

A thick black L-shaped frame surrounds the text. The top horizontal bar is on the left, the left vertical bar is on the left, and the bottom horizontal bar is on the right.

ETIOLOGY AND TREATMENT OF LONG COVID

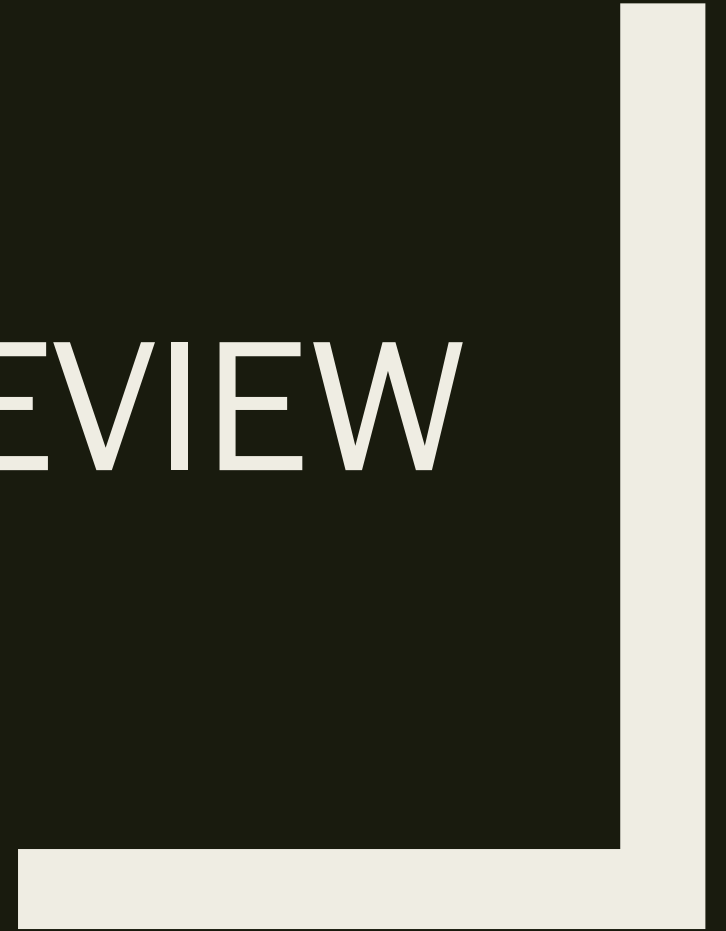
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Disclosures

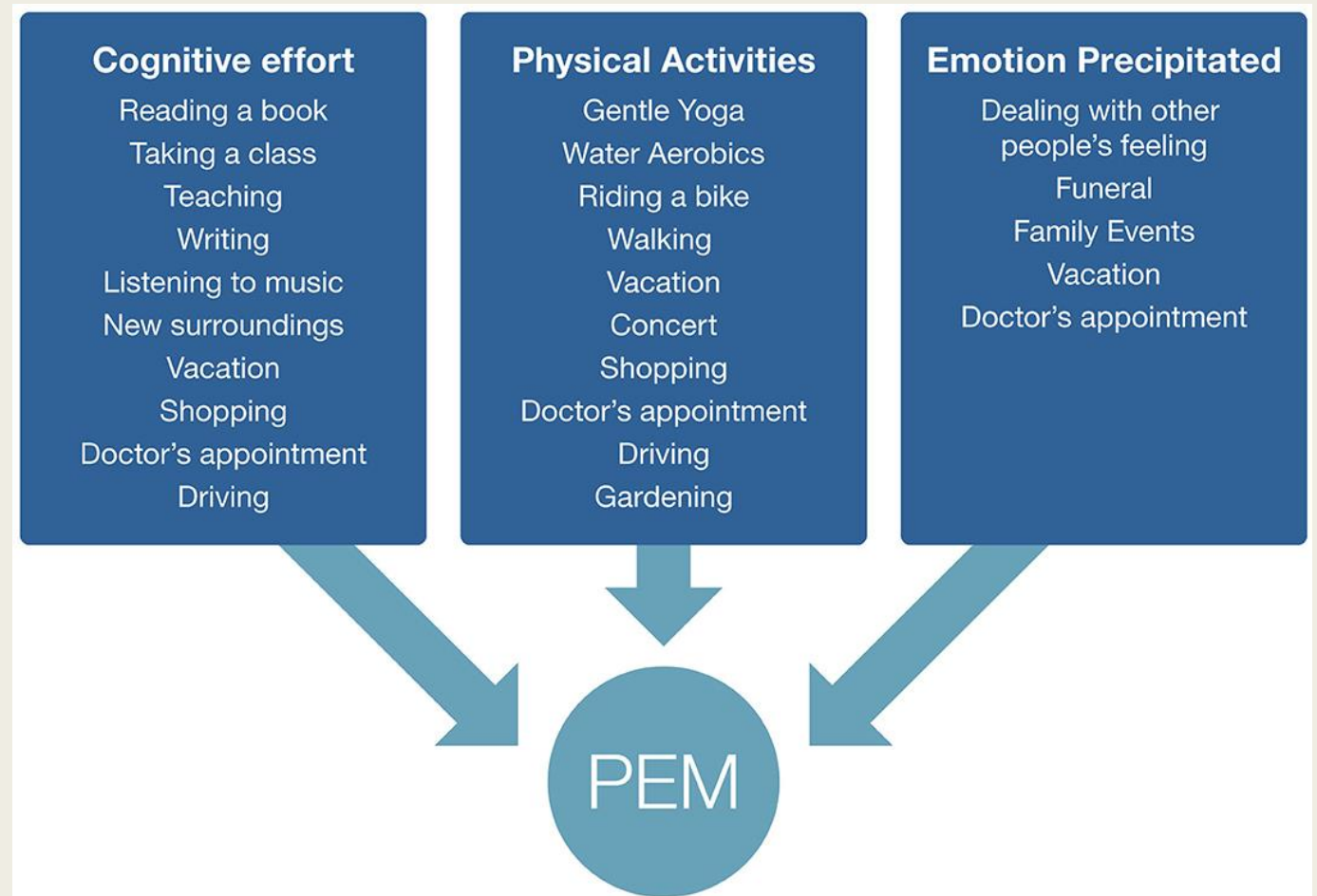
- I have no disclosures.

