Long COVID: Epidemiology and Proposed Mechanisms

October 25, 2021
New York State Department of Health
Commissioner's Medical Grand Rounds

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Division of Infectious Diseases

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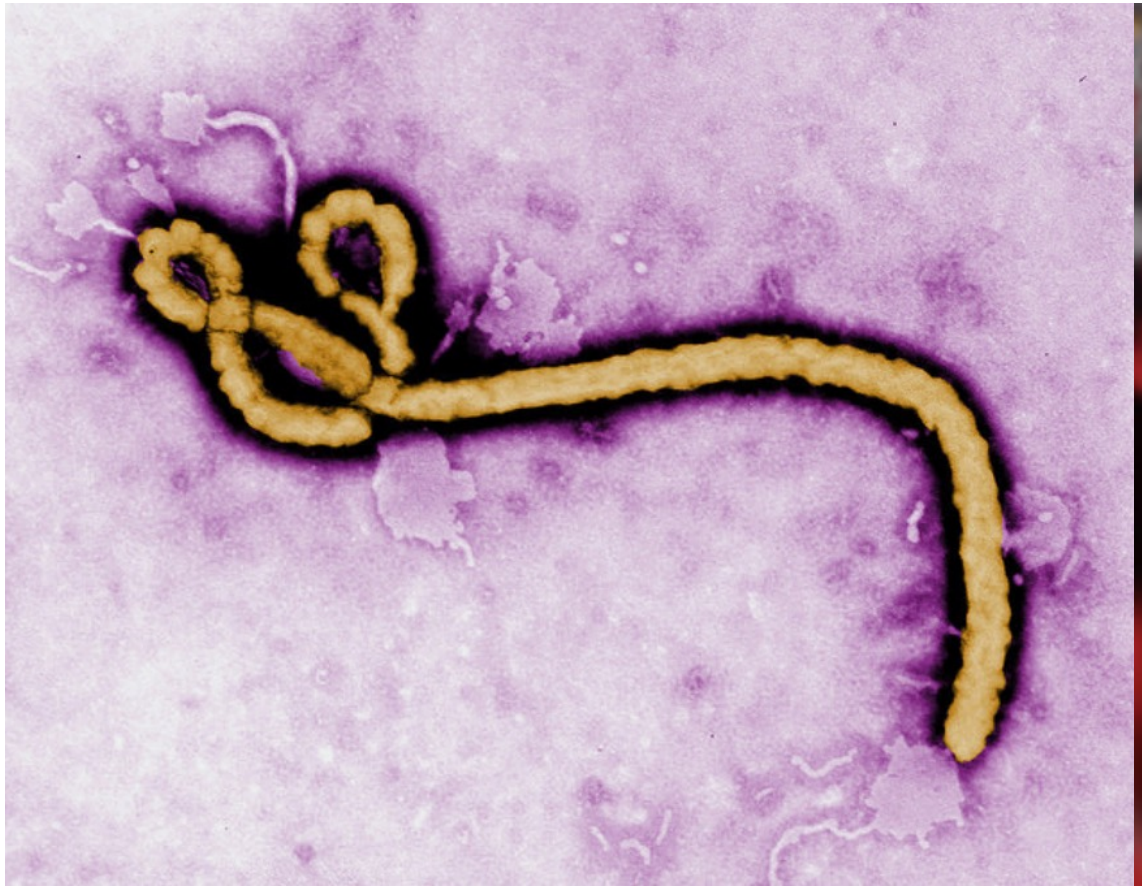
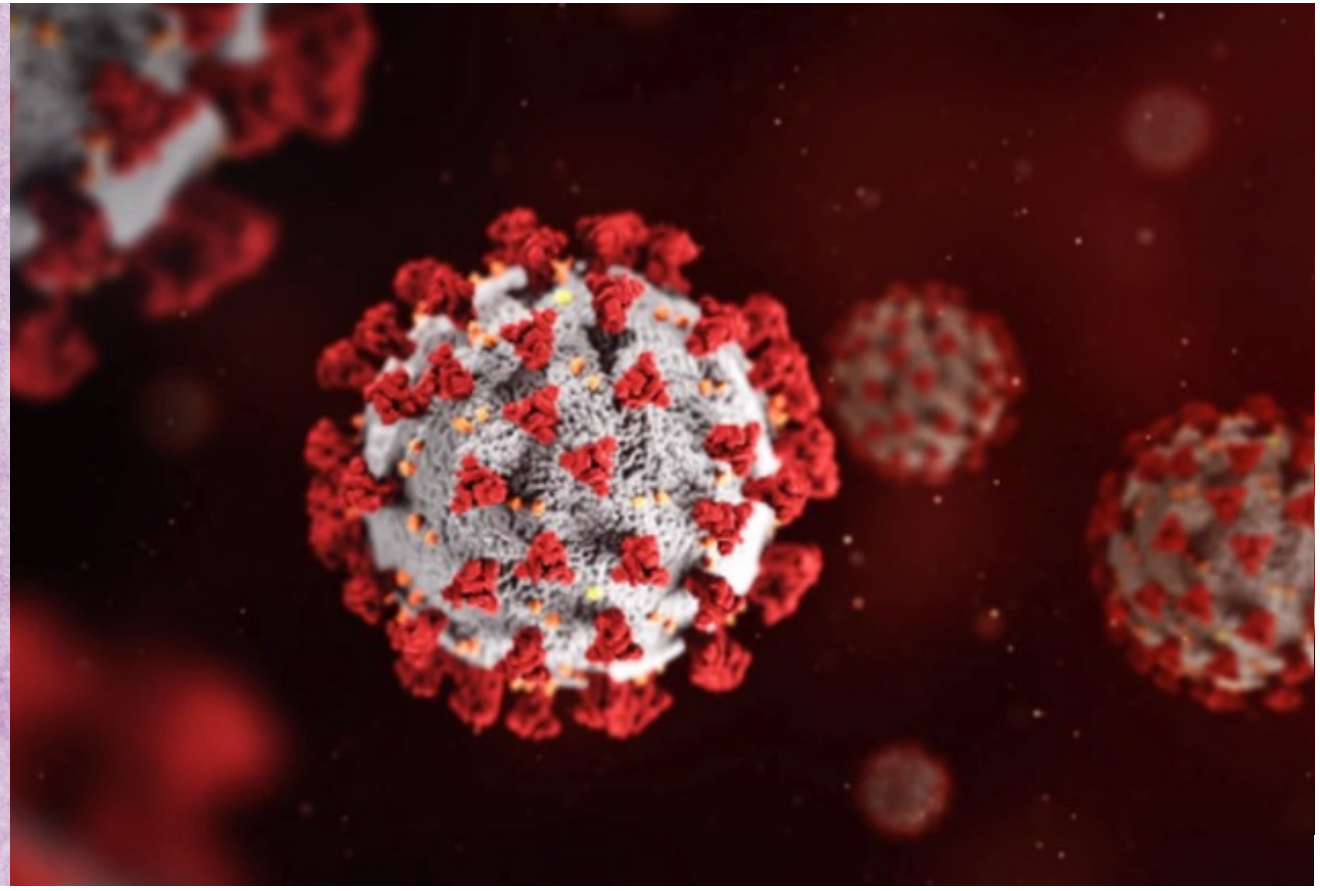
Disclosures

