POST COVID SYNDROME
CLINICAL PERSPECTIVE

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Mayo Clinic

Updated 9/12/22

THE STORY

ICU Nurse

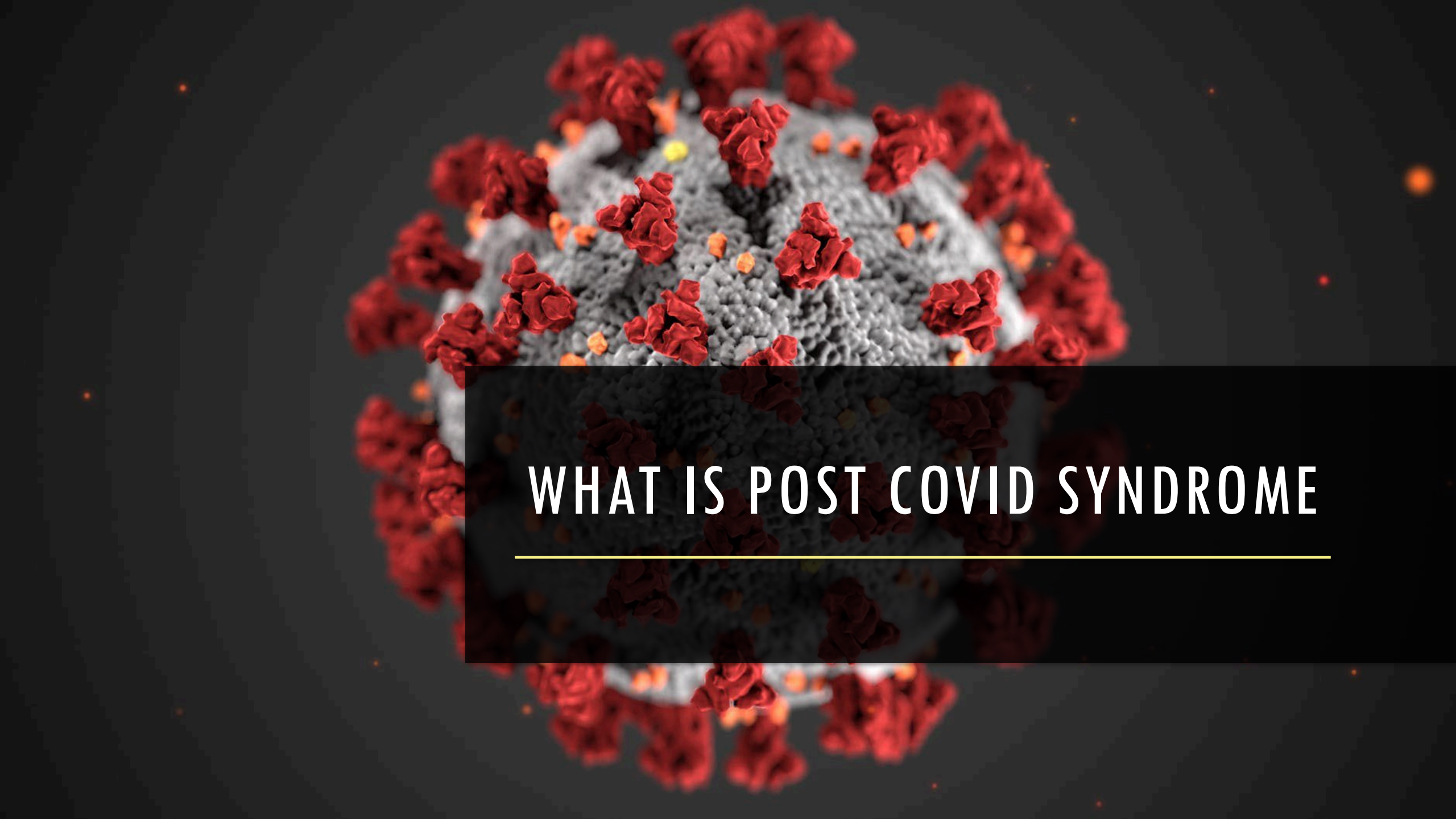
COVID-19 6 weeks ago

Work related

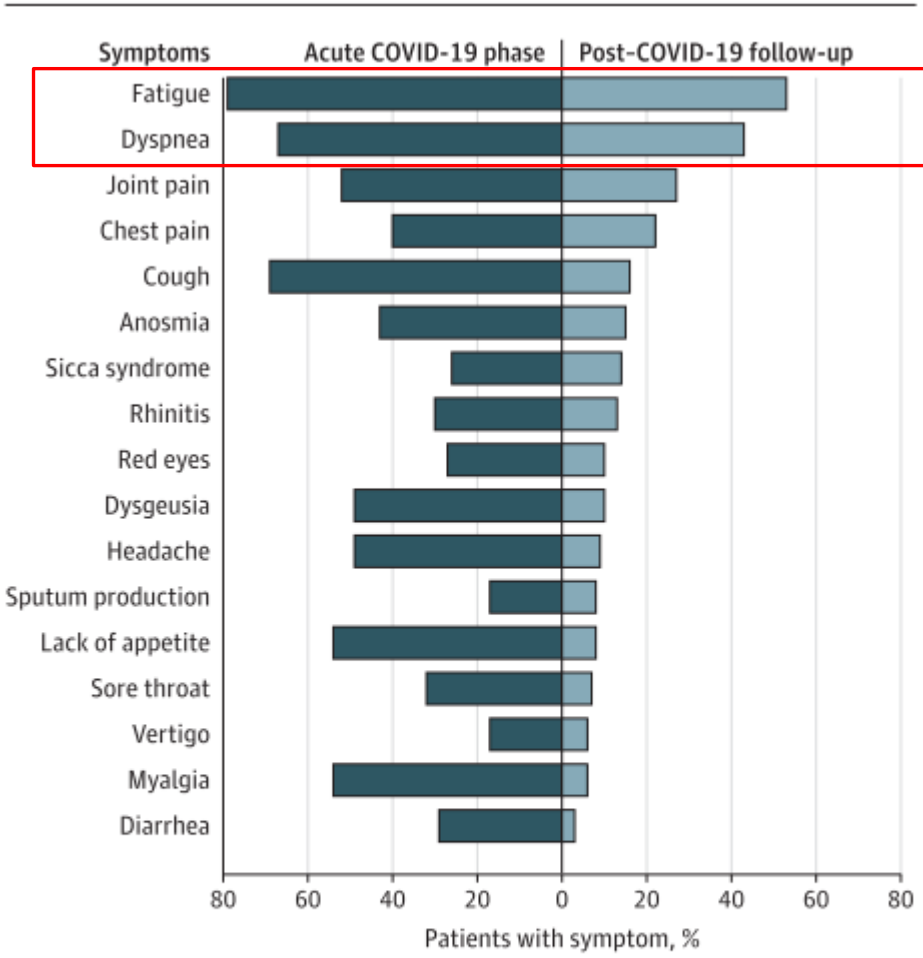
Symptoms:

- Fatigue
- Troubles thinking
- Food sensitivity
- Anxious

Off work for 1.5 months



WHAT IS POST COVID SYNDROME



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)–related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

Carfì A, Bernabei R, Landi F, Group GAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. Aug 2020;324(6):603-605. doi:10.1001/jama.2020.12603

CARP POPULATION

- Fatigue 80%
- Respiratory 59%
- Neurologic 59%
- Cognitive impairment 45%
- Sleep disturbance 30%
- Mental health sx 26%

Vanichkachorn G, Vanichkachorn.greg@mayo.edu, Newcomb R, et al. Post COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at the Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clinic Proceedings*. 2021;0(0)doi:10.1016/j.mayocp.2021.04.02

CARP POPULATION UNIQUE SX

- Tinnitus
- Prolonged loss of taste and smell
- Hair shedding (telogen effluvium)
- Syncope
- Sinus discomfort
- GI Symptoms

RISK FACTORS

June 2022 study

1.1 million patients (EHR and survey)

- Advanced age
- Female gender
- White ethnicity
- Poor pre infection health
- Elevated BMI
- Asthma

EJ T, DM W, AJ W, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nature communications*. 06/28/2022 2022;13(1)doi:10.1038/s41467-022-30836-0

RISK FACTORS

August 2022

732 Patients

56% reported mild or asymptomatic acute infection

Group	Odds of Long COVID
Moderate infection	3.01 (95% CI 1.21, 7.47)
Severe infection	3.62 (95% CI 1.31, 10.03)

Moy FM, Hairi NN, Lim ERJ, Bulgiba A. Long COVID and its associated factors among COVID survivors in the community from a middle-income country-An online cross-sectional study. *PLoS One.* 2022;17(8):e0273364.