QUICK REVIEW

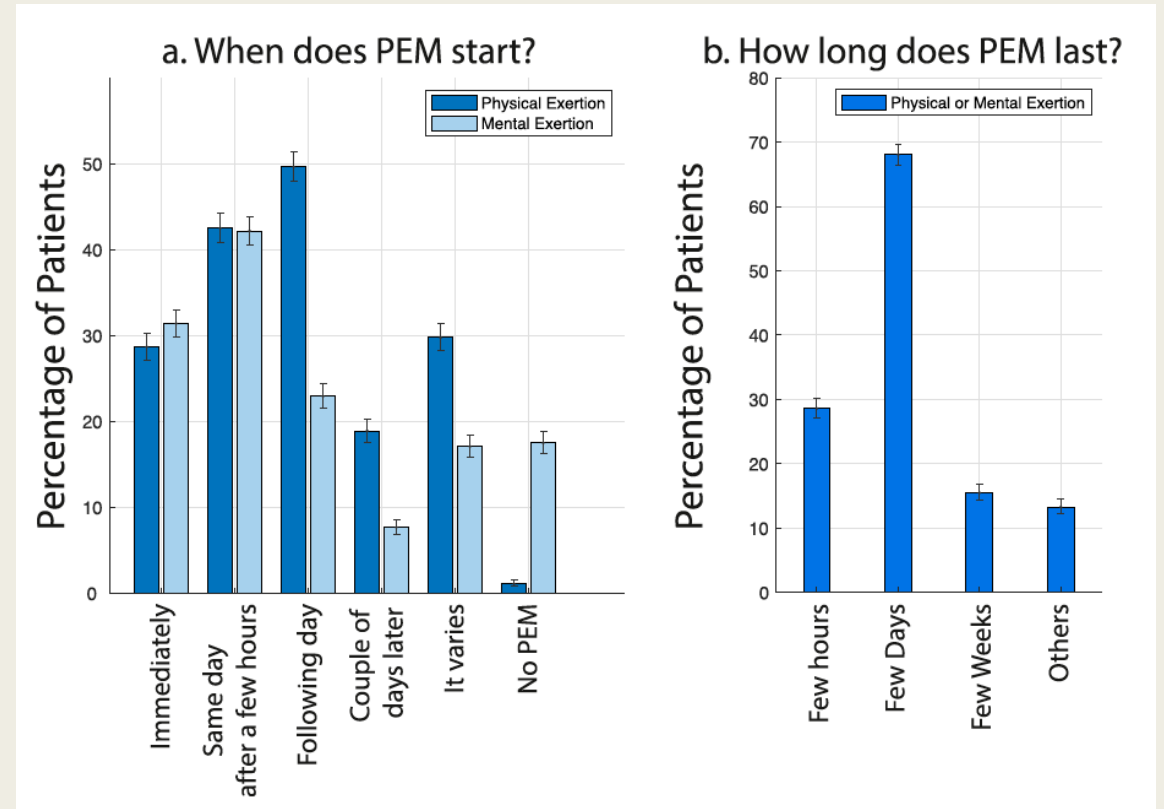
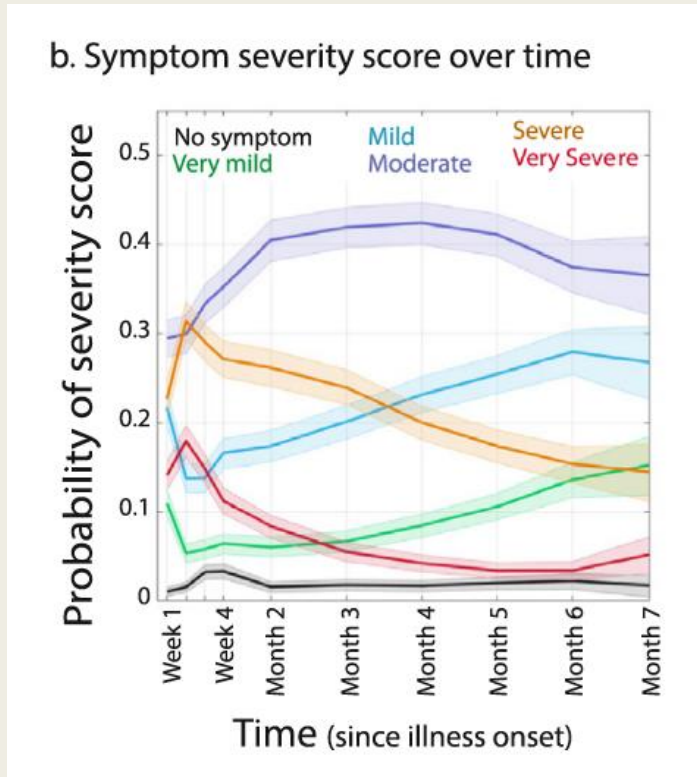


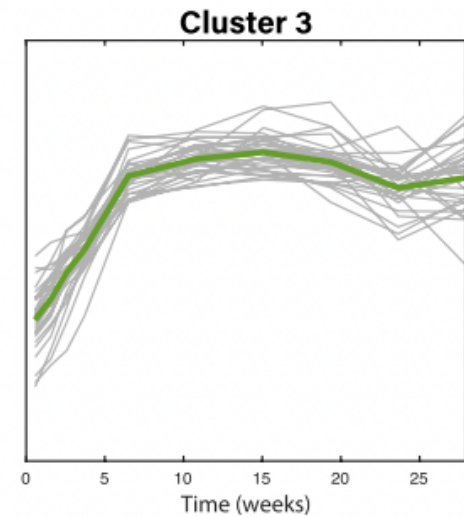
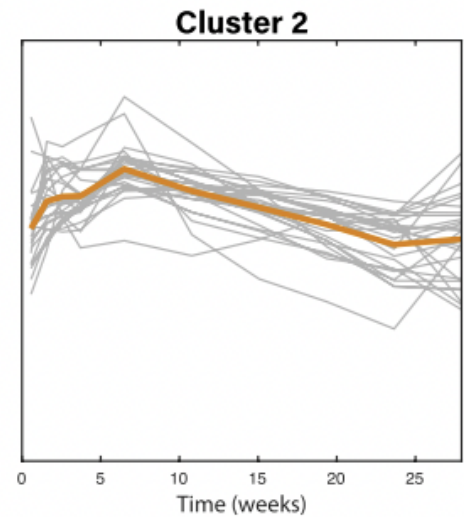
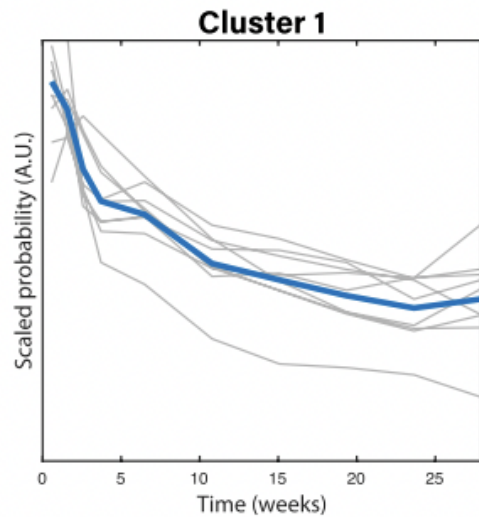
Definition

