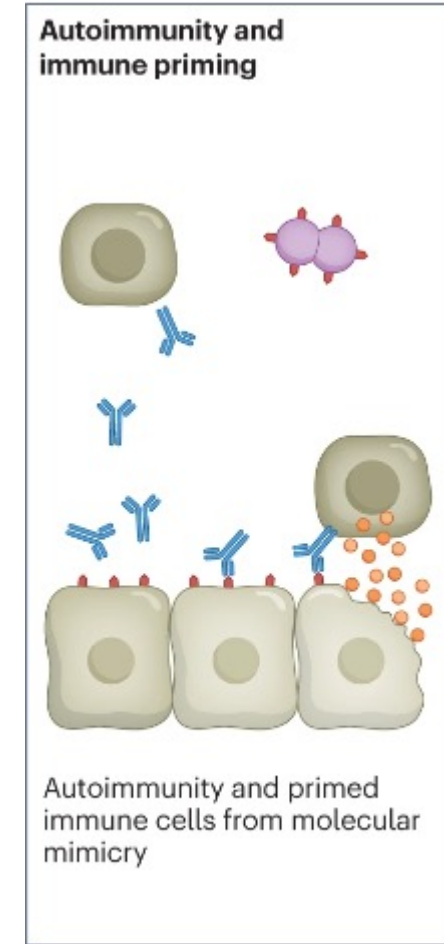
Viral Persistence

- Viral Reactivation
  - EBV
  - HHV-6
- Low Antibody Production/Insufficient Immune Response Acute Infection
- Widespread viral proteins/RNA
  - **GI,** CV, brain, muscles, eyes, lymph nodes, liver, lung tissue…
  - SARS-CoV-2 Spike Antigen
    - 60% long COVID at 12 months
    - 0% without long COVID

Immune dysregulation

Persistent infection

Viral replication

Reactivation

Immune dysregulation, with or without reactivation of underlying pathogens, including herpesviruses such as EBV and HHV-6
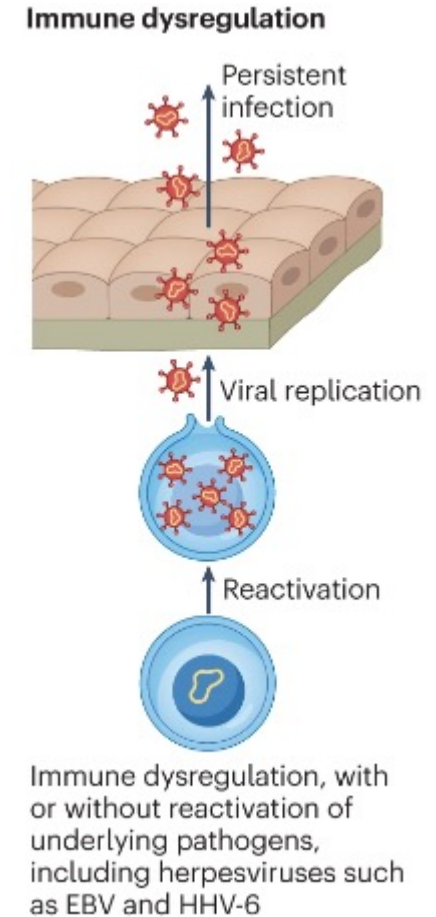
Others

- Microbiome alterations
- Microvascular blood clotting/endothelial dysfunction
- Brainstem or vagal nerve dysfunctional signaling-> Dysautonomia
- Low cortisol levels
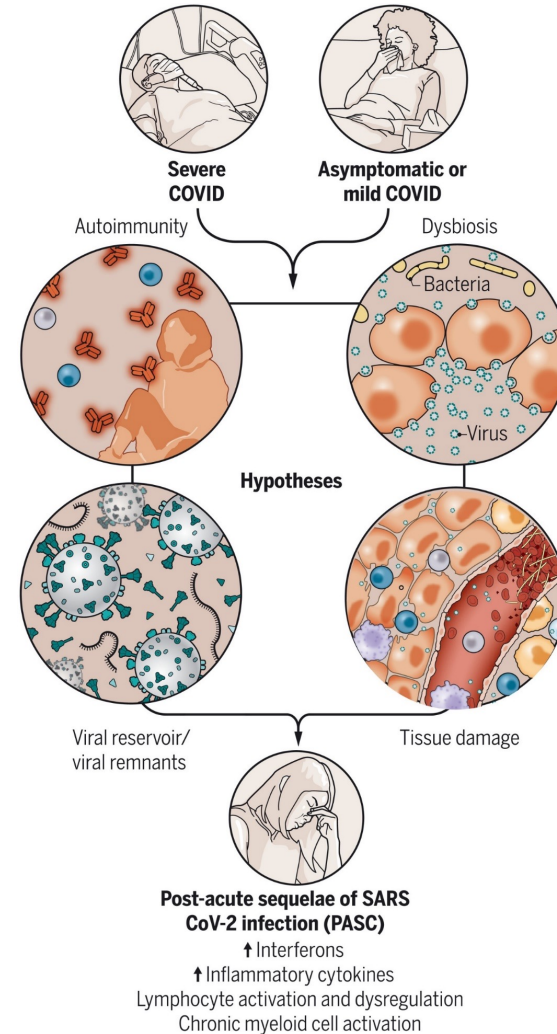
Serotonin Metabolism

Serotonin reduction in post-acute sequelae of viral infection
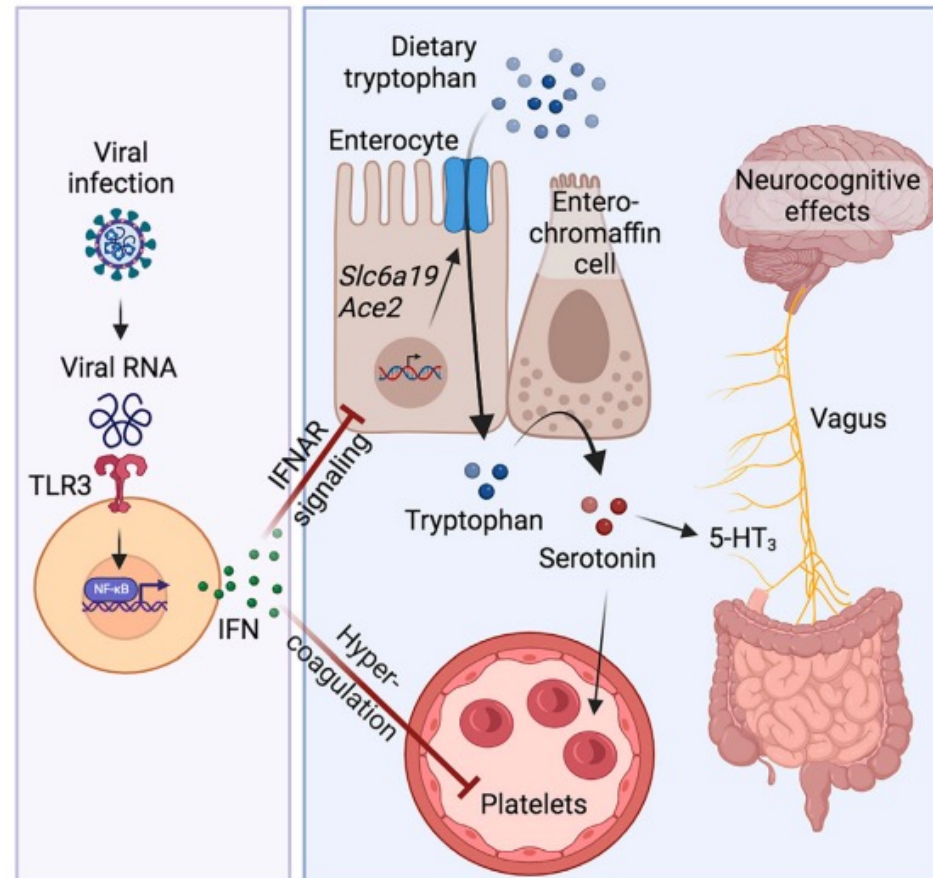
Serotonin Metabolism

Cell

Serotonin reduction in post-acute sequelae of viral infection

- 1,500 individuals with Long COVID
- Biomarkers that distinguish individuals with Long COVID from Recovered

Cluster 1: severe initial infection, long-term mobility impairment
Cluster 2: initial hospitalization, regained mobility, persistent fatigue
Cluster 3: persistent cardiorespiratory problems and fatigue
Cluster 4: strongly impaired mobility
Cluster 5: persistent memory problems and fatigue
Cluster 6: cardiorespiratory symptoms but regained mobility
Cluster 7: severe neurocognitive and cardiorespiratory symptoms
Cluster 8: mild neurocognitive symptoms

UMAP axis 2

UMAP axis 1

What is Missing?

- **CDC:** "Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions."

- Biomarkers

- Biomarkers!