RISK AND EPIDEMIOLOGY

75% not hospitalized

22% pre-existing respiratory/cardiac dx

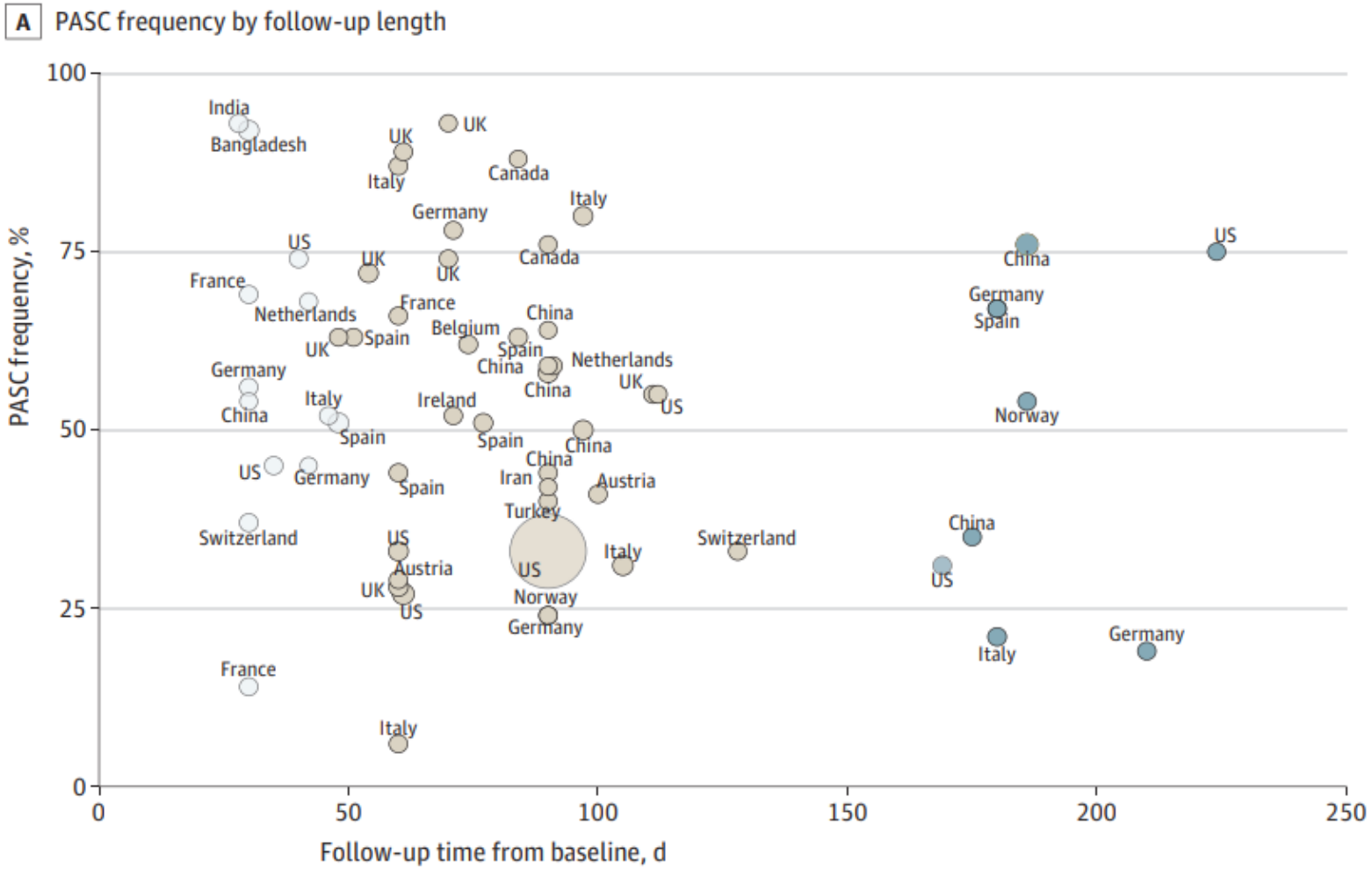
34% pre-existing depression/anxiety

4% pre-existing chronic fatigue/fibromyalgia

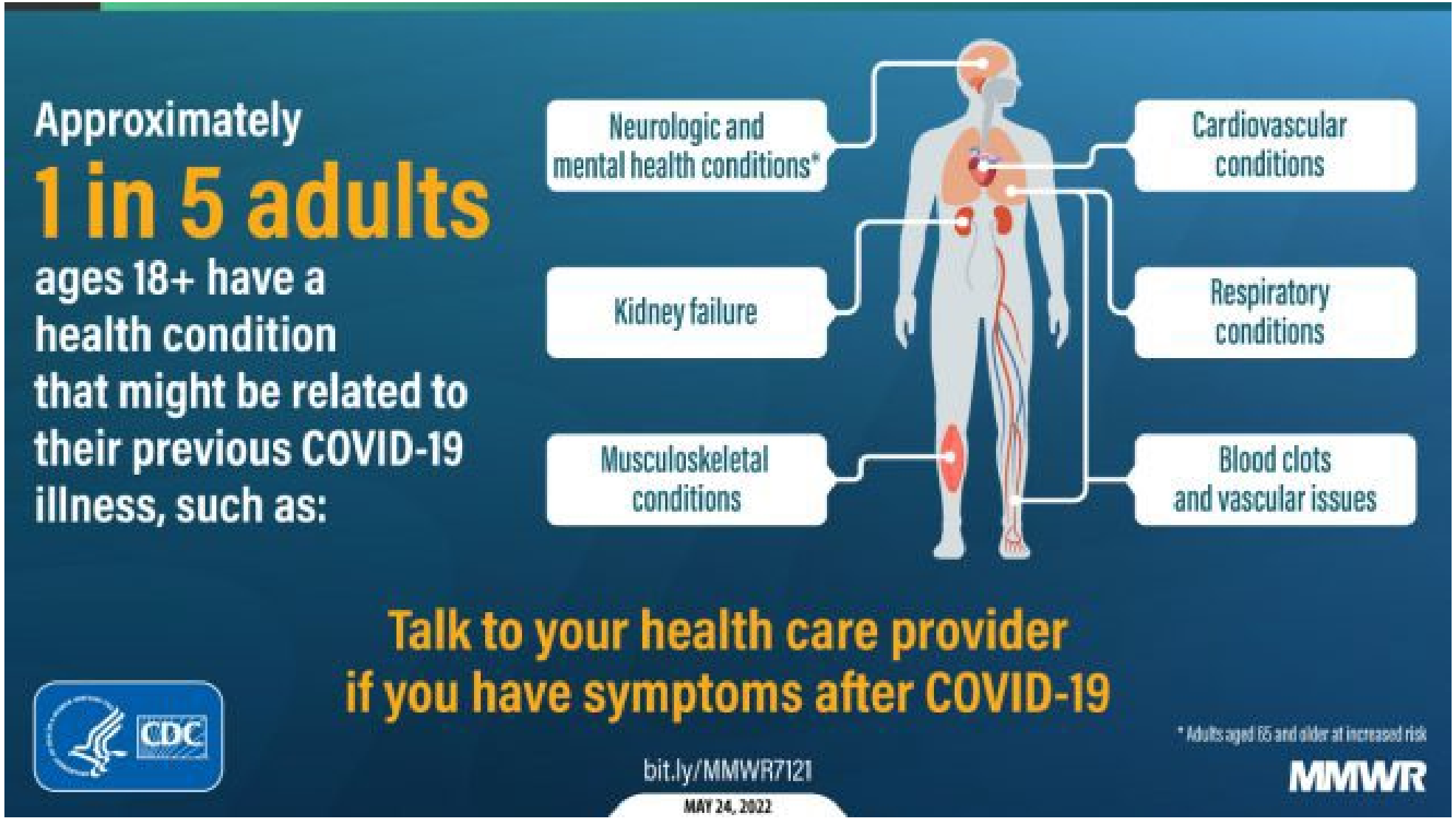
Average age 45.4

68% female

HOW OFTEN WILL THIS OCCUR?



Groff D, Department of Surgery PSCoMaMSHMC, Hershey, Pennsylvania, Sun A, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Network Open*. 2021;4(10)doi:10.1001/jamanetworkopen.2021.28568


Approximately
1 in 5 adults
ages 18+ have a health condition that might be related to their previous COVID-19 illness, such as:
Neurologic and mental health conditions*
Kidney failure
Musculoskeletal conditions
Cardiovascular conditions
Respiratory conditions
Blood clots and vascular issues
Talk to your health care provider if you have symptoms after COVID-19
CDC
* Adults aged 65 and older at increased risk
bit.ly/MMWR7121
MAY 24, 2022
MMWR