- >1-3 months after confirmed or probable infection
 - *CDC: >4 weeks*
 - *WHO: 3+ months*
 - *NASEM: 3+ months*
- Regardless of infection severity
- Impact on everyday functioning
- Cannot be explained by alternative diagnosis
- Relapsing and remitting course



Post-exertional malaise





Cardiovascular

- 25. Fainting
- 19. Pain/burning in chest
- 33. Tachycardia

- 49. Bradycardia
- 38. Palpitations
- 64. Visibly inflamed/bulging veins

Dermatologic

- 30. COVID toe

- 53. Dermatographia
- 55. Other Skin and Allergy
- 42. Peeling skin
- 54. Petechiae
- 44. Skin rashes

Gastrointestinal

- 9. Diarrhea
- 2. Loss of Appetite
- 4. Vomiting

- 26. Abdominal pain
- 18. Nausea

- 45. Constipation
- 43. Gastroesophageal reflux

**HEENT
(Head, ears,
eyes, nose,
throat)**

- 7. Runny nose
- 6. Sore Throat

- 48. Hearing loss
- 51. Other ear/hearing issues
- 39. Other eye symptoms
- 58. Tinnitus
- 59. Vision symptoms

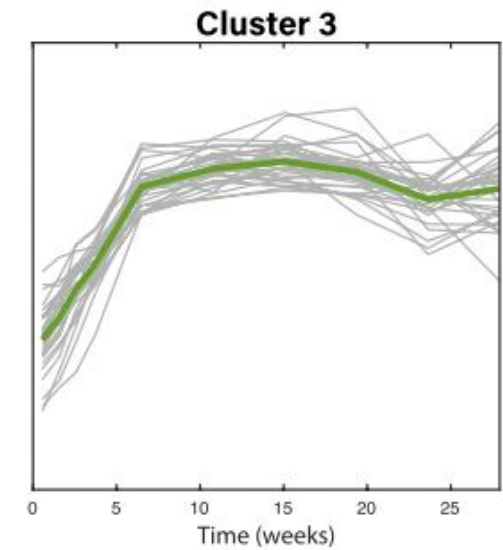
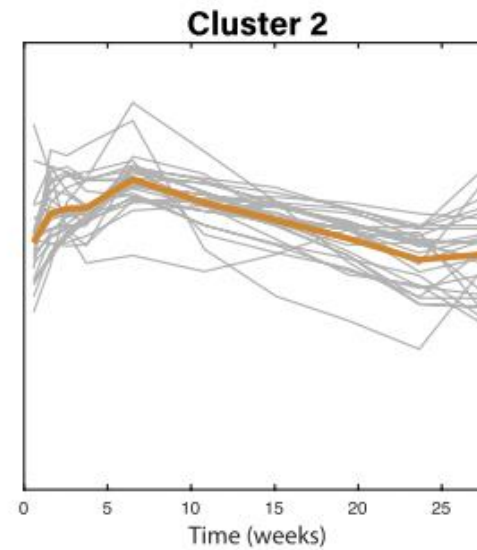
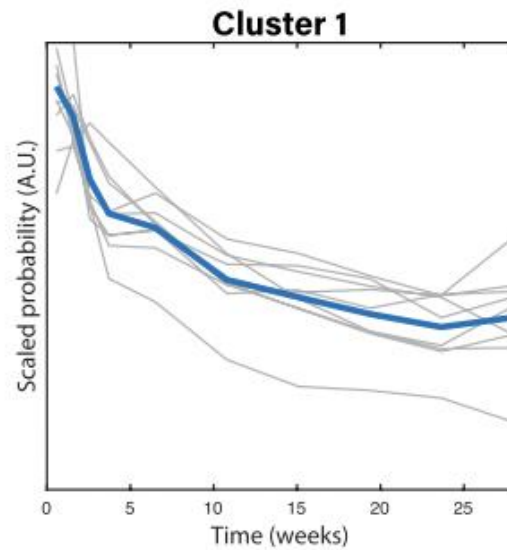
**Immunologic/
Autoimmune**

- 65. New allergies
- 63. New anaphylaxis reaction

Musculoskeletal

- 32. Bone ache or burning
- 21. Muscle aches
- 15. Tightness of Chest

- 37. Joint pain
- 40. Muscle spasms



Neuropsychiatric

- 20. Acute (sudden) confusion/disorientation
- 12. Changes to sense of smell and taste
- 22. Dizziness, unsteadiness or balance issues
- 31. Hallucinations
- 29. Headaches and related symptoms
- 35. Insomnia
- 27. Other sleeping symptoms
- 34. Sleep apnea
- 36. Slurring words/speech

- 41. All sensorimotor symptoms
- 47. Brain fog
- 61. Memory issues
- 50. Neuralgia (nerve pain)
- 62. Speech/language issues
- 52. Tremors
- 56. Vibrating Sensations

**Pulmonary/
Respiratory**

- 3. Dry cough
- 5. Rattling of breath

- 14. Breathing difficulty (normal O2 saturation level)
- 17. Cough with mucus production
- 10. Coughing up Blood
- 24. Other Respiratory and Sinus
- 16. Shortness of Breath
- 13. Sneezing