- Key to understanding true prevalence
  - What cohorts
  - Monitor
  - Treatment Effects

Category	Biomarker
Acute phase protein	Albumin, C5b-9, CRP, Ferritin, Fibrinogen
Biochemical marker	1-Methylnicotinamide, 2-Phenylphenol, 3,5-Dihydroxybenzoic acid, ADA, ALT, AST, β-glucan, CPA3, Glutamine/Glutamate ratio, Indole-3-lactic acid, L-Cystein, LDH, L-Glutamine, L-Methionine, Ornithine, Pipecolic acid, Quinolinic acid, Quinolinic acid/Tryptophan, Sarcosine, S-Sulfocysteine, ST1A1, Taurine, Tryptase, uPA
Cytokine/chemokine	CCL2, CCL3, CCL4, CCL5, CCL7, CCL19, CCL20, CCL23, CXCL1, CXCL9, CXCL10, CXCL11, Flt3L, G-CSF, GM-CSF, IFN-α, IFN-β, IFN-γ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-10, IL-10Rβ, IL-12β, IL-13, IL-17, IL-18, IL-33, IP-10, M-CSF, SCF, TGF-α, TGF-β, TNF-α, TNF-β
Neurological marker	GDNF, GFAP, NGF-β, NFL, NT-3, pGFAP/pNFL
Vascular marker	Ang-2, Col1A2, Col3A1, D-dimer, ESR, ET-1, Factor VIII:C, Hemoglobin, MMP-1, MMP-9, MPO, NO, PDGF-BB, sICAM-1, sTM, sVEGFR, sVCAM-1, VEGF, VWF:Ag, VWF:pp
Others	Ab, ARTN, α-SMA, AXIN, CASP-8, CST-5, Cystatin C, Hs TnT, IGFBP-4, LBP, miRNA21, MRP8/14, NGAL, NT-proBNP/NT-BNP, OPG, OSM, SIRT2, STAMBP, TNFRSF9, Zonulin

Managing Long COVID Cases

Barriers

- Very little evidence
- Based on clinical experience and other related conditions

Evaluating and Caring for Patients with Post-COVID Conditions: Interim Guidance

Stand with AAPM&R in Our National Call to Action

Millions of Americans are Suffering from Long COVID and AAPM&R is Calling for a Comprehensive Plan to Address their Needs

COVID-19 rapid guideline: managing the long-term effects of COVID-19

NICE guideline [NG188]   Published date: 18 December 2020

STOP
DO NOT ENTER

Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients

🛑 Correction(s) for this article ⌄

Joseph E. Herrera DO, William N. Niehaus MD, Jonathan Whiteson MD, Alba Azola MD, John M. Baratta MD, MBA, Talya K. Fleming MD, Soo Yeon Kim MD, Huma Naqvi MD ... See all authors ⌄

Initial Evaluation

- Optimum timing unknown
  - Shortly after hospital discharge
  - Within a month for ongoing symptoms
  - Conservative response (allow natural recovery) for 3 months

- COVID Positivity
  - Helpful but not essential
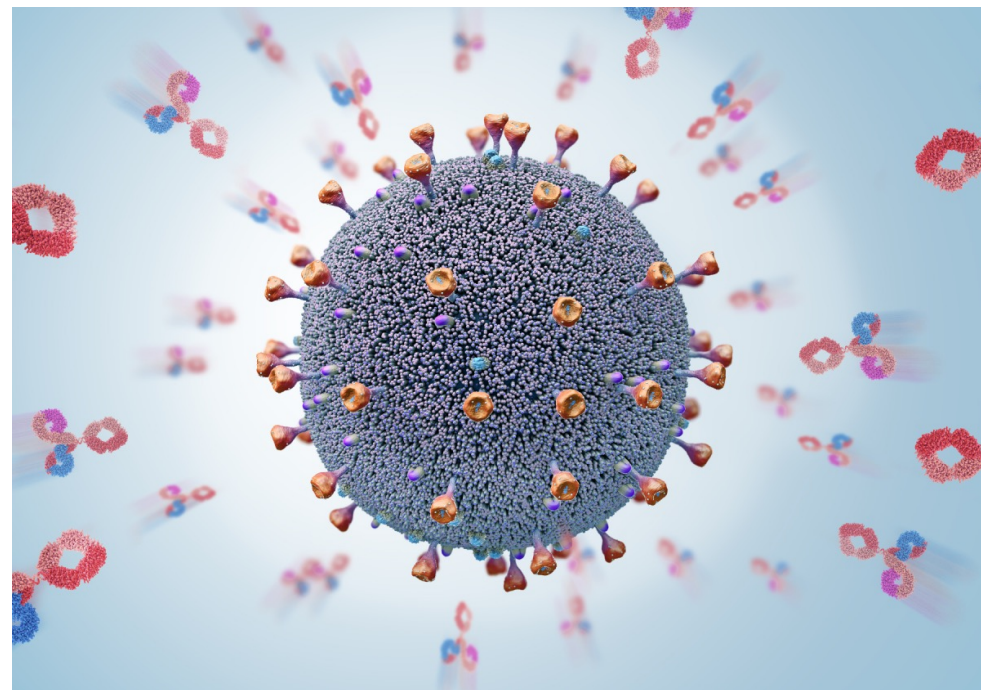
General Evaluation of Long COVID

- No universal work-up
  - Based primarily on symptoms and to rule out other conditions
  - CBC, CMP, TSH, ESR/CRP, CK, Vitamin B12, Vitamin D, ANA
  - Usually normal in Long COVID
- Harms from Excessive Testing/Referrals
  - Incidental findings
  - Anxiety
  - Radiation
  - Cost
  - Shuffled feeling

General Treatment of Long COVID

- ## No universal treatment of Long COVID
  - Underlying pathophysiology unknown- Frustrating
  - Must by tailored to symptoms of the individual
  - Palliative
  - Focus on function and quality of life
- Address Comorbidities
  - Insomnia, Sleep Disordered Breathing
  - Mood-Anxiety, Depression, PTSD, Life Stressors
  - Autonomic Symptoms
  - Pain
  - Cognitive Dysfunction
  - Dyspnea
  - Symptoms interconnected
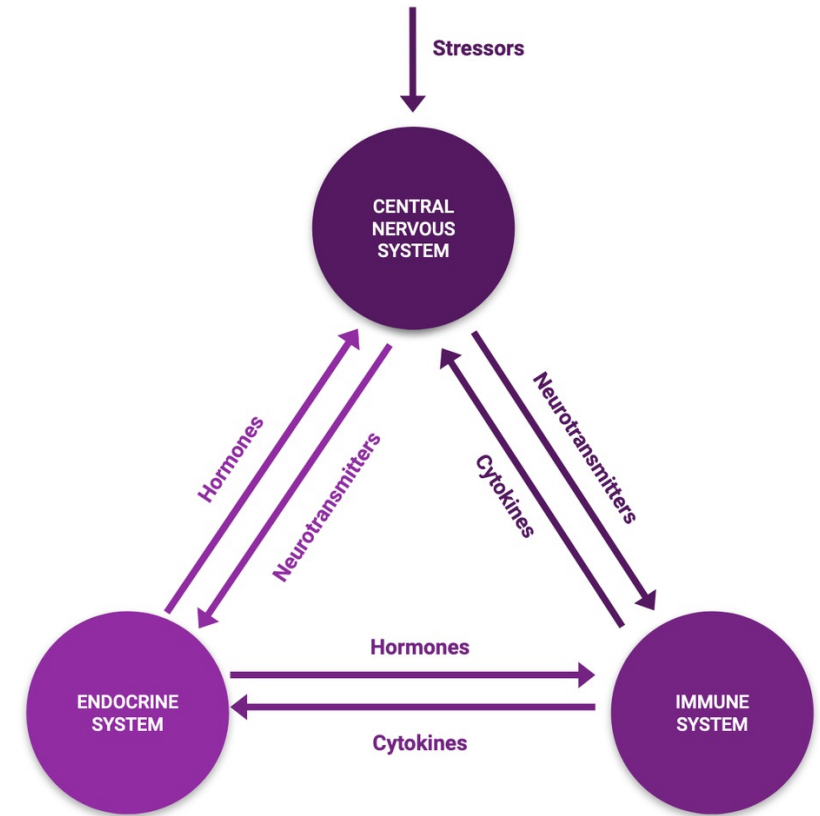
Long COVID Fatigue, Poor Endurance and Impaired Function

- **Very common!**
  - Most debilitating symptom fatigue (71%)
  - Functional impairment (9-40%)
- **Initial Assessment**
  - Screen: Nature of Fatigue, Endurance, Functional Impairment (ADLs/iADLs)
  - Fatigue Measures
    - Fatigue Assessment Scale
    - Fatigue Severity Scale
    - Functional Assessment of Chronic Illness Therapy-Fatigue
  - PEM Measure
    - De Paul Symptom Questionnaire
  - Physical Function Measure
    - 30 Second Sit-to-stand
    - 2-Minute Step
    - 6-Minute Walk

1	I am bothered by fatigue
2	I get tired very quickly
3	I don't do much during the day
4	I have enough energy for everyday life
5	Physically, I feel exhausted
6	I have problems to start things
7	I have problems to think clearly
8	I feel no desire to do anything
9	Mentally, I feel exhausted
10	When I am doing something, I can concentrate quite well