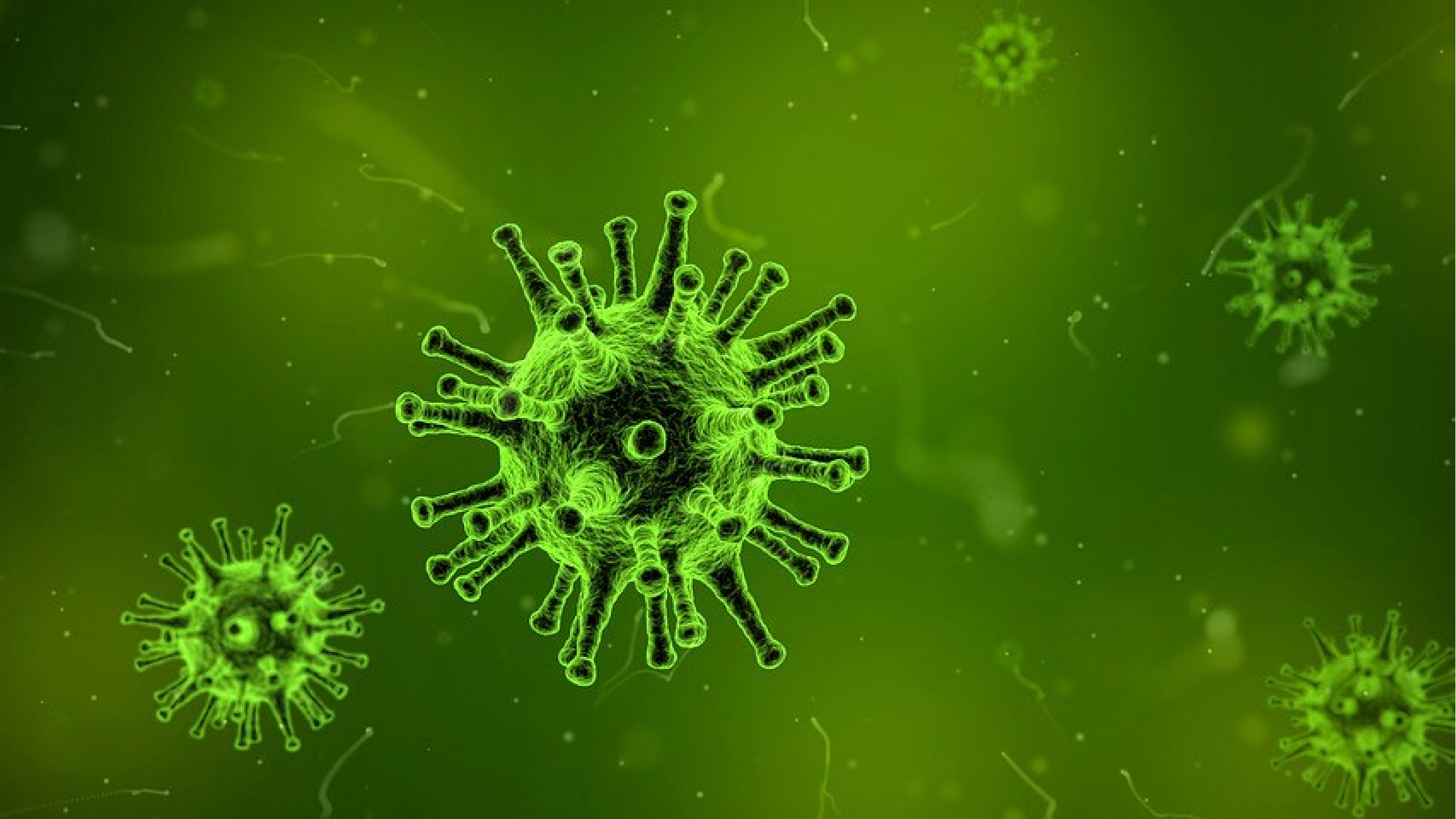
PROGNOSIS

Follow up of hospitalized patients, discharged Jan – May 2020

1276 participants

	6 months	12 months
At least one symptom	68%	49%
Anxiety/depression	23%	26%

Adapted from Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *The Lancet*. 08/28/2021 2021;398(10302):747-758. doi:10.1016/s0140-6736(21)01755-4



DEJA VU

1918 Spanish Flu

- 1000 patients, 20% had ongoing symptoms

2016 Ebolavirus

- Fatigue in 28%

Epstein-Barr virus

- Fatigue 38% at 2 months

SARS 2003

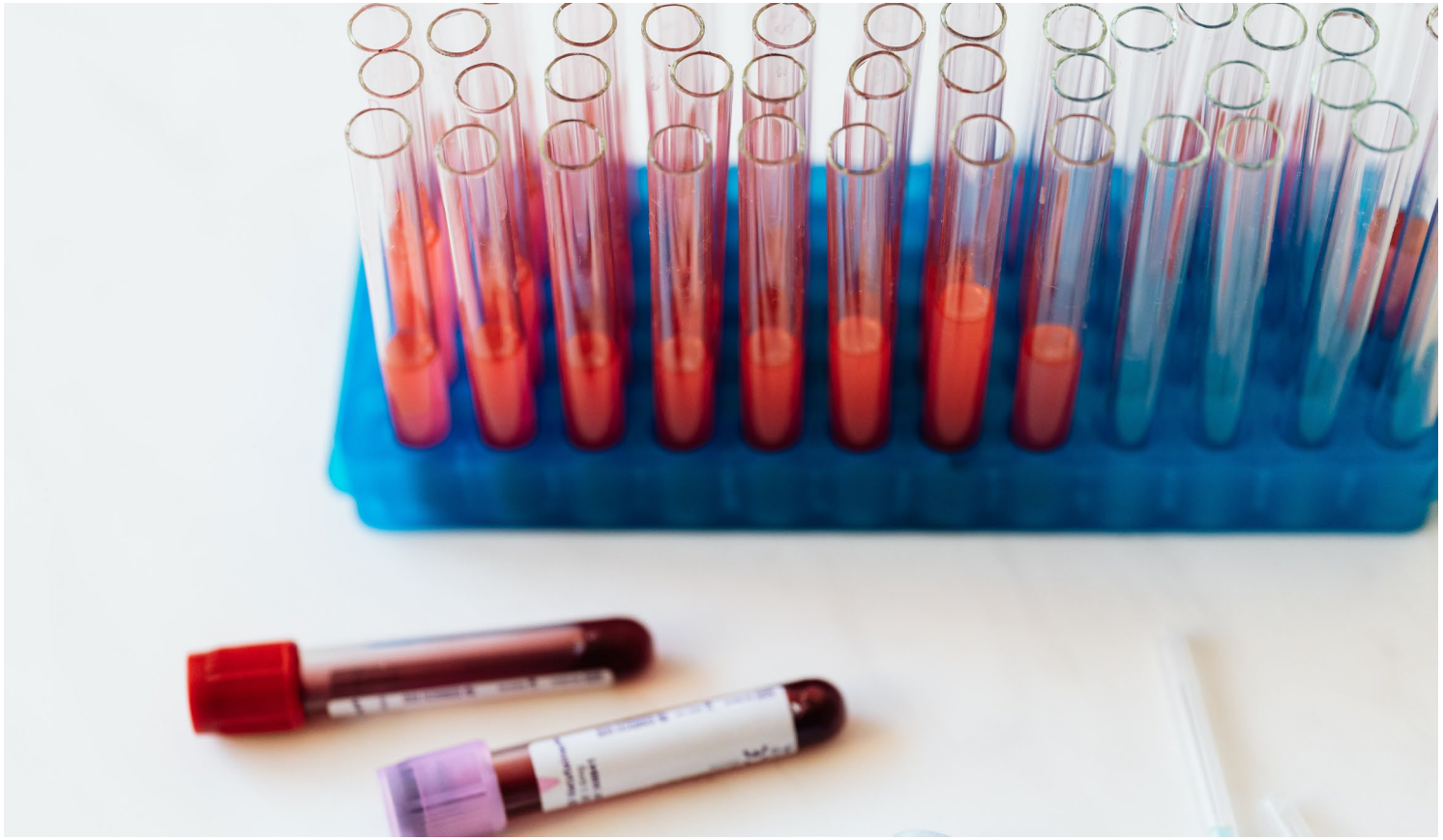
- Fatigue in 60% at 12 months

1. Post-viral fatigue and COVID-19: lessons from past epidemics
2. Post-COVID-19 fatigue as a major health problem: a cross-sectional study from Missouri, USA

IMMUNE SYSTEM ABNORMALITIES

- Some evidence for ongoing immune dysregulation
- 111 patients at Northwestern Memorial Hospital Neuro COVID clinic
- Sx > 6 wks after infection
- **Reduced effectiveness of cells that develop protective antibodies**

Visvabharathy L, Hanson B, Orban Z, et al. Neuro-COVID long-haulers exhibit broad dysfunction in T cell memory generation and responses to vaccination. *medRxiv*. Aug 9 2021;medRxiv. doi:10.1101/2021.08.08.21261763



AUTOANTIBODIES

67 patients with COVID

Found antibodies against ACE2

93% of acute hospitalized patients	None in SARS negative patients	ACE2 activity reduce in patients with auto-antibodies

NEURO-PATHOLOGY

November 2021

42 patients, 90 days after COVID

Abnormal functional connectivity

White and grey matter changes

S R, L S, H D, Y L, X L, AR M. Alzheimer's-like signaling in brains of COVID-19 patients. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 02/03/2022 2022;doi:10.1002/alz.12558

ALZHEIMER'S LINK?