**Reproductive/
Genitourinary/
Endocrine**

- 60. All menstrual/period issues
- 46. Bladder control issues

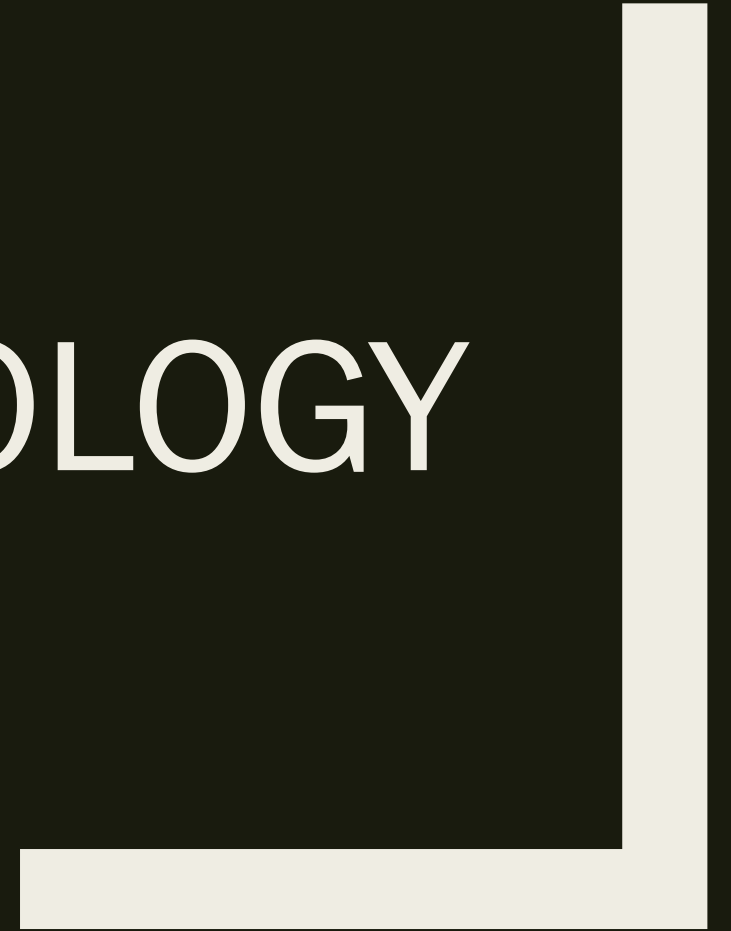
Systemic

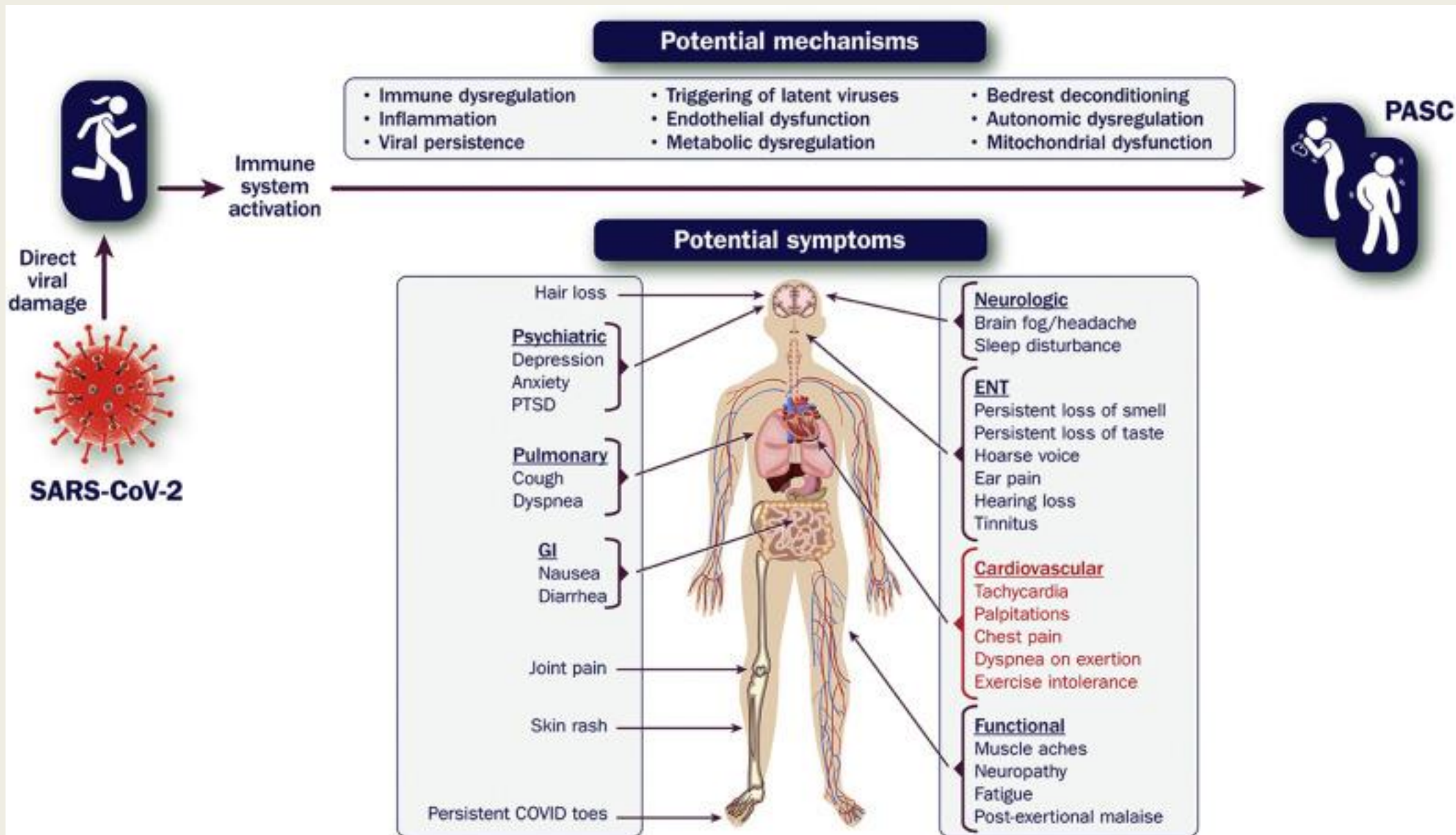
- 8. Elevated temperature (98.8-100.4F)
- 1. Fever ($\geq 100.4F$)