Post-Exertional Malaise

- Key feature of ME/CFS and often long COVID
- Severe exhaustion after physical, cognitive or mental exertion
- Good day-> activities-> Crash needing several days of recovery
- Patient reported 73.3% (out of 80% with fatigue) at 6 months
- Triggers

a. Triggers of relapses
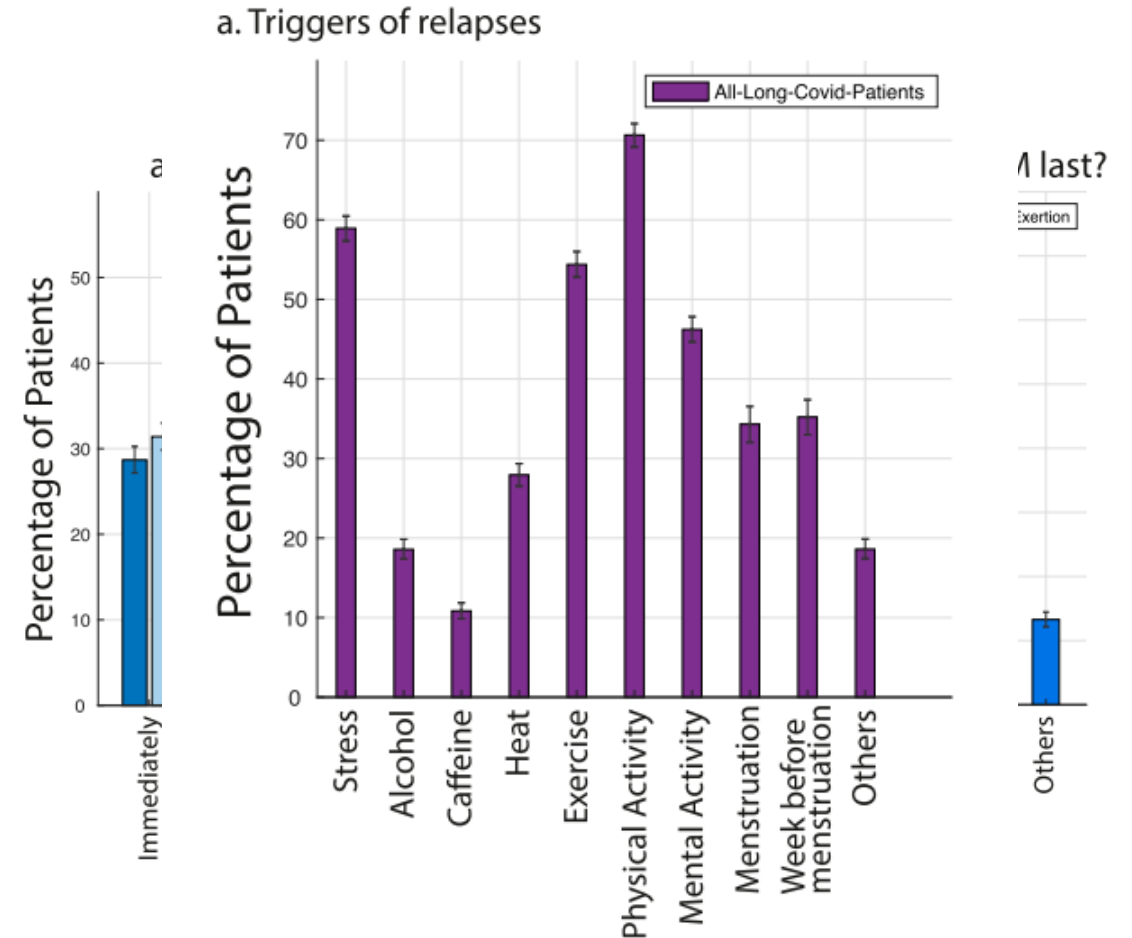
Treatment
- Post-COV...
  - Indivic...
  - Not G...
  - Famili...
- Example F...
  - Light s...
  - Isome...
  - Energ...
  - Once...
  - Mainta...
  - Incorp... diaphr...
  - Monit... follow... to cut...
- Energy Conserva... **P**ositioning

The Spoon Theory

DYSAUTONOMIA INTERNATIONAL
AWARENESS ADVOCACY ADVANCEMENT

The Spoon Theory is a creative way to explain to healthy friends and family what it's like living with a chronic illness. Dysautonomia patients often have limited energy, represented by spoons. Doing too much in one day can leave you short on spoons the next day.

If you only had 12 spoons per day, how would you use them? Take away 1 spoon if you didn't sleep well last night, forgot to take your meds, or skipped a meal. Take away 4 spoons if you have a cold.

- get out of bed
- bathe
- make & eat a meal
- go to work/school
- get dressed
- style hair
- make plans & socialize
- go shopping
- take pills
- surf the internet
- light housework
- go to the doctor
- watch TV
- read/study
- drive somewhere
- exercise

The Spoon Theory was written by Christine Miserando, which you can check out on her website www.butyoudontlooksick.com.

World PT Day 2021

TOP trying to push your limits. ...verexertion may be detrimental ...your recovery.

REST is your most important management strategy. Do not wait until you feel symptoms to rest.

...ACE your daily physical and cognitive ...tivities. This is a safe approach to ...vigate triggers of symptoms.

2021). Humility and acceptance: ...with long covid and myalgic ...ic fatigue syndrome. journal of ...sical therapy, 51(5), 197-200.

World Physiotherapy
w.world.physio/wptday

...xertional symptom

www.dysautonomiainternational.org

Date:
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Mark each ho... exacerbation,...
High ...
Low ...

	8	9	10	11

Penn Medicine

Long COVID Fatigue, Poor Endurance and Impaired Function

- **Support return to activity**
  - DME-tub shower benches
  - Parking placards
  - Work accommodations
  - Vocational counseling

TYPES OF REASONABLE ACCOMMODATIONS

1. Acquiring or modifying necessary equipment
2. Providing ergonomic furniture or computer equipment
3. Restructuring the job or work schedule
4. Adjusting training material or policies
5. Making physical changes to the building or property

DirectEmployers   #NDEAM18

Nurse J.'s Fatigue

- On further questioning
  - Sleep is restless
  - Staying awake late into the night
- Educated on sleep hygiene
- Prescribed trazadone
- Took off from work for 2 weeks to focus on recovery
- Added 15 minute breaks every two hours
- Began a structured PT program

Long COVID Fatigue, Poor Endurance and Impaired Function

- **Medications**
  - Low Dose Naltrexone
    - Weak but evolving evidence
    - Active RCTs
  - Pyridostigmine
  - Neurostimulants
    - Adderall
    - Ritalin
  - Amantadine
  - Provigil/Nuvigil

Dyspnea

◆ **Initial Assessment**
  • Symptoms: Cardiac and Pulmonary Review of Symptoms
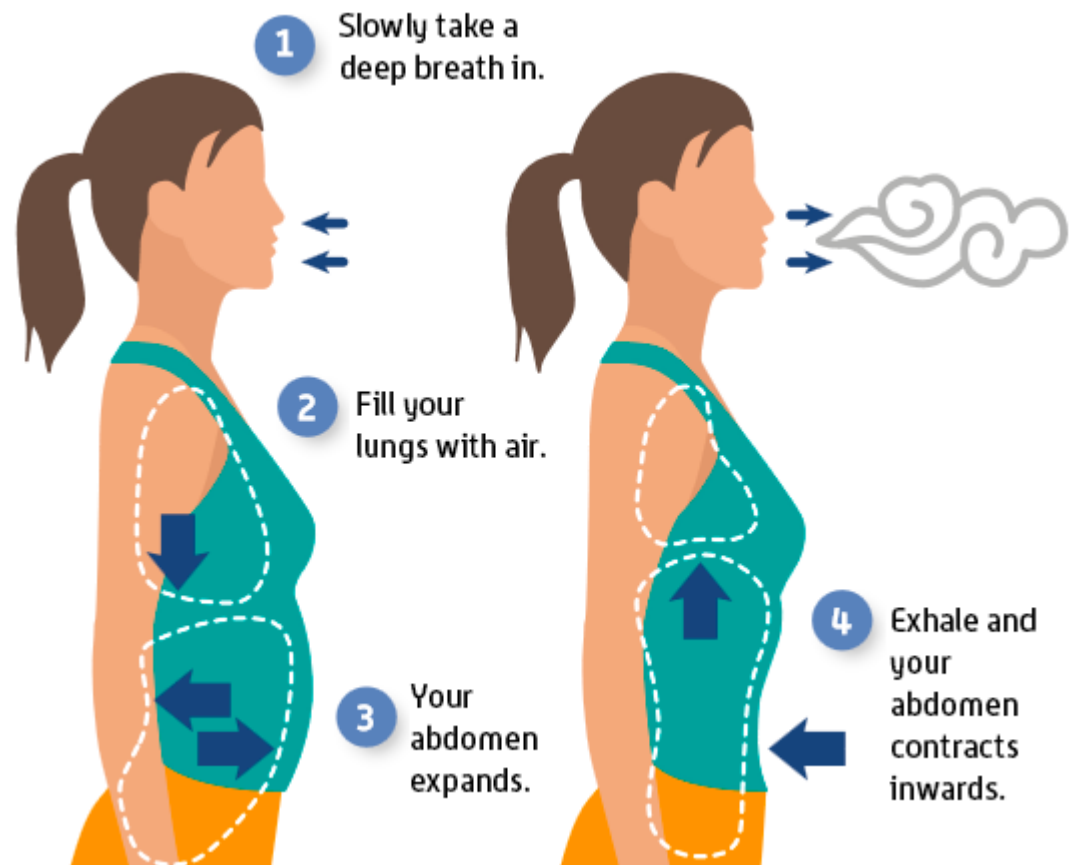 • Home pulse ox, Supplemental oxygen use