- I have no financial interests to disclose

Post-viral Sequelae





Latest

The Atlantic

SCIENCE

LONG-HAULERS ARE FIGHTING FOR THEIR FUTURE

Many people with long COVID feel that science is failing them. Neglecting them could make the pandemic even worse.

By Ed Yong

SEPTEMBER 1, 2021

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The Backstory: Long COVID causes fatigue, pain. Here's what long-haulers want you to know.

Nicole Carroll USA TODAY

Published 5:01 a.m. ET Sep. 17, 2021

Science

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PERSPECTIVE | VIEWPOINT: COVID-19

The road to addressing Long Covid

NISREEN A. ALWAN

SCIENCE • 30 Jul 2021 • Vol 373, Issue 6554 • pp. 491-493 • DOI: 10.1126/science.abg7113

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NEWS | 14 July 2021

Long COVID and kids: scientists race to find answers

Children get long COVID too, but researchers are still working to determine how frequently and how severely.

The New York Times

'This Is Really Scary': Kids Struggle With Long Covid

Lingering physical, mental and neurological symptoms are affecting children as well as adults, including many who had mild reactions to the initial coronavirus infection.

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PUBLIC HEALTH | OPINION

A Tsunami of Disability Is Coming as a Result of 'Long COVID'

We need to plan for a future where millions of survivors are chronically ill

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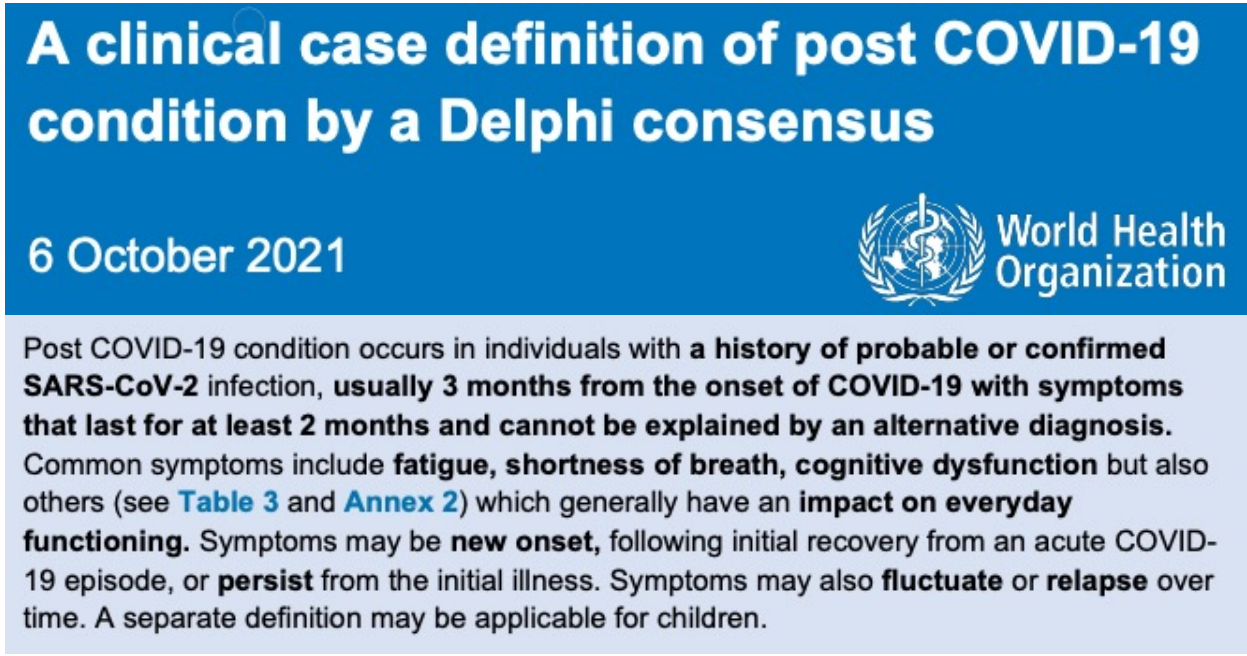
Post-viral Sequelae

- EBV
  - 23% of college students met criteria for ME/CFS at 6 months.[1]
- Post-Ebola Syndrome
  - At year 1: 48% headache, 18% fatigue, 23% muscle pain, 29% memory loss, 48% joint pain.[2]
- Chikungunya: “chronic chikungunya arthritis”
  - >40% with polyarthralgia lasting >3 months[3]
- Zika
  - Congenital abnormalities/microcephaly[4]

[1]Jason et al. Clin Inf Dis. 2020. PMID 33367564
[2]PREVAIL Study Group. N Engl J Med. 2019. PMID 30855742
[3]Amaral. Am J Med. 2020. PMID 31705850
[4]Peterson. N Engl J Med. 2016. PMID 27028561

What is Long COVID?