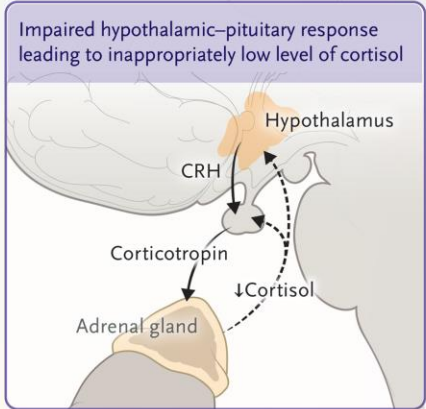
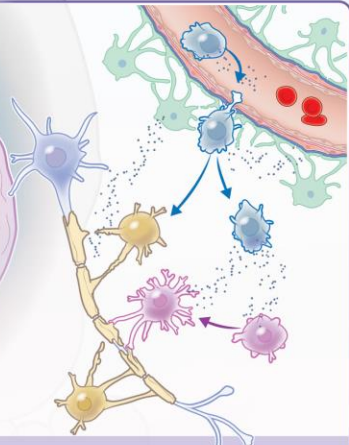
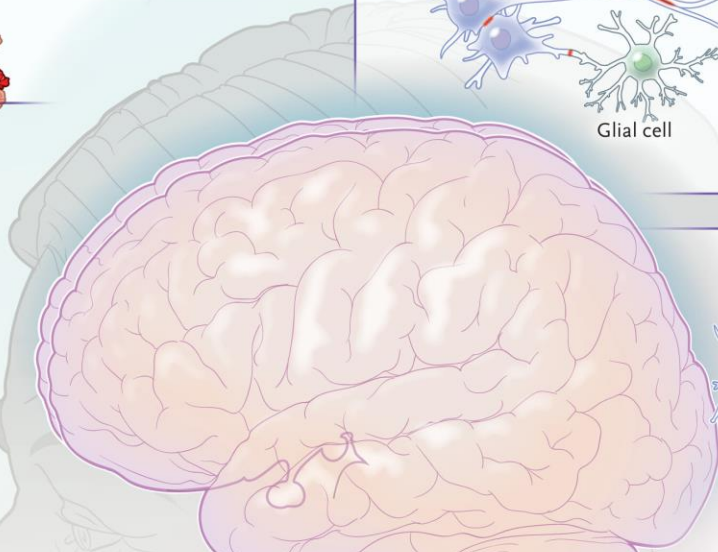
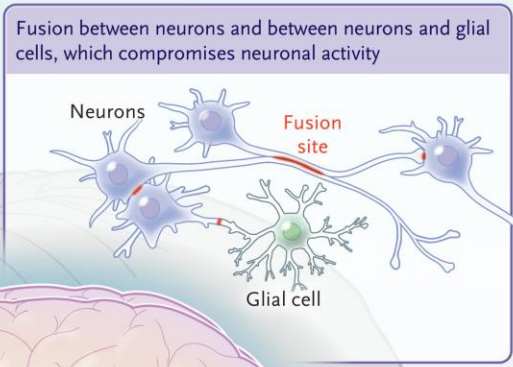
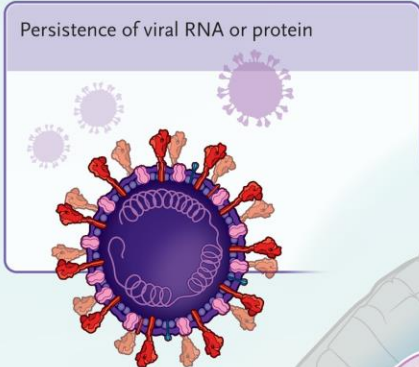
- 11. Chills/flushing/sweats
- 28. Fatigue
- 23. Low temperature

- 39. Other temperature issues
- 57. Post Exertional Malaise

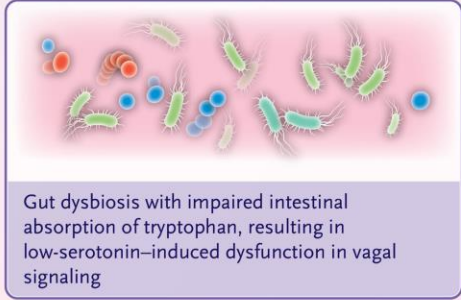
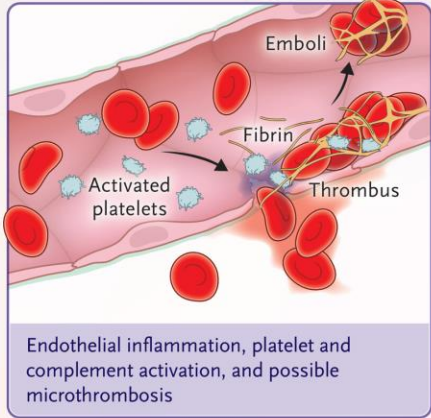
PATHOPHYSIOLOGY







Elevation in cytokine levels and increased microglial reactivity; activation of hippocampal microglia and reduced neurogenesis; persistent loss of oligodendrocytes and myelinated axons



Overlap with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?

■ 2015 Institute of Medicine Diagnostic Criteria

- *Required symptoms*
 - Substantial reduction in pre-illness activities
 - 6+ months
 - +++fatigue
 - Post-exertional malaise
 - Unrefreshing sleep
- *Additional symptoms*
 - Cognitive impairment
 - Orthostasis
- *Other symptoms*
 - Tender cervical or axillary lymphadenopathy
 - Headache
 - Myalgias/artralgias
 - Sore throat

■ Associated with:

- Female sex
- Major stressful life event
- *Coxiella burnetii*
- Epstein-Barr virus
- Ebola virus
- Ross River virus
- Chikungunya virus
- West Nile virus
- SARS-CoV-1

DIAGNOSIS



Long covid produces a wide variety of general and organ specific symptoms. Some patients have profound functional impairment including difficulties with daily activities. This graphic gives a quick overview of what to look out for in primary care, and when to refer.