◆ **Work-up**
  • **Pulmonary Function Tests**
  • **Ambulatory Pulse Ox**
  • Other studies likely to be of lower yield
    – CT Chest
    – CPET
    – Holter Monitor
    – Echocardiogram
    – Holter Monitoring

Management of Long COVID Dyspnea

- ◆ **Shortness of Breath**
  - • Pharmacotherapy for identified underlying cardiac or pulmonary disease
  - • Breathing exercises and breathlessness management strategies
  - • Pulmonary rehabilitation

Breathing techniques and rehabilitation

Long COVID Breathing and Wellness Program with the Sadhguru Center BIDMC

1 Slowly take a deep breath in.

2 Fill your lungs with air.

3 Your abdomen expands.

4 Exhale and your abdomen contracts inwards.

Inhale
∨

THE BREATHER ™

Penn Medicine

Nurse J.'s Dyspnea

- On further questioning
    - Regular use of Advair and albuterol into her 20s
    - No longer using

- Recommended repeat PFTs and empiric treatment with albuterol

- Structured breathing program
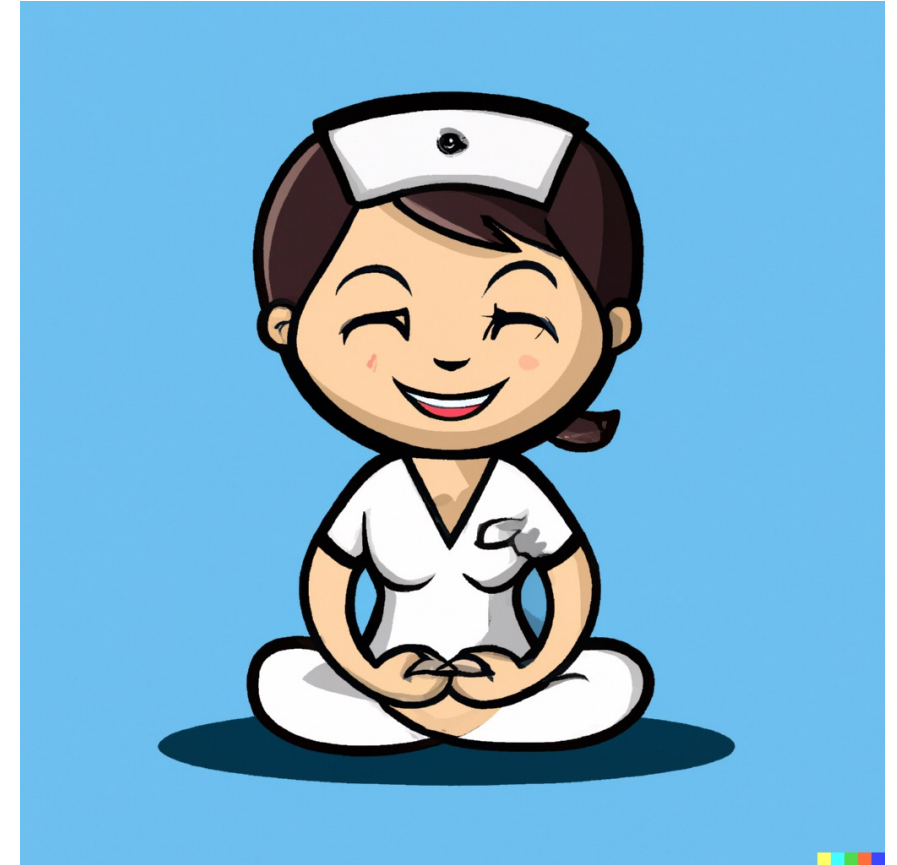
Dysautonomia Evaluation

- **NASA Lean Test**
- **Tilt-table testing**
- **Autonomic panel**

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Table I	Examinations of the autonomic nervous systems[4]	
Function test	**Test item**	**Tested system**
Ewing test	Heart rate quotient (30:15 ratio)	Parasympathetic
Breath test	Heart rate difference	Parasympathetic
Valsalva's maneuver	Heart rate quotient (Valsalva's ratio)	Parasympathetic
Schellong's test	Difference in blood pressure	Sympathetic
Grip test	Difference in blood pressure	Sympathetic

Orthostatic Vital Signs/The NASA 10-minute Lean Test

	Blood Pressure (BP)		Pulse	Comments
	Systolic	Diastolic		
Supine 1 minute				
Supine 2 minute				
Standing 0 minute				
Standing 1 minute				
Standing 2 minute				
Standing 3 minute				
Standing 4 minute				
Standing 5 minute				
Standing 6 minute				
Standing 7 minute				
Standing 8 minute				
Standing 9 minute				
Standing 10 minute				

Dysautonomia Management

- **Orthostasis/Dysautonomia/POTS**
  - Initially treat conservatively
    - Compression stockings/abdominal binder
    - Hydration/salt
    - Physical therapy
    - Recovery techniques/behavioral modification
  - Example Therapy Program
    - Supine based therapeutic movement
    - Open-chain activity
    - Symptom titrated
    - Time based-intervals
    - After 2 weeks, progress to upright activity
    - Physical counter-measures
    - Levine/CHOP
  - Pharmacologic treatment for failure of above or with notable changes on tilt table/orthostatic vital signs

Long COVID Neurologic Symptoms

- **Initial Assessment**
  - Symptoms: Confusion, memory changes, new weakness, word finding difficulty
  - Montreal Cognitive Assessment (MoCA)
 - Neuropsychological Testing
- **Cognitive Impairment**
  - Evaluate medications/polypharmacy
  - Cognitive therapy
    - Speech Language Pathology
    - Neuropsychology
      - Restorative
      - Compensatory
  - Neuro-stimulants

Nurse J.'s Cognitive Symptoms

- Nurse J. begins cognitive therapy
- Noted to have deficits of attention
  - Metacognitive strategies
  - Distraction management
  - Attention process training for verbal and non-verbal tasks
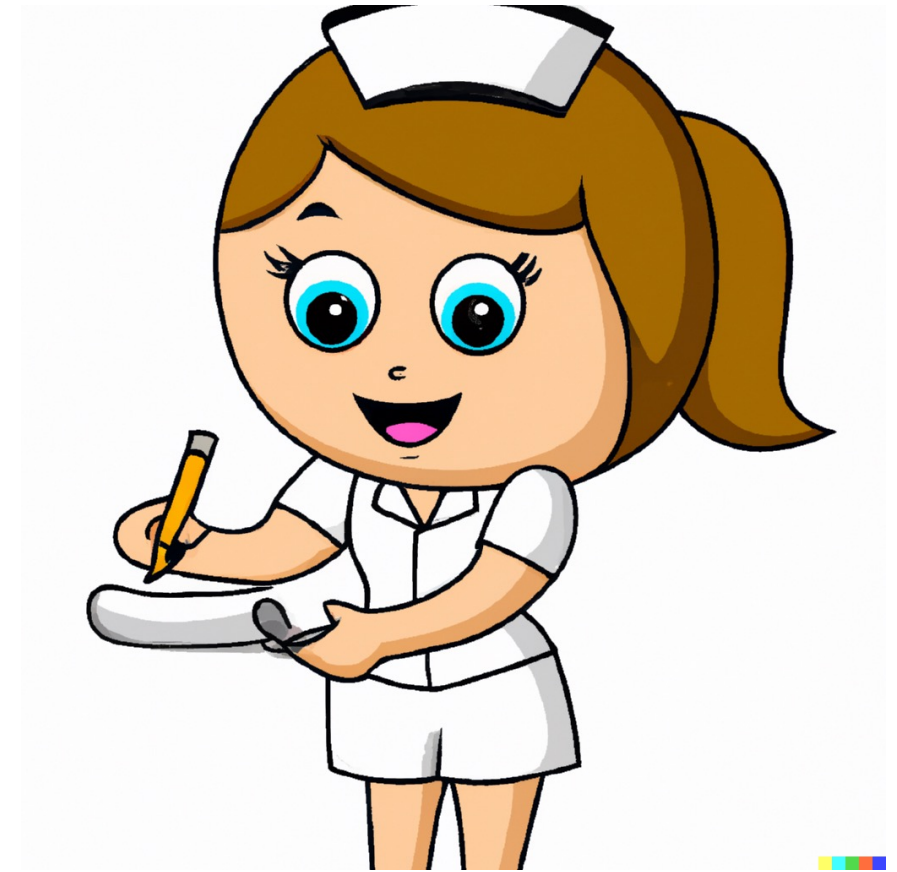
Long COVID Psychological and Emotional Issues

- **Initial Assessment**
  - Symptoms: Depression, Anxiety, PTSD, Insomnia, Suicidality
  - Hospital Anxiety and Depression Scale, PHQ, GAD-7
  - Impact of Events Scale
  - **The framing of this conversation is very important**
- **Treatment**
  - Social work: Work/employment, housing, childcare stressors
  - Anxiety and Depression
    - Psychology/Counseling
    - Psychiatric evaluation
    - Medications
  - Sleep
    - Sleep Hygiene
    - CBT
    - Medications
  - **Address uncertainty**

HEALTHY SLEEP HABITS

Improve your sleep with some positive lifestyle changes and consistent sleep habits

1 REGULAR SLEEP SCHEDULE
Try to maintain a consistent sleep pattern 7 days a week. Getting up at the same time every day can help.