Feb 2022

10 brain samples

Changes consistent with Alzheimer's disease

S R, L S, H D, Y L, X L, AR M. Alzheimer's-like signaling in brains of COVID-19 patients. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 02/03/2022 2022;doi:10.1002/alz.12558

TREATMENT PROCESS OVERVIEW

Post Acute Phase (0-4 weeks post infection)

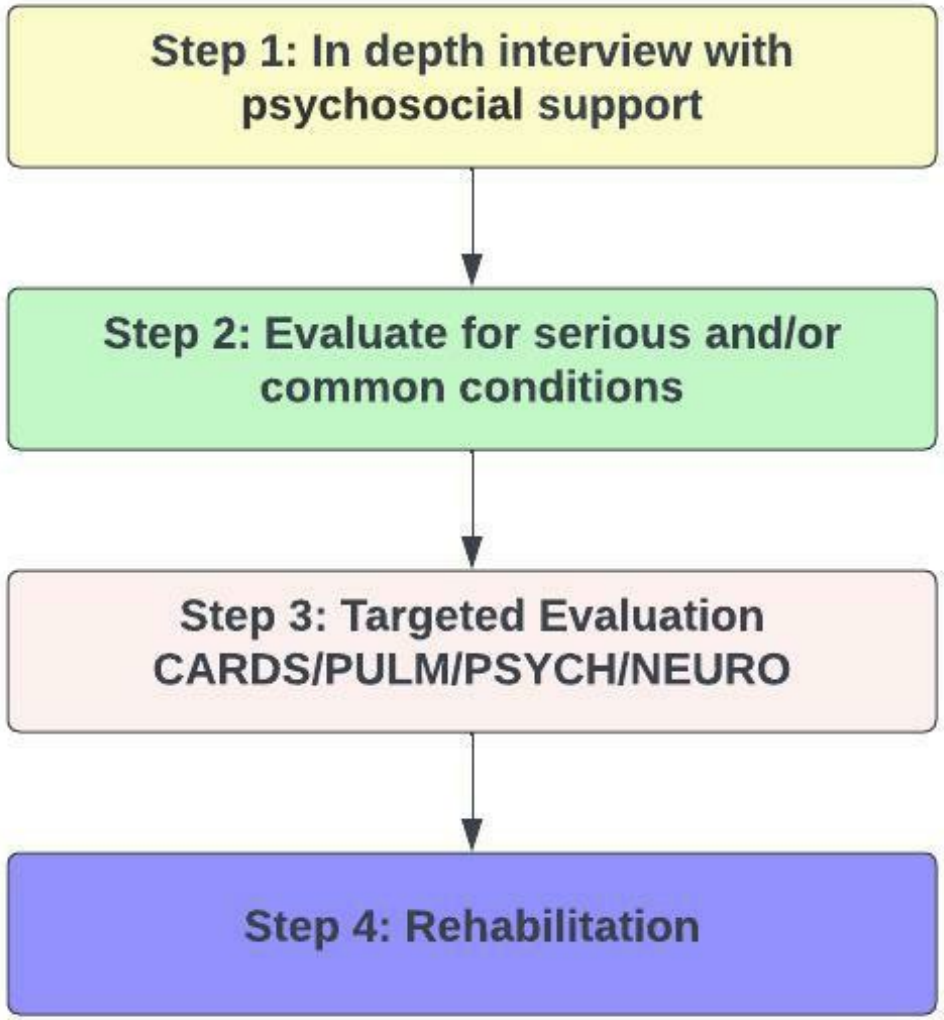
-Check for complications
-Ensure hydration and nutrition
-Educate on paced activity
-Address return to work

Early PCS/PASC Phase 5-12 weeks

-Continue graded activity increases, minimizing post exertional malaise
-Addtional testing and treatment as needed
-Monitor functional improvements
-Address return to work

PCS/PASC Phase >12 weeks

-Possible longer recovery course, up to a year
-Develop coping skills
-Education on central sensitization
-Uses experts in chronic fatigue and fibromyalgia


Step 1: In depth interview with psychosocial support
Step 2: Evaluate for serious and/or common conditions
Step 3: Targeted Evaluation CARDS/PULM/PSYCH/NEURO
Step 4: Rehabilitation

STEP 1: PSYCHOSOCIAL SUPPORT

-Patients Feel “abandoned”

-Guilt/self doubt

-Clinical depression/anxiety/PTSD

LISTEN AND VALIDATE

Li Z, Zheng C, Duan C, et al. Rehabilitation needs of the first cohort of post-acute COVID-19 patients in Hubei, China. *Eur J Phys RehablMed.* 2020;56(3):339-344

STEP 2: INITIAL EVALUATION

-**Rule out other serious conditions**

-31% of ICU patients – thromboembolic event

-60% myocardial inflammation at 70 days

-1250 discharged patients

- Within 60 days
- 10.4% ICU patients died
- 6.7% general ward patients died
- 15% readmitted

-Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147-=
-Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(11):1265-1273.
-Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *https://doiorg/107326/M20-5661*. 2020.

STEP 2: INITIAL EVALUATION

-Initial diagnostics
  - CBC
  - CMP
  - Thyroid panel
  - Vitamin-B12
  - Iron studies

First 100 patients

Tests performed	Abnormal tests
29 echocardiograms	13.8% (n=4)
28 pulmonary function tests	25.0% (n=7)
35 chest x-rays	2.9% (n=1)
21 autonomic reflex test (tilt and QSART)	57.1% (n=12)

DIAGNOSTICS

CYTOKINE PROFILE

June 2022

Brazil study

317 patients

135 with long haul covid

Group	Profile
Long COVID	↑ IL-17 and IL-2
No Long COVID	↑ IL-10, IL-6, IL-4

Queiroz MAF, Neves P, Lima SS, et al. Cytokine Profiles Associated With Acute COVID-19 and Long COVID-19 Syndrome. *Front Cell Infect Microbiol.* 2022;12:922422.

STEP 3: TARGETED EVALUATIONS


4 BUCKETS
PULM
NEURO
CARDS
PSYCH

CARDIOVASCULAR COMPLICATIONS

Symptoms

- 20% chest pain at 60 days
- 9% chest pain at 180 days
- 5% palpitations at 180 days

416 patients – 6/2020

- 20% myocardial injury
- Troponin I > 0.04ng/ml

100 patients 11/2020

- Using cardiac MRI
- 60% myocardial inflammation

Elseidy SA, Awad AK, Vorla M, et al. Cardiovascular complications in the Post-Acute COVID-19 syndrome (PACS). *Int J Cardiol Heart Vasc.* 2022;40:101012.

Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(11):1265-1273.

Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J.* 2020;41(22):2070-2079.

TARGETED EVALUATION: CARDIAC

Evaluation

- Echocardiogram
- Cardiac MRI
- CPET (caution)

Most Common:

- Myocarditis
- New HTN
- Pericarditis

Have not seen more serious cardiac conditions

TARGETED EVALUATION: PULMONARY

- Dyspnea can occur for months after coronavirus
- Delay evaluation until 12 weeks
- Earlier if pre-existing lung disease
- Evaluation
  - Chest CT
  - Pulmonary function test
  - Dec DLCO and pulmonary fibrosis
- Tx with inhalers and pulmonary rehab

Barker-Davies RM, O'Sullivan O, Senaratne KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. Aug 2020;54(16):949-959. doi:10.1136/bjsports-2020-102596

TARGETED EVALUATION: PSYCH

Psychiatry (Mind AND Body)

- Therapy
- Psychiatry consult
- SNRIs – Duloxetine, Venlafaxine
- SSRISs – Sertaline, Fluvoxamine, Prozac
- Anti-anxiety – Hydroxyzine
- SAFETY CONCERN

Sleep

- Sleep hygiene
- Melatonin 5mg
- Overnight sleep study
- CPAP
- SAFETY CONCERN

THE BIG BUCKET TARGETED EVALUATION: NEURO - GENERAL

Headaches

- Usual headache tactics
- Optimize sleep
- Appetite/hydration
- Medications
- Headache consult

Tremor

- Propranolol

Taste/Smell difficulties

- Dysfunction in 36.6%
- 5% still having sx at 6 months
- Rec olfactory retraining
- SAFETY CONCERN

-KH W, GCY L, KCF P, et al. Ocular surface disturbance in patients after acute COVID-19. *Clinical & experimental ophthalmology*. 02/26/2022 2022;doi:10.1111/ceo.14066
-JR L, CM C-E, E B, et al. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *Journal of internal medicine*. 2021 Aug 2021;290(2)doi:10.1111/joim.13209