- Consensus definition is still evolving:
  - “Long COVID”
  - “Long-haulers”
- Convalescent periods
  - >4 weeks: “post-acute COVID-19” or “post-acute sequelae of COVID-19” (PASC) or “post-COVID Conditions”
    - 4-12 weeks: “ongoing symptomatic COVID-19”
    - >12 weeks: “post-COVID syndrome”



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

6 October 2021

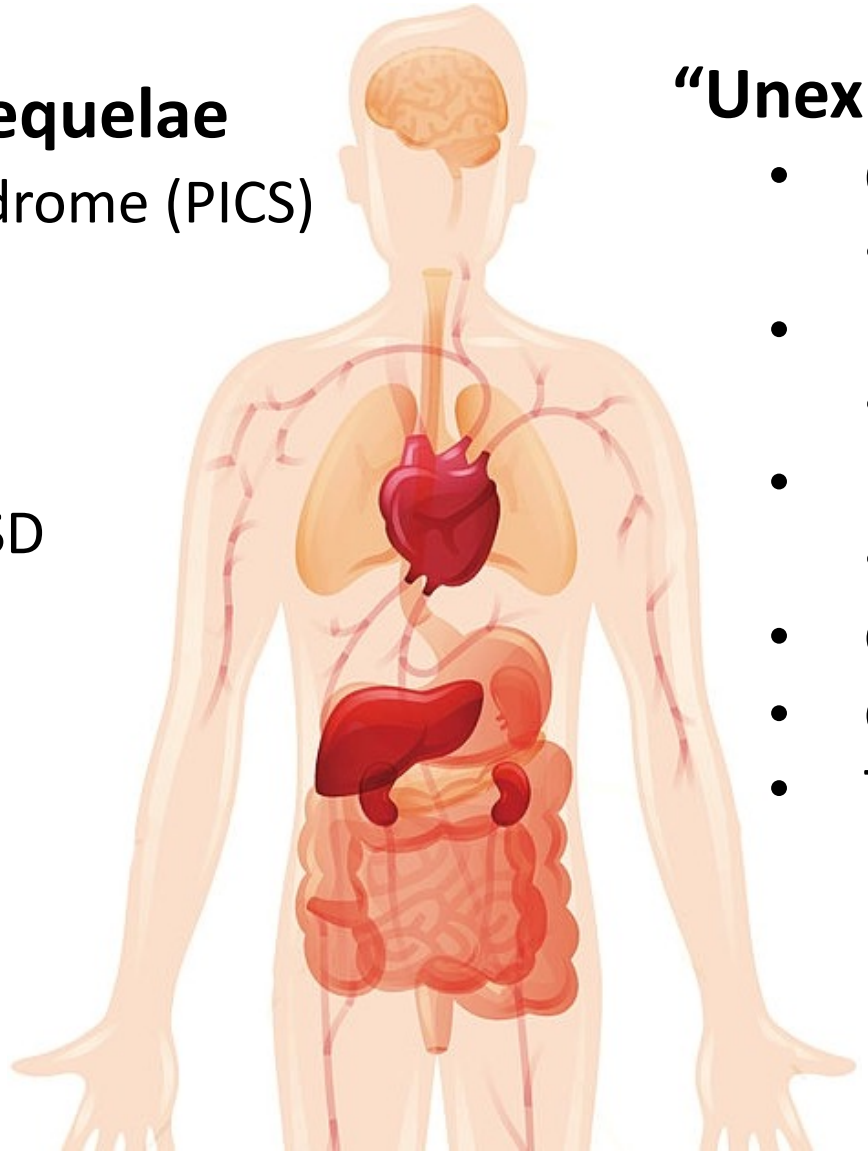
World Health Organization

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 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 (see Table 3 and Annex 2) which 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 separate definition may be applicable for children.

Nalbandian, et al. Nature. March 2021. PMID 33753937
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

Long COVID Phenotypes

- **“Expected” post-viral sequelae**
  - Post-intensive Care Syndrome (PICS)
  - Pulmonary fibrosis
  - Cardiomyopathy
  - Alopecia
  - Anxiety, depression, PTSD



“Unexpected” post-viral sequelae

- Cognitive dysfunction
  - Brain fog
- ME/CFS
  - Post-exertional malaise
- Dysautonomia
  - POTS
- Gustatory/olfactory
- Gastrointestinal
- Thromboembolism