2 RELAXING BEDTIME ROUTINE
Spend time before bed relaxing: read a book, meditate, stretch, do yoga, have a shower or bath. Avoid difficult conversations, activities or work.

3 AVOID STIMULANTS
Don't drink caffeine, sugary or energy drinks in the evening. Avoid nicotine before bed. Only drink alcohol in moderation at night, if at all.

4 GOOD SLEEP ENVIRONMENT
Keep your bedroom clean, tidy and comfortable. Use a quality mattress and bedding. Keep the bedroom aired, and a temperature between 60 -70 °F (17-21 °C)

5 BLOCK OUT NOISE AND LIGHT
Make sure the bedroom is dark and quiet. Use blackout curtains or a sleep mask. Use earplugs, white noise, a fan or music to mask external noise.

6 ONLY SLEEP AND INTIMACY
Only use the bed for sleep and intimacy with a partner. Avoid watching TV or using other devices in bed. That will help associate the bed with sleep.

7 EXERCISE AND DAYLIGHT
Try to do regular exercise, but not too intense before bedtime. Spend time outside in the daylight. Even a short walk during the day can improve sleep.

8 EAT WELL
Try to eat a balanced, healthy diet. Avoid heavy, fatty, fried or spicy food late in the evening if you get indigestion. Bananas, yogurt or healthy cereal are good bedtime snacks.

Created by No Sleepless Nights

Should individuals get the vaccine and when?

- Yes, recommended by CDC

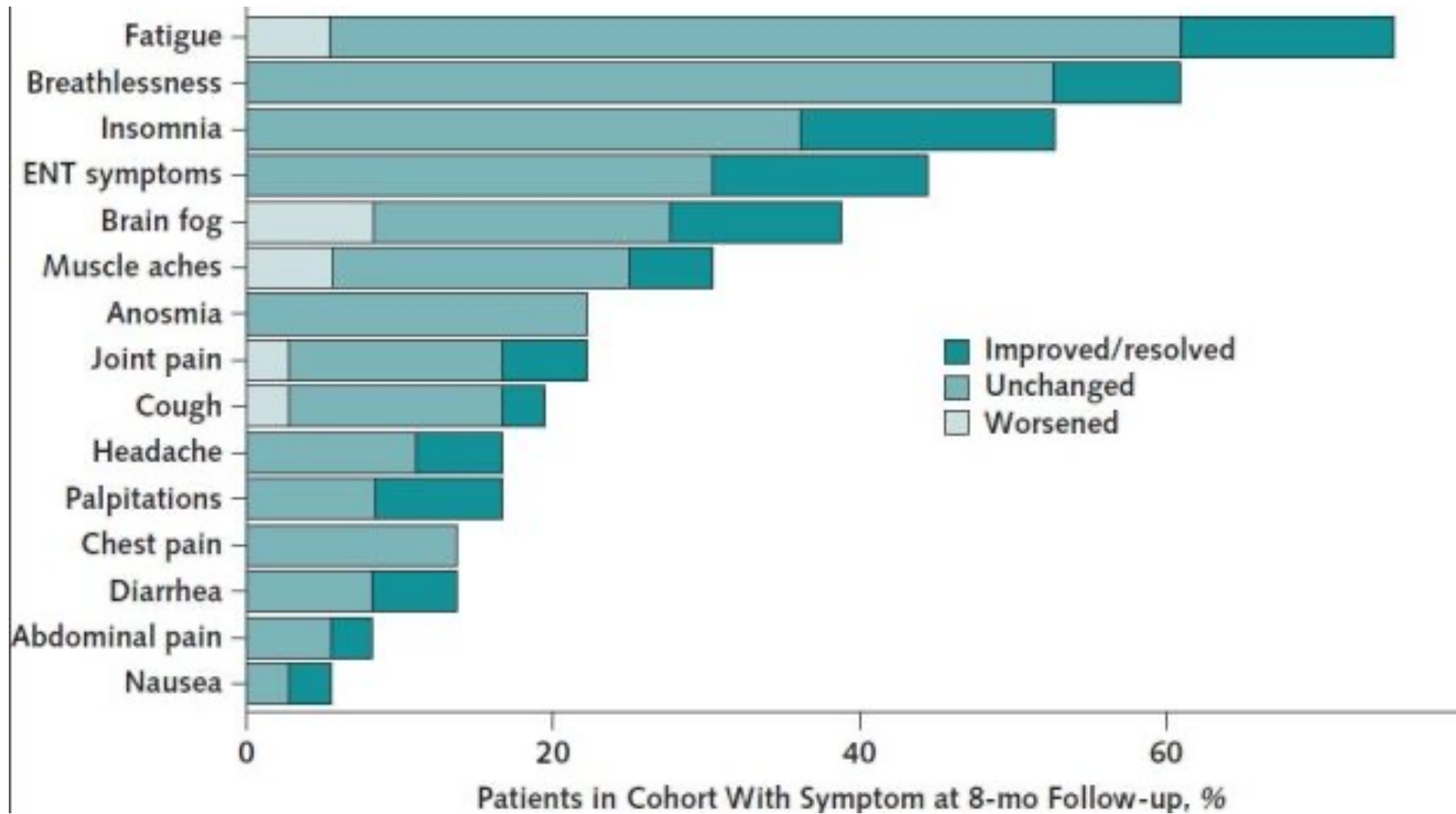Figure: Horizontal stacked bar chart showing percentage of patients in cohort with each symptom at 8-month follow-up, categorized as Improved/resolved, Unchanged, or Worsened.

Symptoms (top to bottom): Fatigue, Breathlessness, Insomnia, ENT symptoms, Brain fog, Muscle aches, Anosmia, Joint pain, Cough, Headache, Palpitations, Chest pain, Diarrhea, Abdominal pain, Nausea

X-axis: Patients in Cohort With Symptom at 8-mo Follow-up, %

Legend:
- Improved/resolved
- Unchanged
- Worsened

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8252827/

Accommodations

Guidance on "Long COVID" as a Disability Under the ADA, Section 504, and Section 1557

U.S. Department of Health
Human Services
Office for Civil Rights

U.S. Department of Justice
Civil Rights Division
Disability Rights Section

Although many people with COVID-19 get better within weeks, some people continue to experience symptoms that can last months after first being infected, or may have new or recurring symptoms at a later time. [1] This can happen to anyone who has had COVID-19, even if the initial illness was mild. People with this condition are sometimes called "long-haulers." This condition is known as "long COVID." [2]

In light of the rise of long COVID as a persistent and significant health issue, the Office for Civil Rights of the Department of Health and Human Services and the Civil Rights Division of the Department of Justice have joined together to provide this guidance.

This guidance explains that long COVID can be a disability under Titles II (state and local government) and III (public accommodations) of the Americans with Disabilities Act (ADA), [3] Section 504 of the Rehabilitation Act of 1973 (Section 504), [4] and Section 1557 of the Patient Protection and Affordable Care Act (Section 1557). [5] Each of these federal laws protects people with disabilities from discrimination. [6] This guidance also provides resources for additional information and best practices. This document focuses solely on long COVID, and does not address when COVID-19 may meet the legal definition of disability.

The civil rights protections and responsibilities of these federal laws apply even during emergencies. [7] They cannot be waived.