OLFACTORY RETRAINING

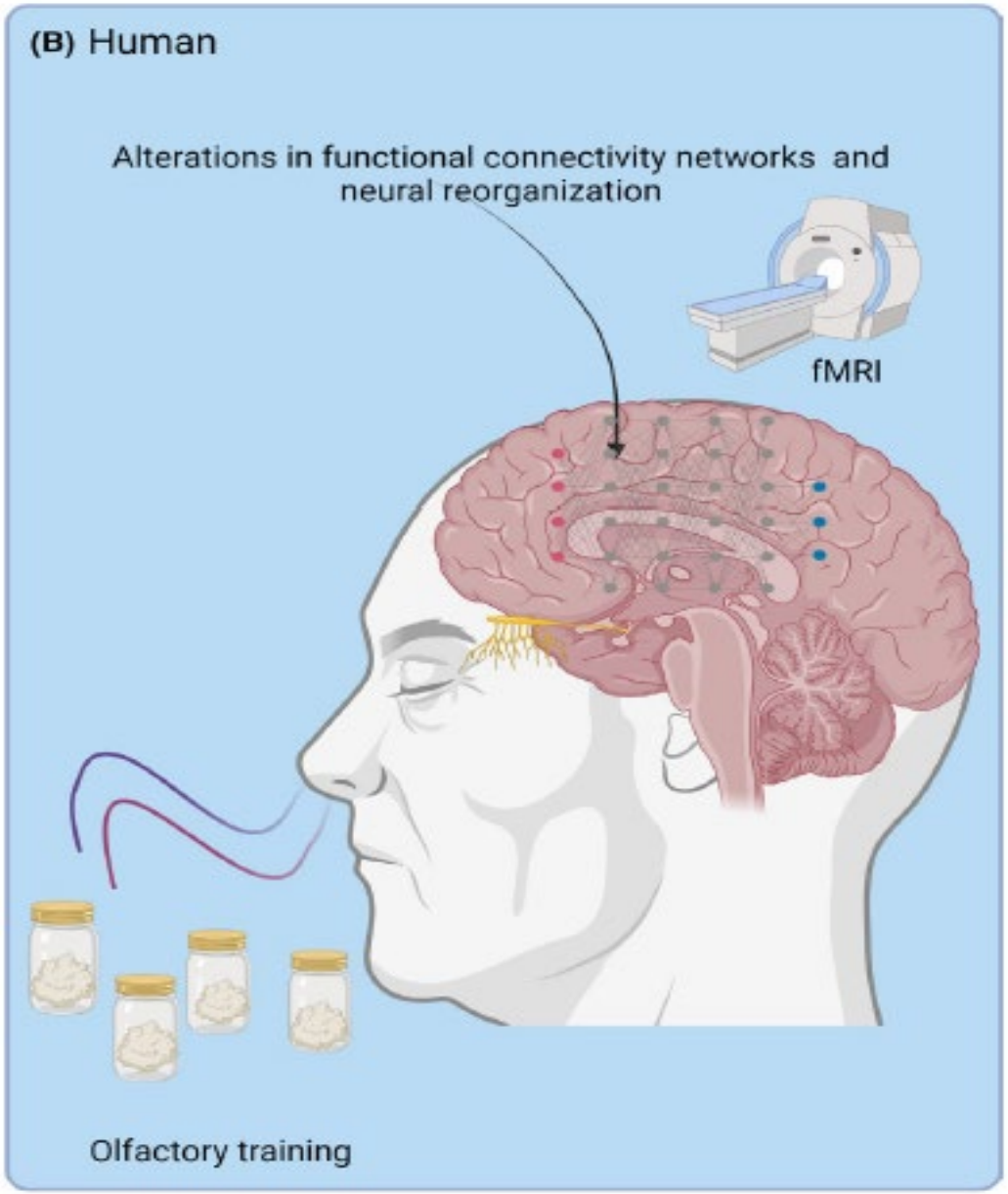
Rose, eucalyptus, lemon, clove

20 seconds

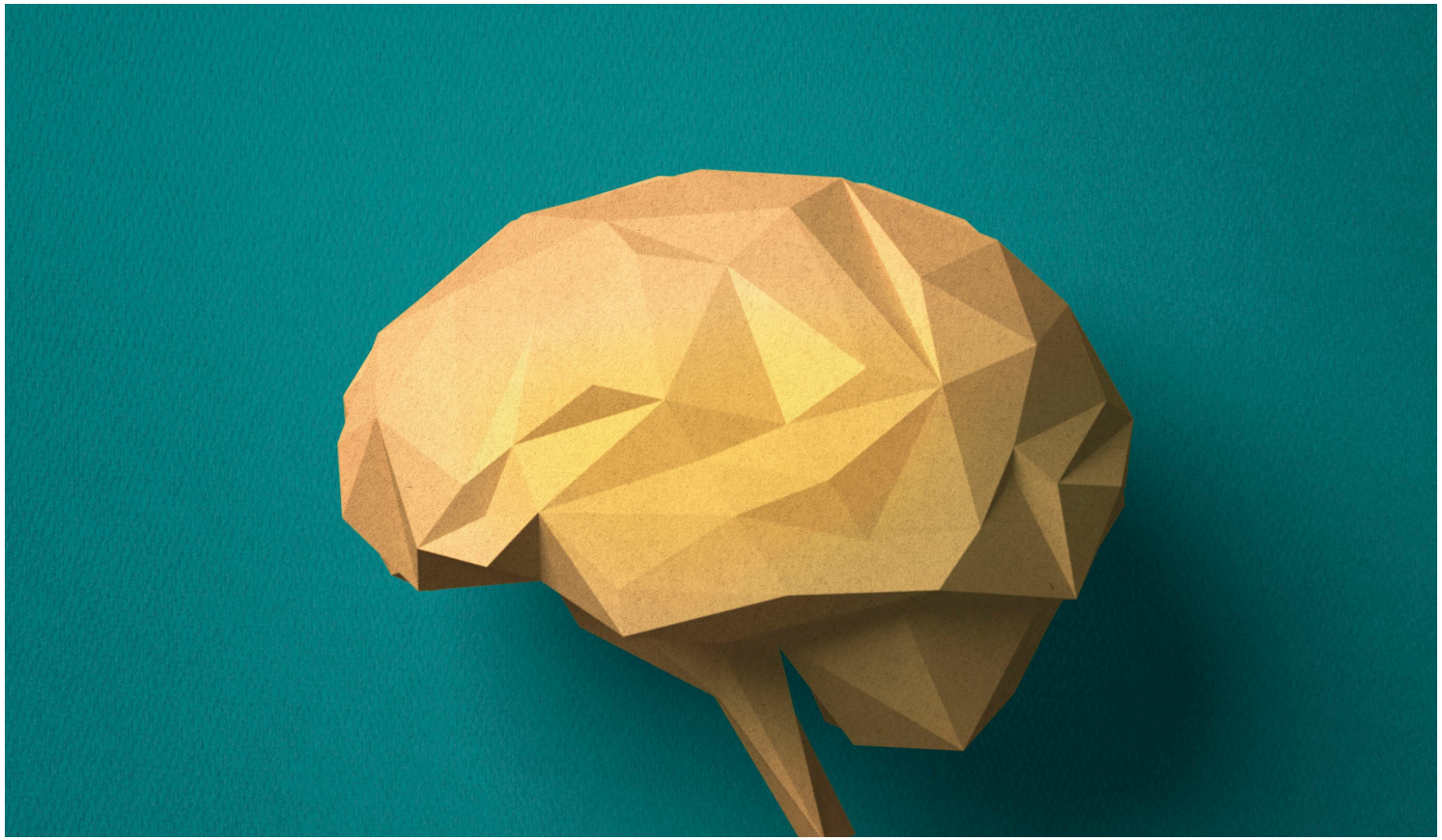
Twice a day – morning and before bed

Three months

Also improve cognition?



Ojha P, Dixit A. Olfactory training for olfactory dysfunction in COVID-19: A promising mitigation amidst looming neurocognitive sequelae of the pandemic. *Clin Exp Pharmacol Physiol. 2022;49(4):462-473.*



TARGETED TREATMENT: NEURO – BRAIN REHAB

- Brain Rehabilitation Clinic
  - SIMILAR TO CONCUSSIONS
  - Neuromuscular retraining
  - Neuropsychometric testing
  - Headache management
  - Sleep improvement
  - Speech therapy*

Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. Jun 1 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127

TARGETED EVALUATION: NEURO - DYSAUTONOMIA


Balance issues/Dizziness


Tachycardia


Pain


Brain fog


Shortness of breath


Exercise intolerance


Sleeping problems


Mood swings

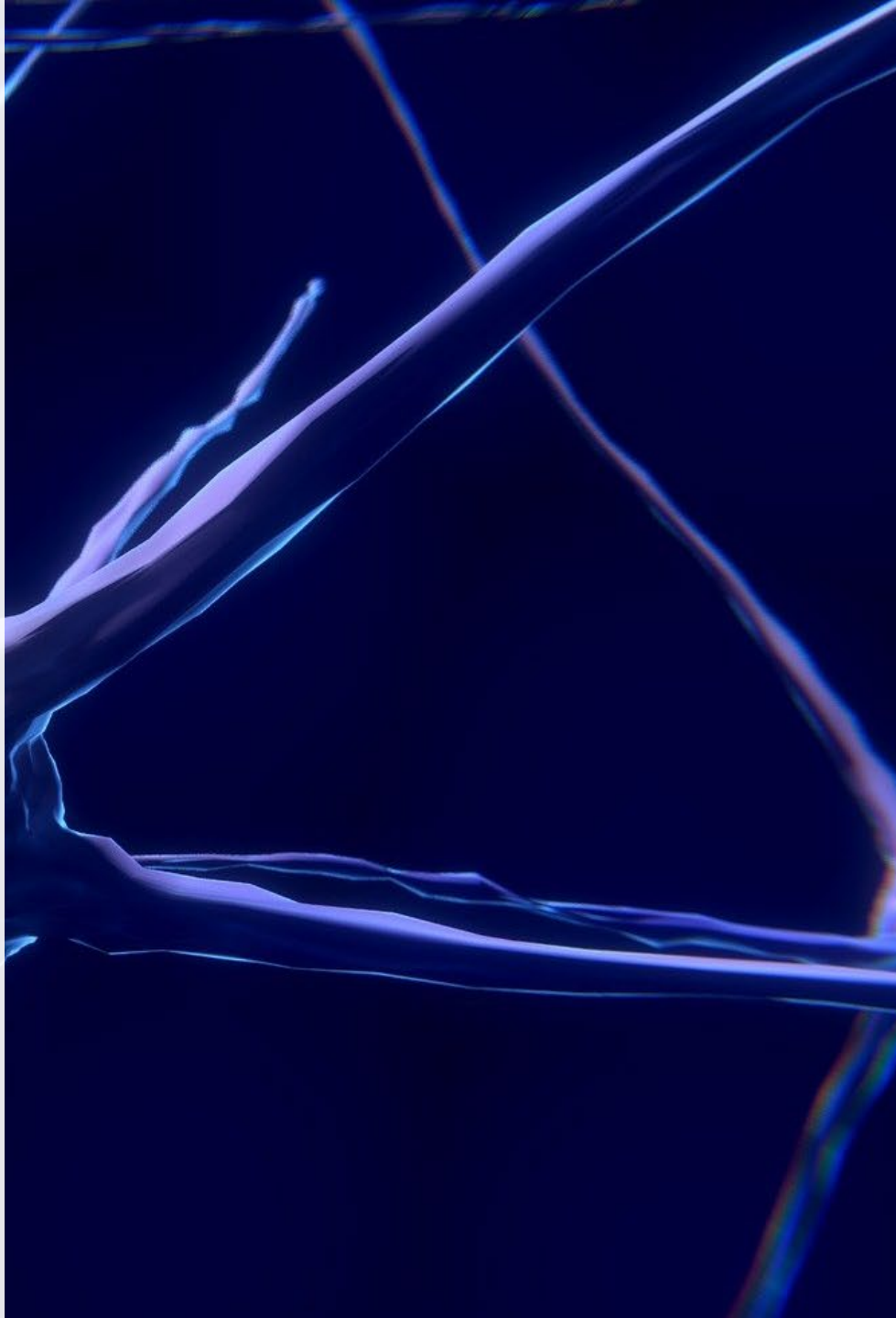

Etc…..