Nalbandian, et al. Nature. March 2021. PMID 33753937

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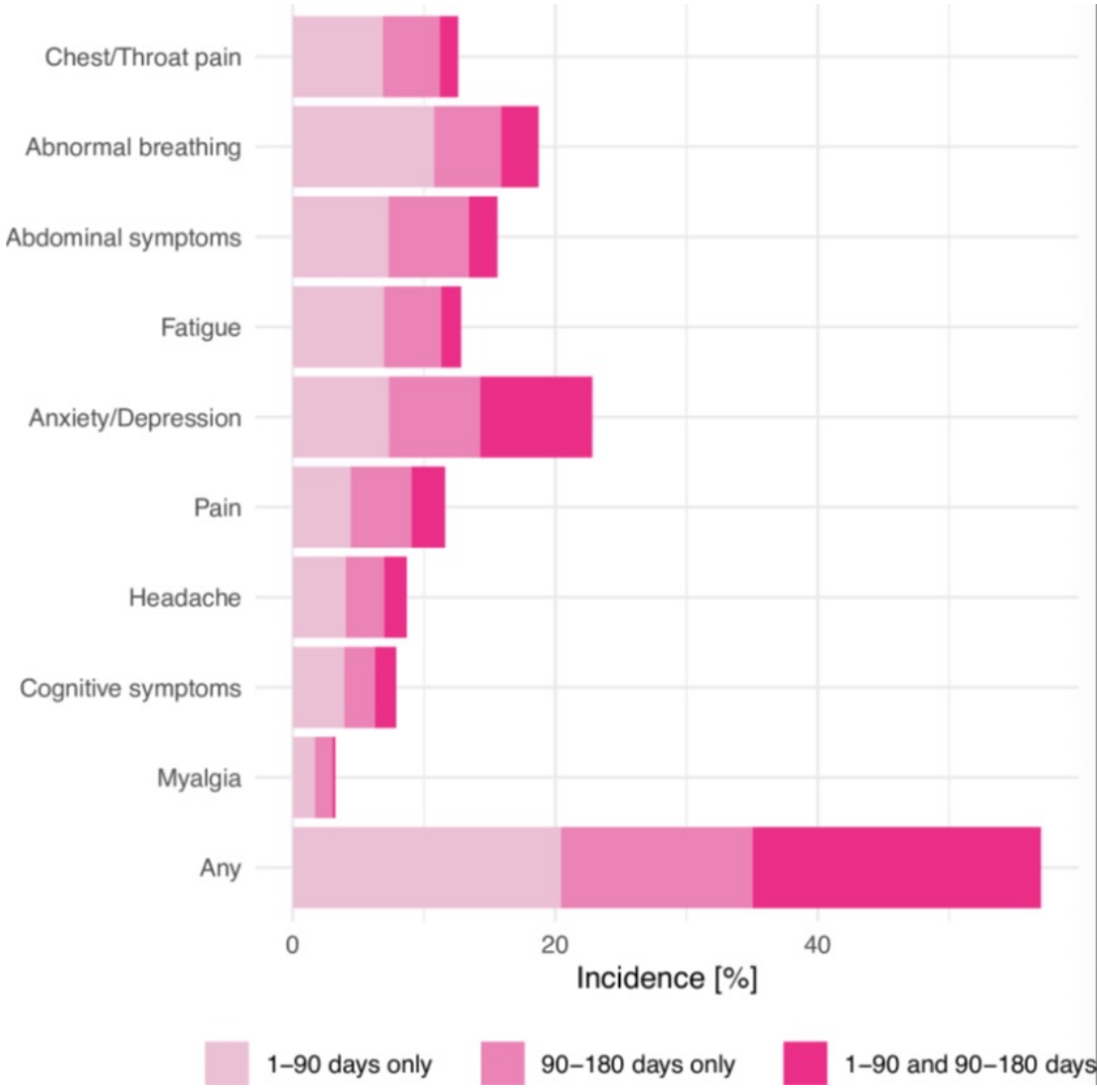
RESEARCH ARTICLE

Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19

Maxime Taquet, Quentin Dercon, Sierra Luciano, John R. Geddes, Masud Husain, Paul J. Harrison

Published: September 28, 2021 • https://doi.org/10.1371/journal.pmed.1003773

- EHR review of 58 HCOs and >270,000 survivors across the US
- 37% reported at least one symptom at 3-6 months