1. **What is long COVID and what are its symptoms?**

Consider Work Accommodations
- Gradual Return
  - Hours
  - Days per Week
- Breaks Throughout The Day
- Positioning
- Parking
- Avoid Exacerbations->Step Back

Nurse J. Outcome

- After 3 months in this program
- Much better, not 100%
  - Improved MOCA
  - Improved SF-36
- Back to full time at work
- Returned to community activities

Care Models for Long COVID

Area of Need

- **Individuals who had survived their initial COVID infection were noted to have significant deficits in physical and cognitive function worsening quality of life.**

- **These patients did not have a home in the medical system.**

- **Feeling of being shuffled from specialist to specialist— "gas-lit"**

- **Lack of expertise in a challenging new condition**

National Guidance

- NICE: **One stop multidisciplinary** clinics are recommended, led by a doctor with relevant specialist skills and experience. NHS England has also emphasized the importance of multidisciplinary assessment and diagnostics being available in long covid clinics to **avoid multiple referrals to different specialists.**

- CDC: **Multidisciplinary** post-COVID care centers based in **a single physical location** can provide a comprehensive and coordinated treatment approach to COVID-19 aftercare

Partnerships-Clinicians

- ◆ **Models**
  - Hub and Spoke
  - Integrated
- ◆ **Commonly Involved**
  - PM&R
  - PT
  - Pulmonology
  - Cardiology
  - Neurology
- ◆ **Interdisciplinary Meetings**
- ◆ **Primary Care Partnership**
  - Education
  - Communication
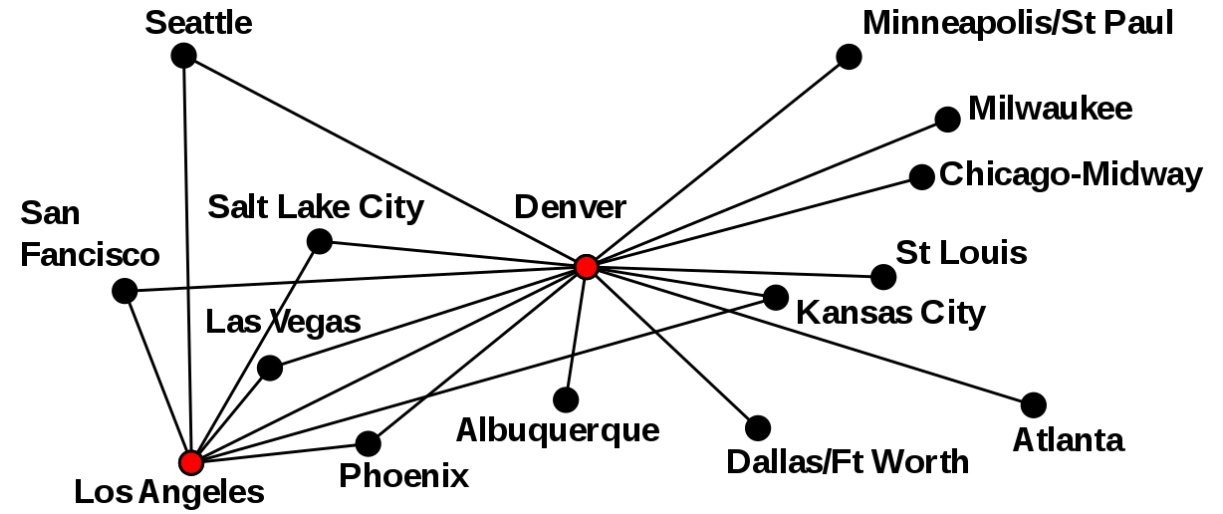
Systematic Review of Long COVID Clinic Models

◆ Decary et al. (2021) review of 12 international care models

- Principles
  - **Multidisciplinary Teams (92%)**
  - **Integrated Teams (67%)**
  - **Self-Management (58%)**
  - **Coordination of Care (58%)**
  - Evidence-Based Care (58%)

- Components
  - Standardized Symptoms Assessment (92%)
  - **Referral System (83%)**
  - **Follow-up System (83%)**
  - Virtual Care (83%)
  - Home-Based Care (58%)

◆ **Point of Contact**

- Synthesize information
- Discuss research/literature
- Available symptom questions

◆ **Accessibility**

- Timely appointments
- Schedule routine follow-up

◆ **Self-Management**

- Tools they can apply to daily life
- Non-pharmacologic techniques
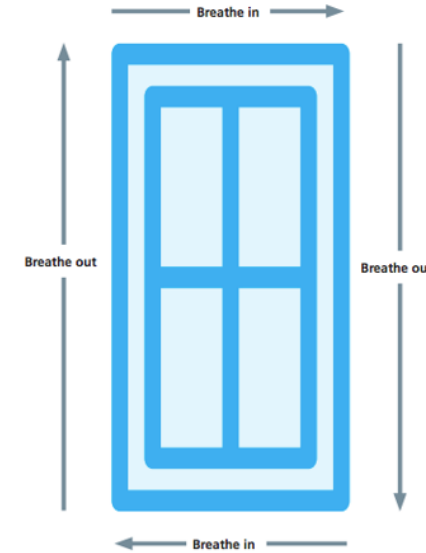
Pursed lip breathing

Breathe in — Breathe out
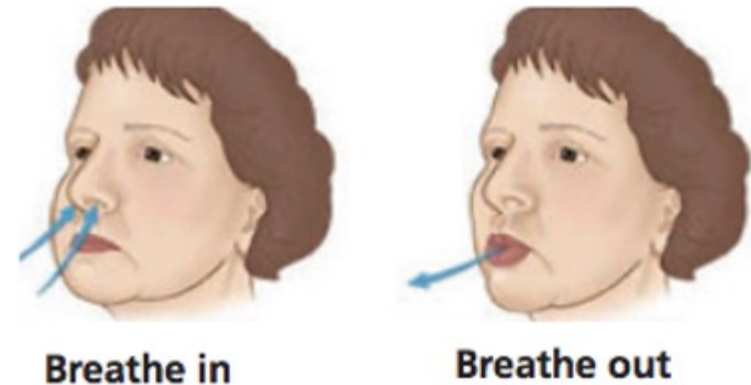
Partnership - Community

- **Social work and case management**
- **Patient advocacy groups**
  - Research
  - Clinical initiatives
- **Support groups**
  - 33% of Long COVID clinics hosted
  - Body Politic
- **Publicly Available Resources**
  - Dysautonomia International
  - ME/CFS and Fibromyalgia Self-Help Program

SURVIVORCORPS.COM/PCCC
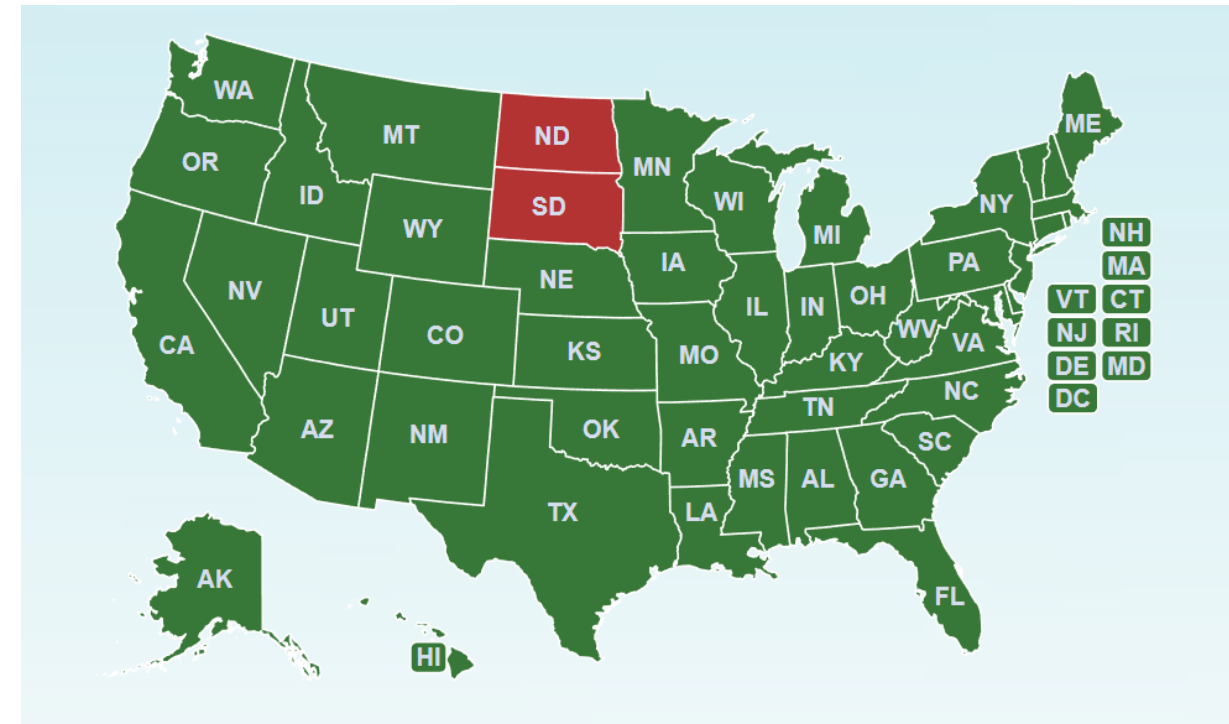
Barriers to Developing a Long COVID Clinic

- **Resource intensive**
  - 24% reported need for more staffing, physicians, or case management
- **Time**
  - Coordination (different EMRs)
  - Record review
  - Communication
- **Paperwork-Disability Forms**
- **Lack of clear evidence**
- **Delays in accessing services**
- **Mental health support**
- **Research Assistance**
- **Administrative Support**

Integrated Care Summary

- Integrated care is a potential method to improve the care of individuals with long COVID

- Numerous integrated care models have been implemented

- Can be resource intensive and requires significant coordination between providers

- Preliminary evidence suggesting benefits of rehabilitation as part of the team

- No research yet that suggests if one model is more effective than others

- **Need for high quality studies on care models**

  - Ultimately will impact insurance reimbursement, policy planning and clinic support

Do People Get Better?