Person with symptoms of long covid

Prolonged symptoms following SARS-CoV-2 infection which are not explained by an alternative diagnosis

A positive covid-19 test is helpful if present but its absence does not exclude the diagnosis

History and examination

Conduct a full examination in a face-to-face appointment.

Factors to look out for include:

Onset in or after January 2020

Course may be constant or relapsing-remitting, perhaps with specific triggers

Fatigue made worse by minor exertion

Functional impairment - unable to do normal job or activities

Occupational risk, such as health worker

Female sex Age 35-69

2 or more pre-existing long term conditions

Risk factors

Red flag symptoms

Wide range of associated symptoms

Associated symptoms, such as:

Sometimes, one organ system predominates

Ear, nose, and throat
Tinnitus, poor hearing
Altered smell Altered voice

Respiratory
Breathlessness
Altered breathing pattern

Skin and hair
Urticaria, chilblains
Hair loss

Neurocognitive
Impaired executive function
Sleep disturbance Poor memory
Poor concentration Headache

Mental health and wellbeing
Anxiety Depression

Muscle and joint pain

Gastrointestinal
Reflux or regurgitation
Bloating Difficulty swallowing Diarrhoea

Cardiovascular
Microvascular angina Dizziness
Tachycardia, especially on standing

Gynaecological
Menstrual irregularity
Premature menopause

Investigations

Guided by history and examination, for example:

General or fatigue

Full blood count
Renal and liver function
Thyroid stimulating hormone
C-reactive protein
Vitamin D
HbA1c

Respiratory

Pulse oximetry
Chest x ray
Lung function tests

Cardiovascular

Resting electrocardiogram
N-terminal BNP*
NASA lean test

An acutely unwell and deteriorating patient requires urgent action

Cardiorespiratory

Chest pain on exertion

Syncope on exertion

Acute and progressive dyspnoea

Tachycardia (>100 bpm) at rest or on minimal exertion

Desaturation >3% on exertion

Blood oxygen <94% at rest

Neurological

New onset confusion

Symptoms suggestive of stroke

Mental health
Worsening anxiety or depression

Thoughts of self-harm

Consider specialist service referral

Diagnosis in doubt

Marked functional impairment

Severe symptoms Not improving

Specific condition requiring assessment (such as tachycardia)

Long covid clinic and rehabilitation

If no long covid clinic locally, consider for example:

Suspected pulmonary embolism or chronic lung damage

Respiratory

If postural tachycardia syndrome is severe or diagnosis is in doubt

Cardiology

Tinnitus, markedly altered voice

Ear, nose, and throat

Difficulty swallowing, chronic diarrhoea

Gastro-enterology

Cognitive dysfunction impairing ability to work

Memory clinic

What can primary care teams do?

Diagnosis

- Hear the patient's story
- Diagnose and code 'post covid-19 syndrome'
- Assess for postural tachycardia
- Exclude other diagnoses

Prognosis

- Share uncertainties
- Help set realistic goals
- Monitor progress
- Sickness certification
- Support return to work

Management

- Whole person care and wellbeing
- Manage symptoms and comorbidities
- Encourage self-management

Symptomatic relief, such as antihistamines for urticaria

Offer covid-19 vaccination if not fully up to date

Diagnosis of Exclusion

- Work-up based on primary symptoms
 - *CXR, Spirometry, Diffusing Capacity*
 - *CBC, TSH*
 - *Polysomnogram*
- Validation, reassurance
- Screen for mental health

TREATMENT



Monday, July 31, 2023

NIH launches long COVID clinical trials through RECOVER Initiative, opening enrollment



Focus Areas

The RECOVER team identified 5 focus areas for clinical trials based on researchers' learnings from RECOVER observational cohort studies and conversations with people living with Long COVID. RECOVER clinical trials focus on 5 groups of symptoms that Long COVID patients reported to be the most burdensome and important to address:

- **Autonomic Dysfunction:** dizziness, fast heart rate, shortness of breath, upset stomach, or other changes in body functions that happen automatically
- **Cognitive Dysfunction:** brain fog, trouble thinking clearly, memory changes, slowed attention, and other symptoms related to brain function
- **Exercise Intolerance and Fatigue:** exhaustion or low energy that interferes with daily activities
- **Sleep Disturbances:** changes in sleep patterns or ability to sleep
- **Viral Persistence:** when the virus that causes COVID-19 stays in the body and causes damage to organs or the immune system to not function properly

Fatigue/Post-Exertional Malaise

- Counseling
 - *Sleep hygiene*
 - *Adequate rest*
- **4 Ps: Planning, Pacing, Prioritizing, and Positioning**
- Cognitive behavioral therapy

CBT for Fatigue

Efficacy of cognitive behavioral therapy targeting severe fatigue following COVID-19: results of a randomized controlled trial

Kuut et al., 2023 | *Clinical Infectious Diseases*



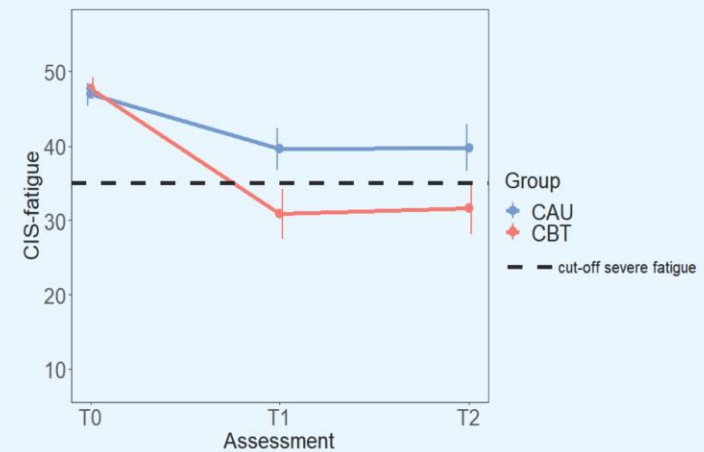
BACKGROUND: Severe fatigue following COVID-19 is prevalent and debilitating. This study investigated the efficacy of cognitive behavioral therapy (CBT) for severe fatigue following COVID-19.



PARTICIPANTS: Eligible patients were diagnosed with a symptomatic, laboratory-confirmed SARS-CoV-2 infection, were severely fatigued, with fatigue starting or increasing substantially directly after the onset of symptoms of COVID-19, were functionally impaired, and were 3-12 months post-COVID-19.