DYSAUTONOMIA

-Autonomic dysfunction was seen in SARS

-POTS preceded by viral illness in 21-40%

-Case reports of POTS in COVID-19



-Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. *Clin Auton Res*. 10 2020;30(5):449-451. doi:10.1007/s10286-020-00727-9

-Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset Postural Orthostatic Tachycardia Syndrome Following Coronavirus Disease 2019 Infection. *J Innov Card Rhythm Manag.* 2020;11(11):4302-4304

DYSAUTONOMIA TESTING

-Autonomic Reflex Test

- Tilt Table
- QSART

-Additional Options

- COMPASS-31 Survey
- Epidermal nerve fiber biopsy
- Thermoregulatory sweat test

MAYO CLINIC

Distribution of sweat loss:

A (distal)

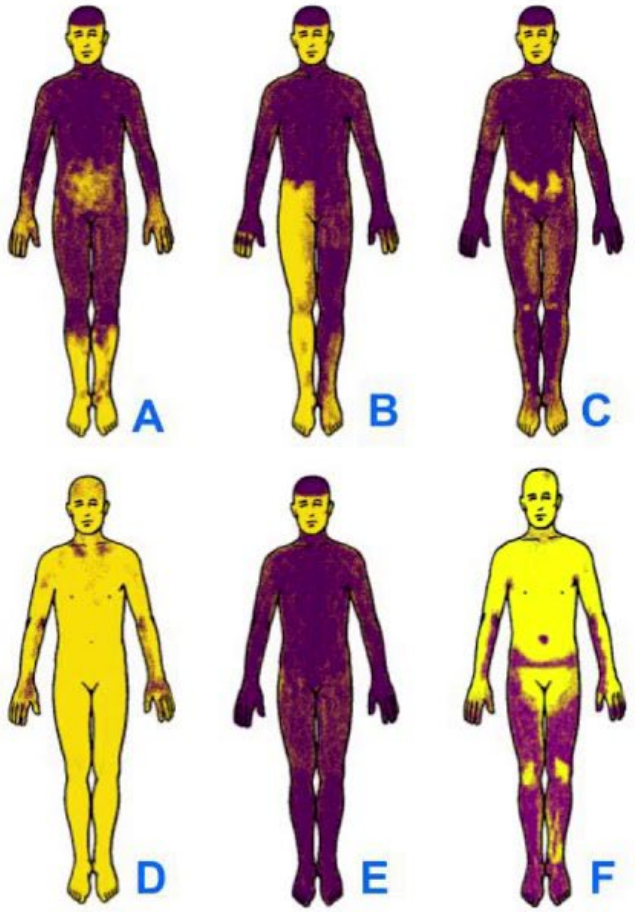
B (segmental)

C (dermatomal)

D (global)

E (normal)

F (regional)



DYSAUTONOMIA CONSERVATIVE TX

- Hydration (2-3L/day)
- Salt Intake (3-10 grams sodium)
- Compression stockings (30-40 mmHg and waist high)
- Abdominal binders, 10 mmHg
- Leg tensing, crossing, weight shifting
- POTS Virtual Education Clinic

DYSAUTONOMIA MEDICATIONS

- Metoprolol
- Propranolol
- Midodrine
- Fludrocortisone
- Methyldopa
- Pyridostigmine


Step 1: In depth interview with psychosocial support
Step 2: Evaluate for serious and/or common conditions
Step 3: Targeted Evaluation CARDS/PULM/PSYCH/NEURO
Step 4: Rehabilitation

STEP 4: REHABILITATION

SARS/MERS

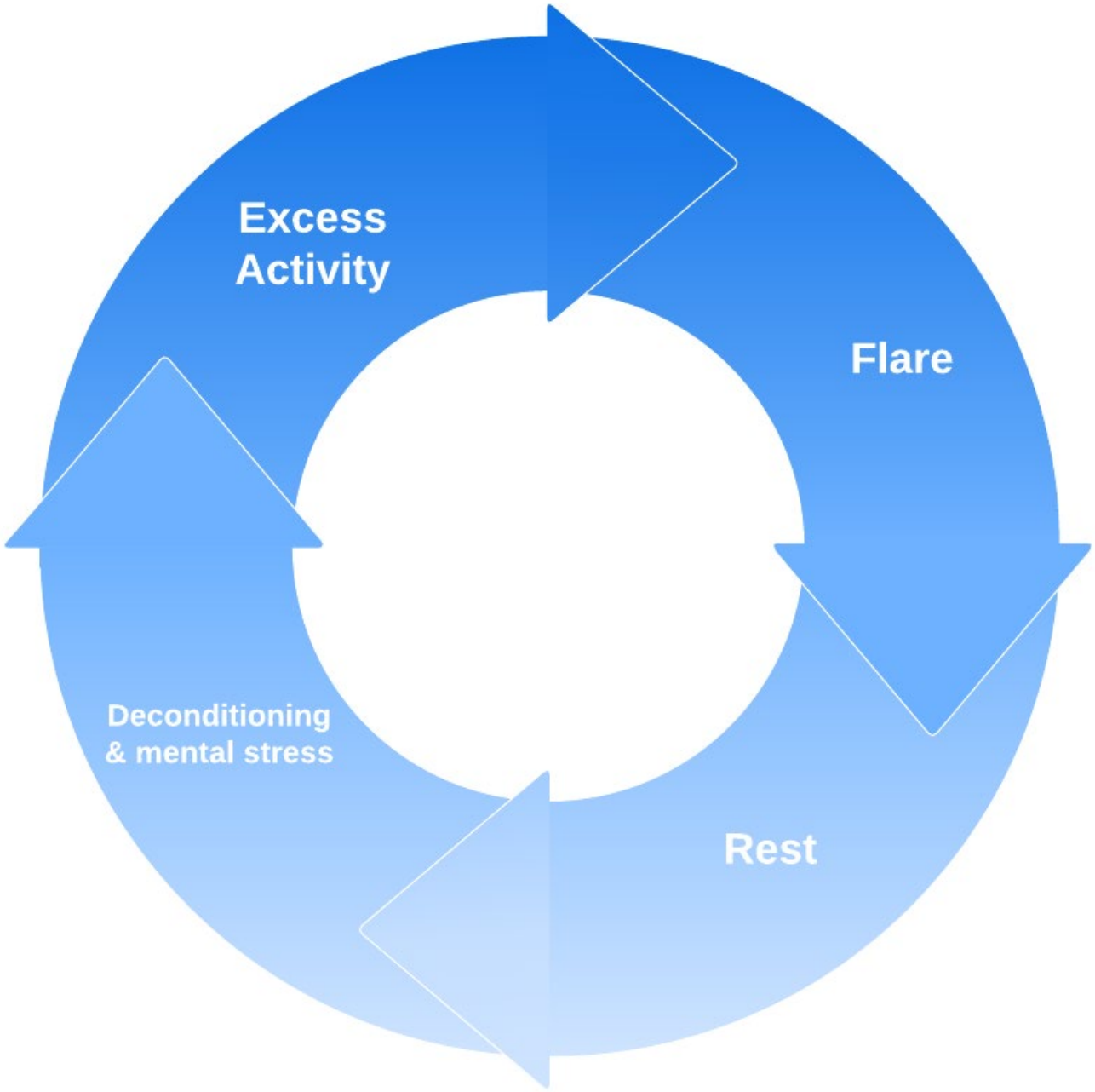
- 19-33% reduction of 6MWD
- 78.6% decreased V02 max

COVID-19

- 41% reduced exercise capacity

-Rooney S, Webster A, Paul L. Systematic Review of Changes and Recovery in Physical Function and Fitness After Severe Acute Respiratory Syndrome-Related Coronavirus Infection: Implications for COVID-19 Rehabilitation. *Phys Ther.* 2020;100(10):1717-1729
-George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. Aug 2020;doi:10.1136/thoraxjnl-2020-215314

“SICK OF BEING SICK”



REHABILITATION

Post Exertional Malaise in Chronic fatigue and Fibromyalgia

After physical stress

- 30% reported fatigue, flu like sx, muscle pain

Graded exercise

- Negative effect in 54-74% of patients

-Geraghty K, Hann M, Kurtev S. Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys. *J Health Psychol.* 2019;24(10):1318-1333

-Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross-sectional survey. *PLoS One.* 2018;13(6):e0197811.

REHABILITATION

- Rehabilitation ≠ exercise

-Use Adaptive Paced Therapy = LOW AND SLOW

Use daily function/activities in addition to rehab activities (i.e., doing the dishes counts)

Not simply “stop when it hurts” – use individual experiences

Gradual increases (i.e., 10 min to 13 min of walking)

PT/OT Help

DOES THERAPY WORK?