	Total (n=1276)		
	6 month	12 month	p value
Sequelae symptom			
Any one of the following symptoms	831/1227 (68%)	620/1272 (49%)	<0·0001
Fatigue or muscle weakness	636/1230 (52%)	255/1272 (20%)	<0·0001
Sleep difficulties	335/1230 (27%)	215/1272 (17%)	<0·0001
Hair loss	268/1230 (22%)	135/1272 (11%)	<0·0001
Smell disorder	135/1230 (11%)	57/1272 (4%)	<0·0001
Palpitations	118/1230 (10%)	117/1272 (9%)	0·88
Joint pain	132/1225 (11%)	157/1272 (12%)	0·13
Decreased appetite	97/1230 (8%)	37/1272 (3%)	<0·0001
Taste disorder	89/1230 (7%)	37/1272 (3%)	<0·0001
Dizziness	69/1230 (6%)	65/1272 (5%)	0·56
Diarrhoea or vomiting	17/1229 (1%)	11/1272 (1%)	0·26
Chest pain	57/1225 (5%)	92/1272 (7%)	0·0023
Sore throat or difficult to swallow	47/1230 (4%)	44/1272 (3%)	0·57
Skin rash	39/1230 (3%)	55/1272 (4%)	0·10
Myalgia	33/1225 (3%)	54/1272 (4%)	0·013
Headache	25/1225 (2%)	61/1272 (5%)	0·0001
mMRC score	..	..	0·014
0	872/1185 (74%)	891/1271 (70%)	..
≥1	313/1185 (26%)	380/1271 (30%)	..
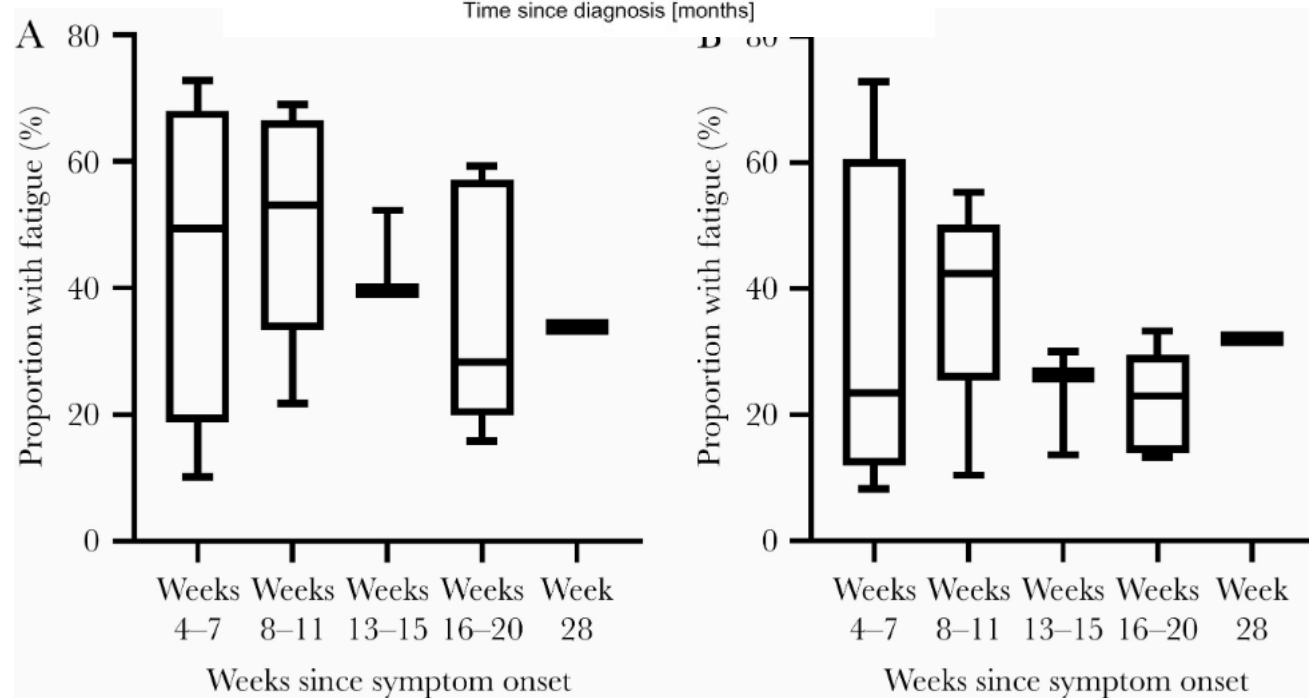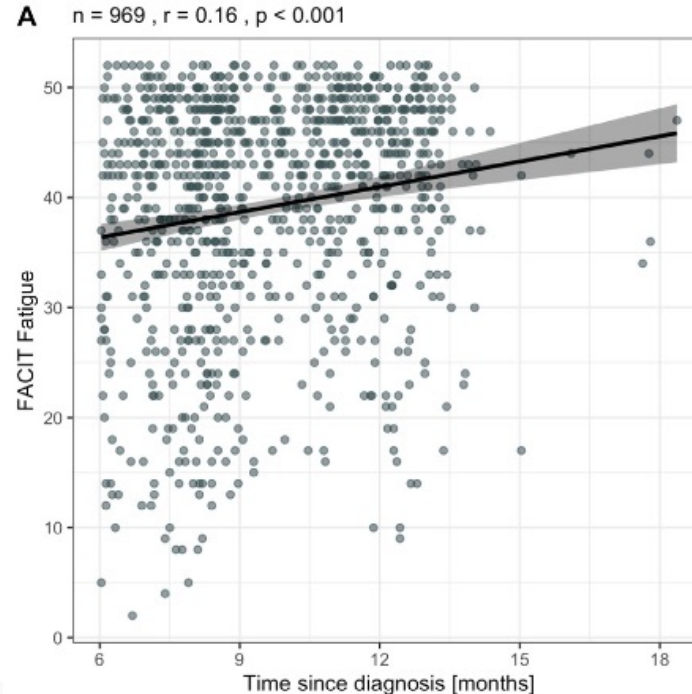
A n = 969 , r = 0.16 , p < 0.001

Do People Get Better?

## Trajectories of the evolution of post-COVID-19 condition, up to two years after symptoms onset

Clemence Servier [1], Raphael Porcher [1,2], Isabelle Pane [1], Philippe Ravaud [1,2,3], Viet-Thi Tran [1,2,*]

[1] Université Paris Cité, METHODS Team, CRESS, INSERM, INRA, Paris, France
[2] Assistance Publique-Hôpitaux de Paris, Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France
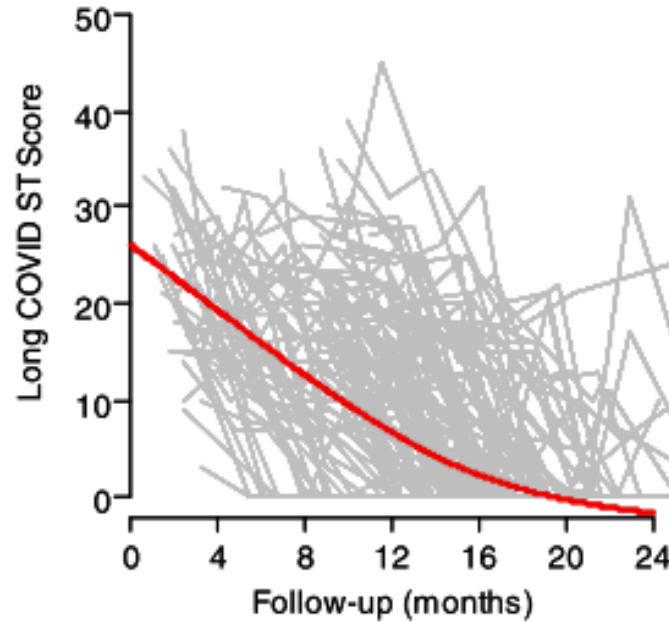[3] Columbia University Mailman School of Public Health, Department of Epidemiology, New York, USA
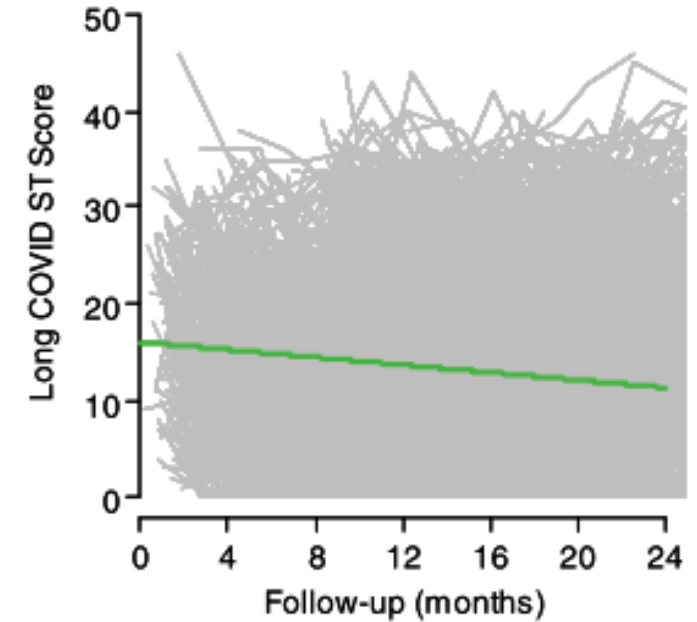
Do People Get Better?
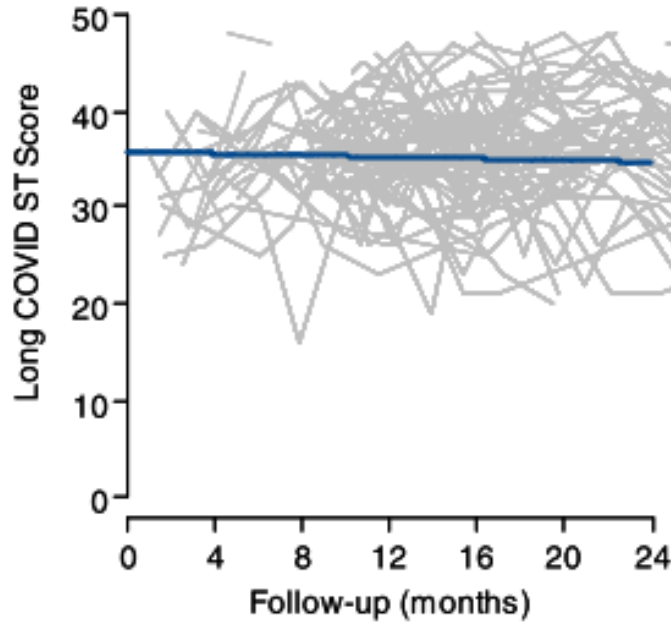
Highly Persistent Symptoms
4%
-Older
-Hx of Systemic Disease
-Palpitations/Cardiac Symptoms