METHODS

A multicenter, 2-arm randomized controlled trial was conducted in the Netherlands. Patients were randomly assigned (1:1) to CBT or care as usual (CAU). Effects were evaluated directly post CBT or CAU (T1), and after six months (T2).



Overall between-group mean difference (95%CI) = -8.8 (-11.9 to -5.8), $p < 0.001$; $d = 0.69$

CONCLUSION: Among patients, who were mainly non-hospitalized and self-referred, CBT was effective in reducing fatigue. The positive effect was sustained at six month follow-up. Of the CBT group 63% was no longer severely fatigue at T2 compared to 26% in the CAU group. All secondary outcomes (Physical functioning, Social functioning, Somatic symptoms, and Problems concentrating) favored CBT.

Neurocognitive Symptoms: RECOVER-NEURO

Original Investigation



Evaluation of Interventions for Cognitive Symptoms in Long COVID A Randomized Clinical Trial

Key Points

Question Do evidence-based rehabilitation strategies improve cognitive symptoms in persons with long COVID (ie, symptoms of fatigue, malaise, weakness, confusion that persist beyond 12 weeks after an initial COVID infection)?

Findings This randomized clinical trial included 328 participants randomly assigned to 3 active interventions over 10 weeks at 22 clinical sites. None of the interventions demonstrated benefits on the modified Everyday Cognition Scale 2 in the intention-to-treat population by the end of the intervention period.

Meaning The trial failed to demonstrate differential benefits from online cognitive training, a structured cognitive rehabilitation program, or transcranial direct current stimulation in participants with cognitive long COVID.

Neurocognitive Symptoms: Promising Therapies

- Cognitive behavioral therapy can improve concentration
 - *Validated with online delivery*
- Preliminarily promising studies without conclusive evidence
 - *Hyperbaric oxygen*
 - *Noninvasive brain stimulation (although negative in RECOVER)*
 - *Supplements*

Hyperbaric Oxygen Therapy

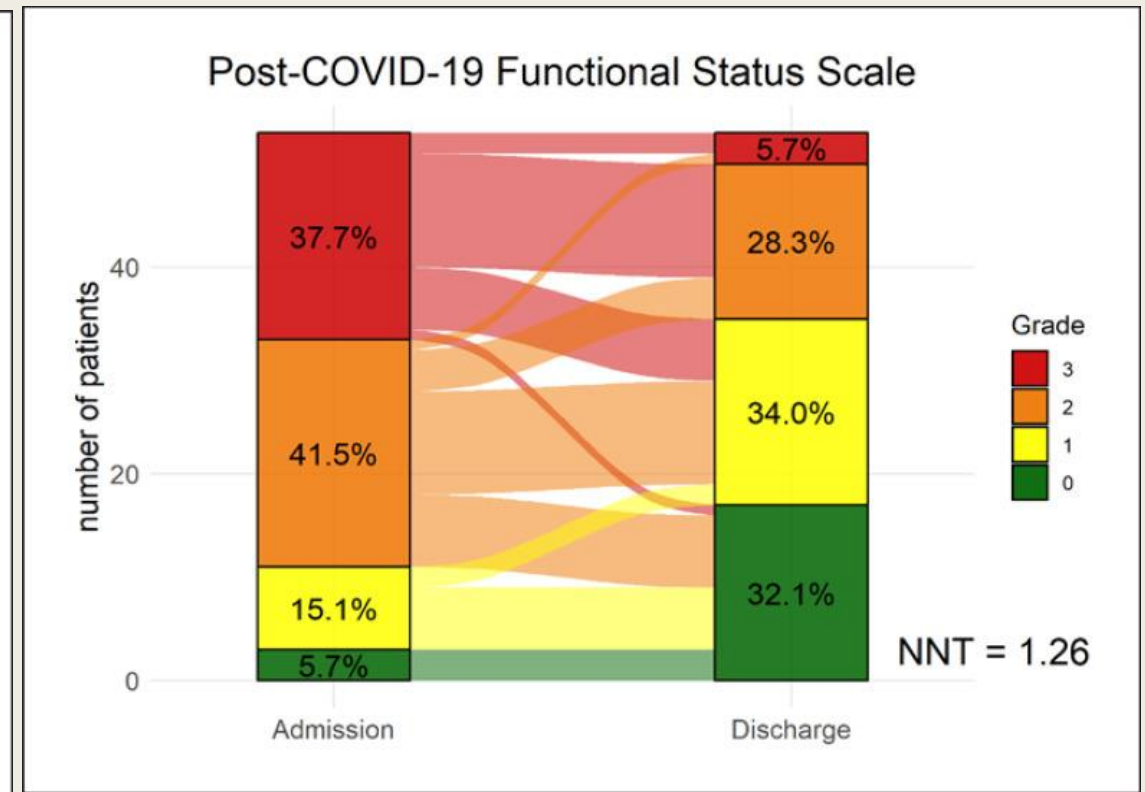
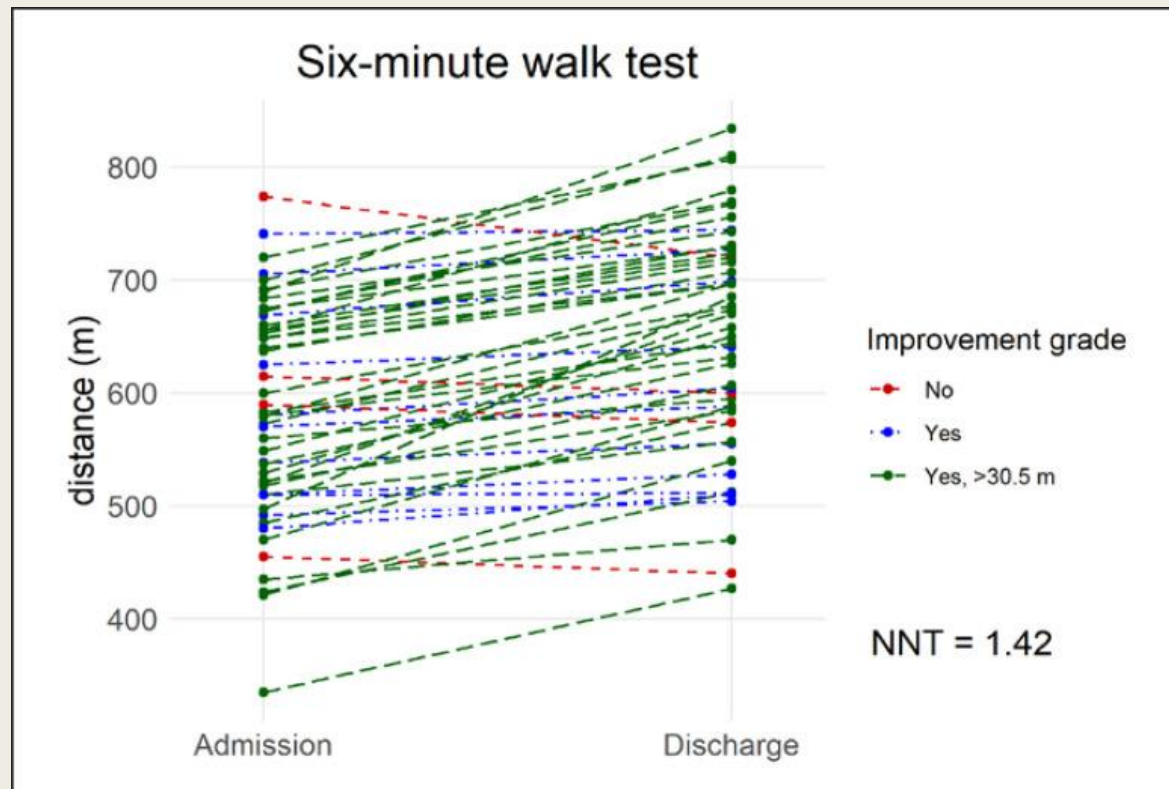
- Intervention n=37 vs sham n=36
- 40 daily sessions
- Impact on neurocognitive symptoms