	BEFORE REHABILITATION	AFTER REHABILITATION
Supplemental O2	83.5%	8.2%
Bedridden	55.3%	2.4%
Wheelchair	22.4%	4.7%

85 patients with severe COVID

Neuromuscular and respiratory reconditioning

30-40 days of treatment

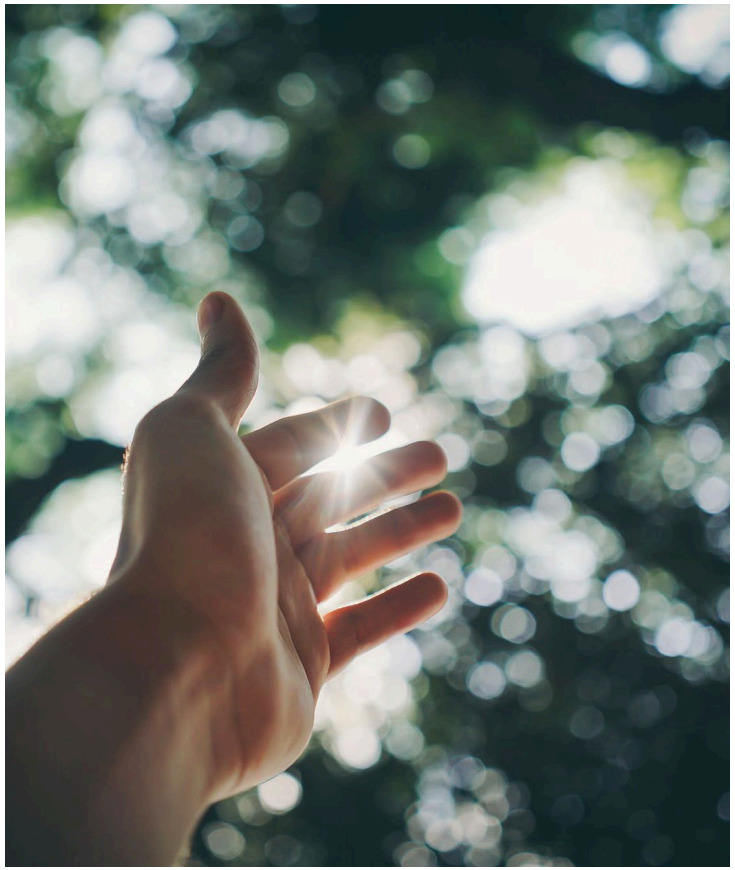
Guler T, Yurdakul FG, Acar Sivas F, et al. Rehabilitative management of post-acute COVID-19: clinical pictures and outcomes. *Rheumatol Int*. Dec 2021;41(12):2167-2175. doi:10.1007/s00296-021-05003-1

BUT WHAT ABOUT_____

-Treatment is the same as without Post COVID Syndrome

-i.e., Sleep disturbance

- Sleep hygiene
- Melatonin
- Sleep consult
- Cognitive behavioral therapy
- Overnight testing
- Pharmacotherapy



POTENTIAL REMEDIES

-Ivermectin

-Monoclonal antibodies

-Paxlovid

-Glutathione

-COVID Vaccine

-Hydroxychloroquine

NOT YET

RESEARCH EXAMPLE: NALTREXONE

Low dose

Impacts immune system

- Chron's Disease
- Fibromyalgia
- Multiple Sclerosis

Ireland study

- 36 patients
- 1-3mg over three months
- Improvement in function, energy, sleep, concentration and **pain**

Limits

- No control
- Not blinded
- Small population

O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G, Lambert JS. Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study. *Brain Behav Immun Health.* 2022;24:100485.

EARLY OUTCOMES

-20% made a full recovery

- Started with very limited function
- Return to normal function
- Full duty work
- Recovered by 4 months after acute infection start
- Earlier start of treatment
- Less cognitive complaints than rest of population
- Observations, NOT inferences

PATIENT COURSE

Step 1: Psychosocial Support

- LISTEN
- VALIDATE

Step 2: Rule Out Other Conditions

- Labs normal
- No concerns for PE
- No chest CT or PFT as dyspnea improved <3 months from infection

PATIENT COURSE

Step 3: Targeted Treatment: Dysautonomia

- Dysautonomia test – widespread postganglionic sympathetic sudomotor impairment
- Enrolled in autonomic virtual education clinic
- Lyrica

Step 3: Targeted Treatment: Brain Rehab

- Speech therapy
- Cognitive rehab

Step 4: Rehabilitation

- Enrolled in PT/OT
- 16 visits
- Progressed to independent program
- 6MWD increased by 330ft

OCCUPATIONAL MEDICINE MANAGEMENT

Provided regular work status updates

- Work statuses every 2 - 4 weeks

Titrated return to work

- Work from home initially (catch up on training, emails)
- 4 hours every other day, max three shifts/week, for 2 weeks

Slowly increases: “Go to 6 hours”

Allow some fluctuation: “8-12 hours as tolerated”

Quality relief

- “no volume sensitive work”
- “allow self pacing”


SWA
SWAT

WORK CHALLENGES

FUNCTIONAL DECLINE

34% impaired ADLS

82% impaired IADLS

63% returned to work in some form

- 46% (29/63) were back at baseline work
- Average time to between infection and presentation was 3 months

CARP POPULATION FUNCTION

PROGNOSIS

-530 patients at Weil Cornell Medicine

-Follow up at12 months

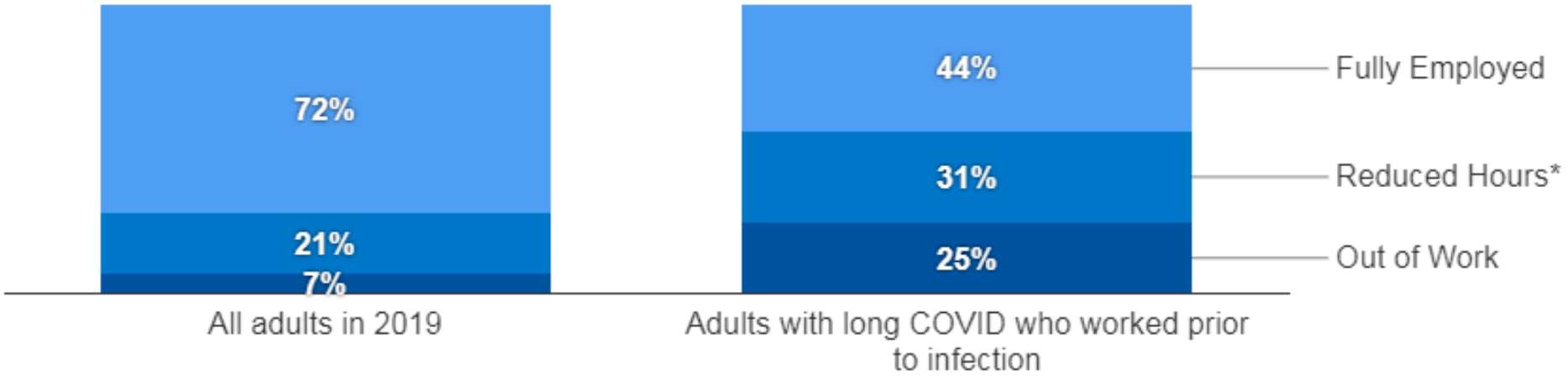
	12 months
Worse health	41.5%
Persistent symptoms	44.2%
Trouble lifting/carrying groceries	36.5%
Limited ability to climb a flight of stairs	38.1%
Troubles walking one block	22.1%

Adapted from Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *The Lancet*. 08/28/2021 2021;398(10302):747-758. doi:10.1016/s0140-6736(21)01755-4

Figure 2

Fewer than Half of Working Age Adults with Long COVID Who Worked Prior to Infection Work Full-Time After Infection

Employment status of working age adults (percent of population) for all adults in 2019 (Current Population Survey) and for survey respondents who worked prior to COVID infection (average of two surveys)



NOTE: KFF Analysis of: Katie Bach, "Is 'Long COVID' Worsening the Labor Shortage?" Brookings (Jan 1, 2022); Hannah E. Davis and others, "Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact, The Lancet, v. 38 (August 1, 2021); Workers' Experiences of Long COVID: A TUC Report (June 2021); and US BLS Labor Force Statistics from the Current Population Survey (2019).

PNG

KFF

WORK CHALLENGES SAFETY

CARP POPULATION

- Fatigue 80%
- Respiratory 59%
- Neurologic 59%
- Brain Fog 45%
- Sleep disturbance 30%
- Mental health sx 26%

Vanichkachorn G, Vanichkachorn.greg@mayo.edu, Newcomb R, et al. Post COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at the Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clinic Proceedings*. 2021;0(0)doi:10.1016/j.mayocp.2021.04.02

WHAT IS BRAIN FOG?

SUBJECTIVELY

- Short term memory
- Word finding
- Multitasking

OBJECTIVELY

February 2022

60 patients

Multidisciplinary assessment

- Quality of life
- Psychiatric
- Neuropsychological battery
- Medical

	Long COVID Group (n=32)	Control (n=28)
Below normal scores on NP	8/11 domains	1/11 domains
% extremely low scores	28% (n=12)	14% (n=4)

Ferrando SJ, Dornbush R, Lynch S, et al. Neuropsychological, medical and psychiatric findings after recovery from acute COVID-19: A cross-sectional study. *J Acad Consult Liaison Psychiatry*. 2022.