Rapidly Decreasing
5%
-Younger
-Confirmed infection
-Diarrhea/Back pain

Slowly Decreasing
91%
-History of IBS/FM/CFS/Tension HA

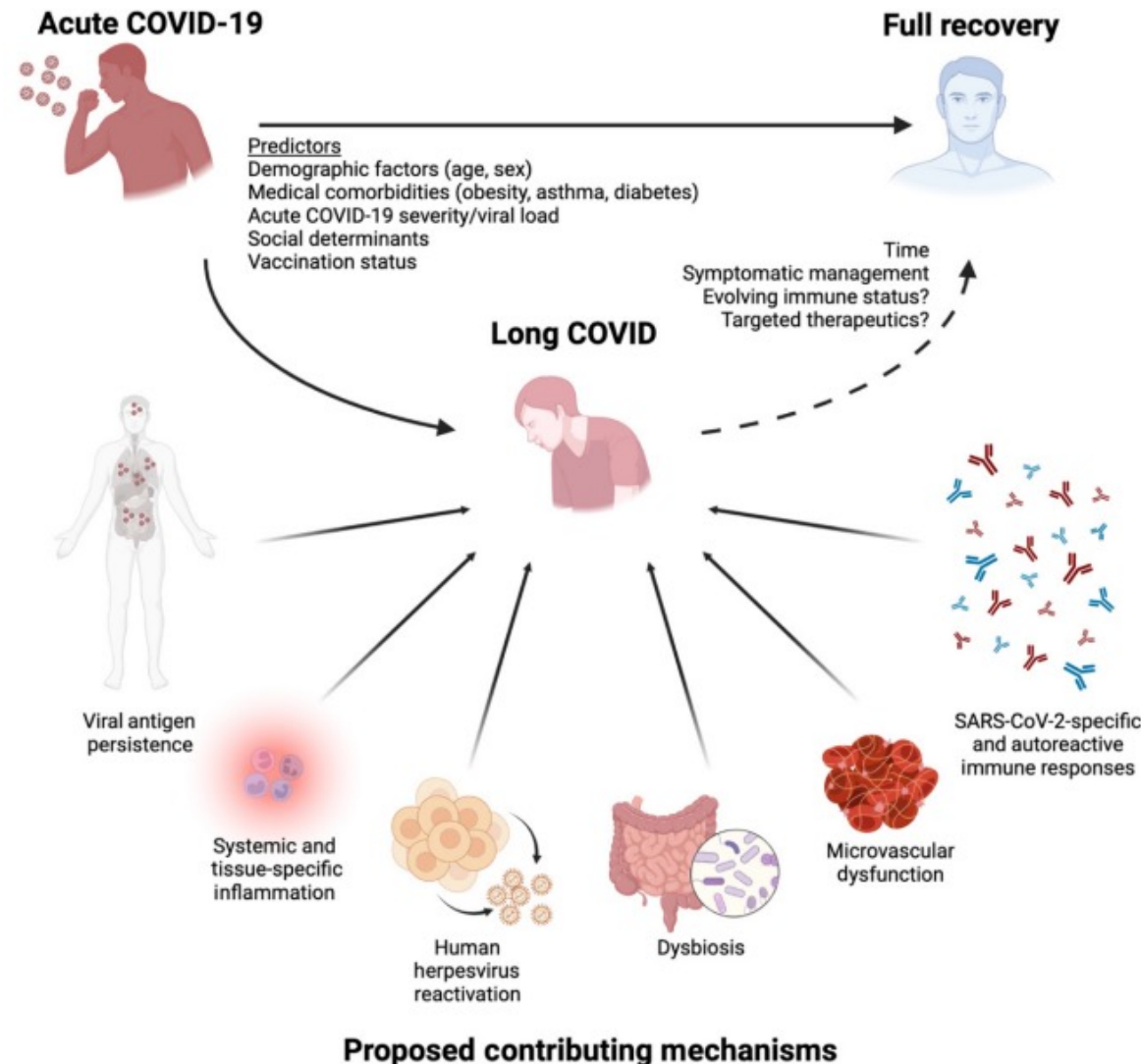**Correlate with Mechanisms/Biomarkers?**

	Mean (SD) composite score^						Diff-in-Diff (95% CI)	P-value
	ME/CFS (N = 104)			PASC (N = 20)				
	Baseline	1-year	P-value	Baseline	1-year	P-value		
Fatigue and sleep								
Fatigue	80.3 (18.4)	74.9 (21.5)	0.053	70.6 (19.1)	56.2 (23.1)	**0.039**	−9.09 (−17.30, −0.88)	**0.03**
Unrefreshed after you wake up in the morning	76.8 (22.7)	70.4 (25.5)	0.057	59.4 (29.5)	45.0 (24.1)	0.100	−7.83 (−19.51, 3.86)	0.189
Post-exertional fatigue								
Minimum exercise makes you physically tired	74.3 (25.2)	70.8 (25.3)	0.32	66.9 (30.7)	51.9 (32.0)	0.14	−11.48 (−21.32, −1.64)	**0.022**
Next-day soreness/fatigue after everyday activities	67.7 (27.6)	66.4 (24.4)	0.72	56.2 (26.7)	46.9 (31.1)	0.31	−8.06 (−19.86, 3.74)	0.181

Lessons

Long COVID - Goal Setting

- **May not be able to address underlying pathology-yet**
- **Address comorbidities**
  - Autonomic Dysfunction
  - Insomnia/Sleep Apnea
  - Depression/Anxiety
- **Palliative and symptom based**
- **Goals**
  - Feel better
  - Improve function
  - Achieve patient objectives
- **Manage expectations**
  - Reassurance in some cases
    - Recovery can be slow and occur late
  - Incremental changes
  - May not get to 100%

Acute COVID-19

Predictors
Demographic factors (age, sex)
Medical comorbidities (obesity, asthma, diabetes)
Acute COVID-19 severity/viral load
Social determinants
Vaccination status

Full recovery

Time
Symptomatic management
Evolving immune status?
Targeted therapeutics?

Long COVID

Viral antigen persistence

Systemic and tissue-specific inflammation

Human herpesvirus reactivation

Dysbiosis

Microvascular dysfunction

SARS-CoV-2-specific and autoreactive immune responses

Proposed contributing mechanisms

Final Thoughts

Long-Haul Covid Patients Put Hope in Experimental Drugs

People suffering from debilitating symptoms for months after getting sick with Covid are searching for relief

- ***Beware…***
  - Misinformation
  - Some people out there trying to sell things…
  - It is not known if OTC vitamins/supplements are helpful, harmful, or have no effect on symptoms
- **Self-Management Tools Can Be Very Helpful**
- **Symptoms Interconnected**
- **Continuity of Care**
  - Generally follow-up 1 to 2 months
  - Point of contact for post-COVID symptoms

Moving Forward

- **Focus will need to change to better understand:**
  - Mechanisms behind persistent symptoms
  - Who is more likely to have post-covid and why
    - Clustering not based on symptoms but pathophysiology
  - What treatments are effective
    - And how they relate to mechanism(s)
  - Long term prognosis
- **Biomarkers**
  - Crucial to identify cohorts
  - Monitor and Evaluate Treatment Responses

Questions

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