	HBOT				Control				p-value baseline	Net effect size*	ANOVA (group-by-time) interaction	
	Pre	Post	p-value**	Change	Pre	Post	p-value**	Change			F	p-value
N	37				36							
Score	98.3±11.1	104.1±7.2	0.0001	5.8±7.9	98.9±8.5	101.3±8.9	0.0105	2.4±5.4	0.821	0.495	4.469	0.038
Memory	93.7±13.4	102.0±10.9	0.0001	8.3±11.2	94.9±12.2	102.1±8.7	0.0000	7.2±8.5	0.695	0.111	0.226	0.636
Executive function	103.5±13.1	109.0±8.2	0.0029	5.6±10.6	102.5±10.3	103.8±10.5	0.2526	1.3±6.8	0.725	0.477	4.159	0.045
Attention	97.3±16.0	101.9±9.0	0.0292	4.6±12.4	99.6±8.2	99.4±10.1	0.8495	- 0.3±8.3	0.434	0.463	3.914	0.052
Information processing speed	94.8±14.2	102.4±13.0	0.0003	7.6±11.4	94.4±14.2	98.3±17.7	0.0734	3.9±12.7	0.910	0.303	1.673	0.200
Motor skills	102.4±12.6	105.3±8.3	0.0827	2.9±10.0	102.9±8.4	102.9±9.0	0.9639	0.1±6.7	0.858	0.338	2.079	0.154

Respiratory Symptoms

- Dyspnea, Exercise Intolerance
 - *Rehabilitation*
 - Supervised exercise
 - Autonomic Conditioning Therapy
 - Breathing Retraining
- Cough
 - *Symptom-directed*

Pulmonary Rehabilitation for PASC



Low-Dose Naltrexone (LDN)

- Immune modulation activity at low doses
- 1 mg daily, increased to 3 mg daily as tolerated
- No control group

Table 3

Incidence of reported symptoms at baseline and at 2 months.

Symptoms	Baseline n (%)	2 month follow up n(%)	P value (2 tailed <0.05)
Total	36	36	
Fatigue	33(91.7)	27(75)	.085
Fevers	6(16.7)	2(5.6)	.185
Sore throat	13(36.1)	8(22.2)	.136
Anosmia/dysgeusia	16(44.4)	11(30.6)	.171
Hair loss	11(30.6)	9(25)	.65
Tinnitus	17(47.2)	12(33.3)	.2
Chest pain/tightness	20(55.6)	12(33.3)	.047
Palpitations	22(61.1)	16(44.4)	.132
Cough	19(37.3)	5(13.9)	.016
Shortness of breath	25(69.4)	19(52.8)	.09
Headache	27(75)	24(63.9)	.314
Dizziness	17(47.2)	14(38.9)	.618
Brain fog	27(75)	20(55.6)	.072
Sleep disturbance	26(72.2)	16(44.4)	.058
Dysthesia	20(55.6)	13(36.1)	.056
Abdominal discomfort/ bloating	17(47.2)	14(38.9)	.449
Nausea/Vomiting	12(33.3)	6(16.7)	.083
Diarrhoea	14(38.9)	9(25)	.166
Joint pain	26(72.2)	13(36.1)	.008
Myalgia	20(55.6)	14(38.9)	.163
Low mood	28(77.8)	17(47.2)	.003
Anxiety	20(55.6)	16(44.4)	.337
Personality change	9(25)	0(0)	.001

Phases of Rehab for Exercise Intolerance/ Dysautonomia

Modified Levine Protocol - Mount Sinai Approach

	Goals	Modality	Level of Effort
Phase 1	Sx stabilization	<ul style="list-style-type: none"> • Introduce exercise • Monitor: VS, RPE, Sx • Supine exercise • Breathing exercises 	Stop & rest if > 3 from starting values
Phase 2	Autonomic regulation Aerobic exercise	<ul style="list-style-type: none"> * Sitting/ standing exercise * Standing 1 min. > short walking bouts gradually over weeks 	same
Phase 3: Submaximal Exercise (Modified Levine Protocol)	Higher intensity aerobic exercise (Sx are stabilized autonomics are regulated)	<ul style="list-style-type: none"> * Modified Levine Protocol, PT supervised for 1st month * Progression from recumbent bike or swimming > upright bike, elliptical, treadmill, over ground walking (3x/ wk.), strengthening (2x/ wk.) 	Monitor HR, Sx, use individualized target HR and RPE

QUESTIONS