WORK CHALLENGES
NO STANDARDS

WHAT IS POST COVID SYNDROME?

-No universal definition

World Health Organization – 10/6/2021

- A history of probable or confirmed SARS COV-2 infection
- Sx ≥ 3 months from onset of infection
- Sx ≥ 2 months
- Can't be explained by an alternative diagnosis

CDC Definition

- Call it "Post-COVID Conditions"
- ≥ 4 weeks from acute infection start (symptoms or test)

1. Organization WH. A clinical case definition of post COVID-19 condition by a Delphi consensus. Accessed 10/6, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
2. @CDCgov. Post-COVID Conditions: Information for Healthcare Providers. @CDCgov. Updated 2021-09-10T04:38:34Z. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

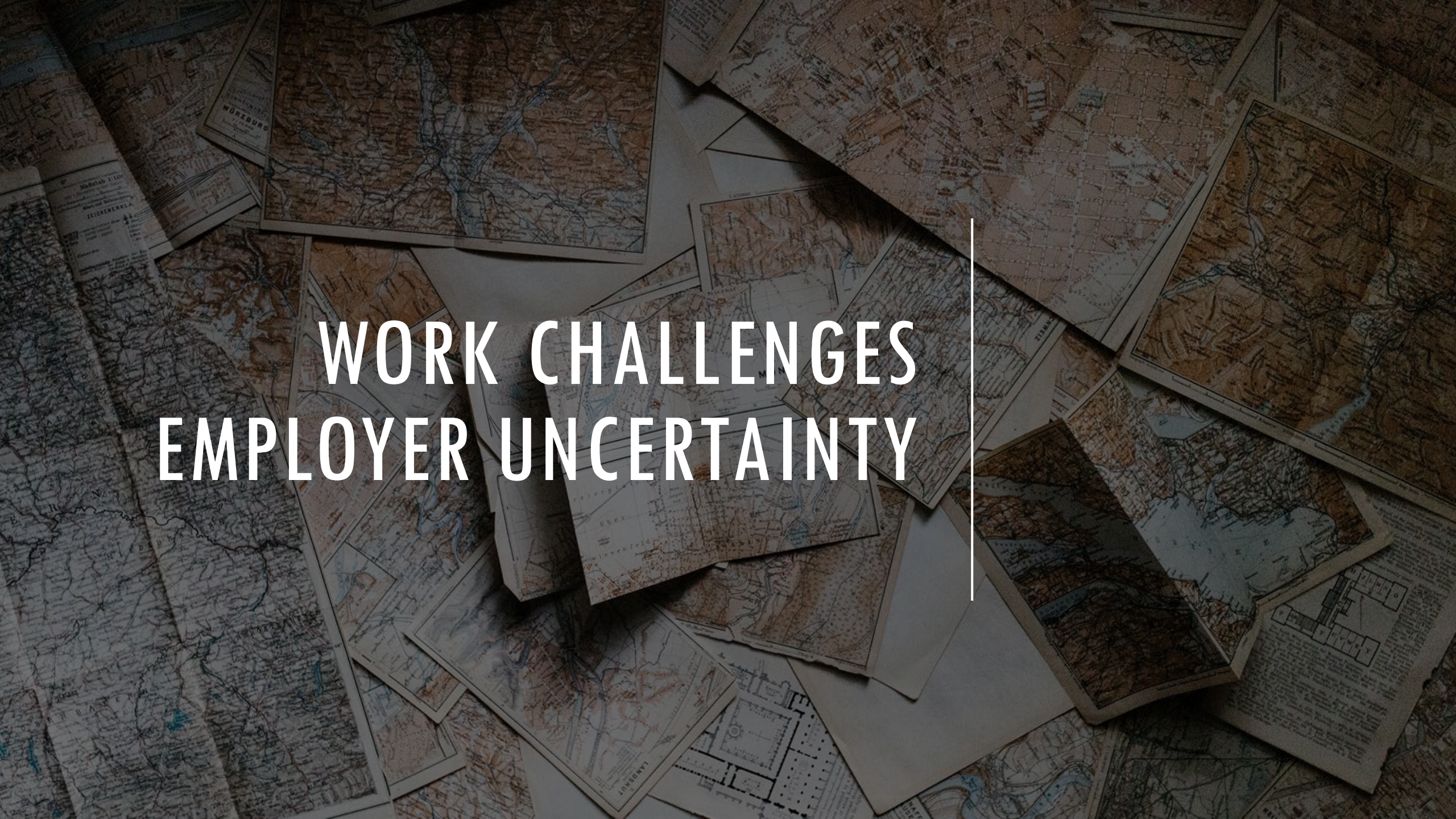
PANDORAS BOX

No single objective test for diagnosis.

No clear cluster of patient groups yet.

No appropriate test for assessing cognition.


WHO REALLY HAS
LONG HAUL COVID?



WORK CHALLENGES EMPLOYER UNCERTAINTY

ADA COVERAGE

July 2021

Government recognized long covid as a protected disability under ADA

“substantially limits one or more major life activities”

Reasonable accommodation in the workplace

EMPLOYER EXPERIENCE

Work restriction and limitations

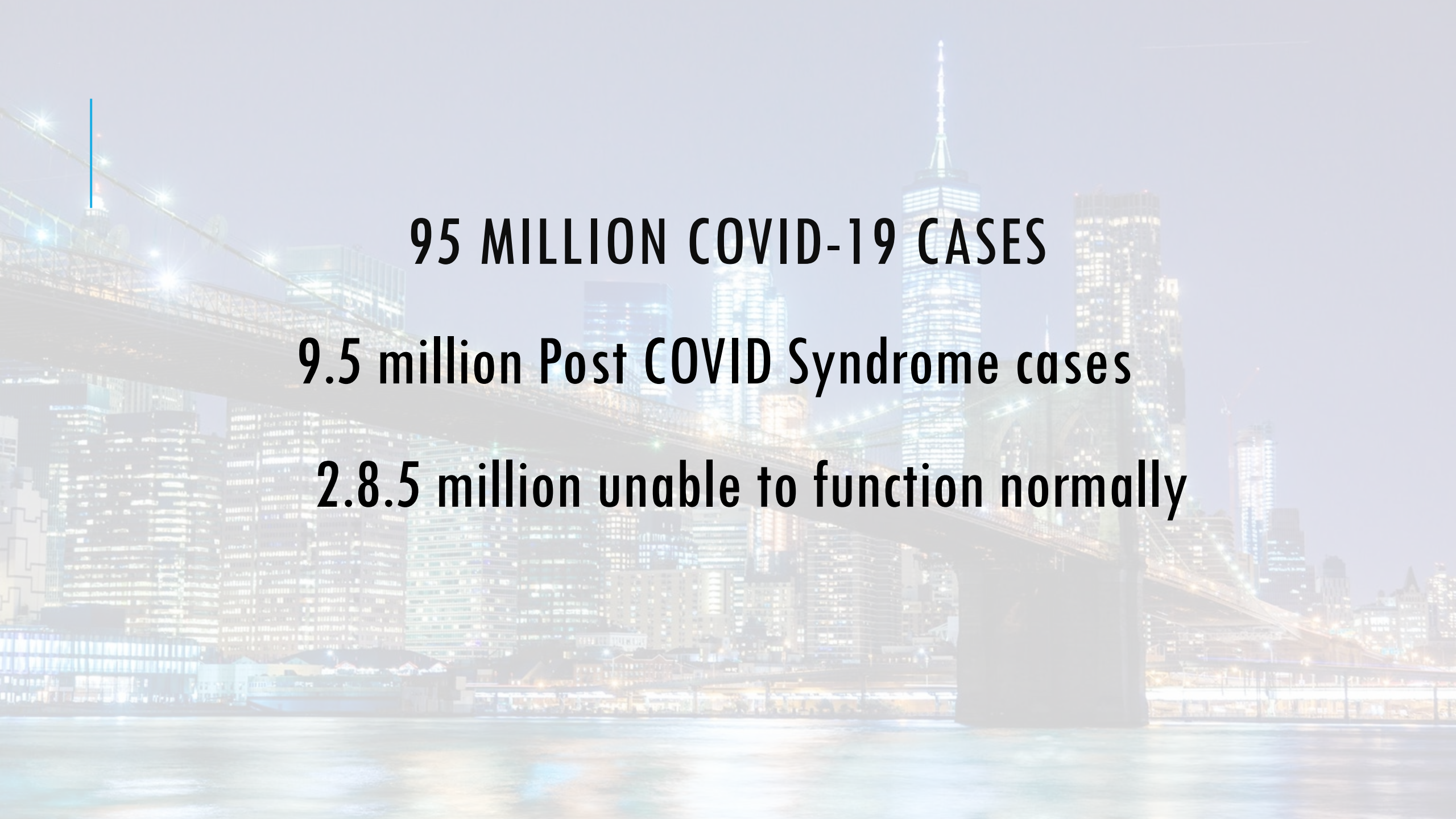
Temporary Alternative Duty

Job Rotations

Culture of support

WHAT IS REASONABLE?

WORK CHALLENGES NOT RARE



95 MILLION COVID-19 CASES

9.5 million Post COVID Syndrome cases

2.8.5 million unable to function normally

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https://www.mayoclinic.org/appointments

Appointment number: 507-538-1377

https://connect.mayoclinic.org/blog/post-covid-recovery/