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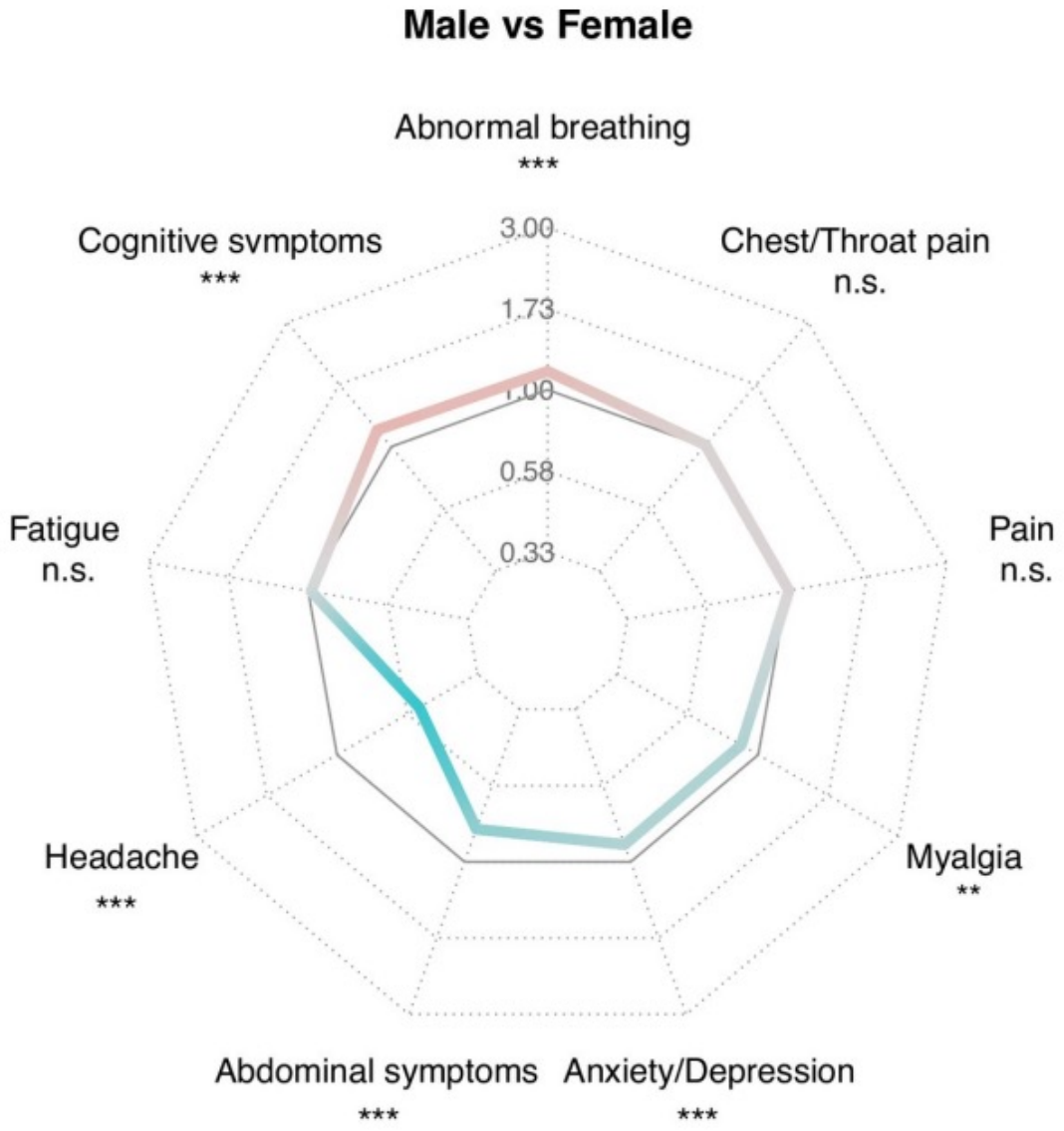
- Risk Factors
  - Gender
    - females more likely to report headache, GI, anxiety/depression
  - Age (range: incidence)
    - Age 10-21: 46%
    - Age 22-44: 55%
    - Age 45-64: 59%
    - Age >65: 61%
  - Acute severity (category: incidence)
    - Outpatient: 55%
    - Inpatient: 64%
    - ICU: 73%



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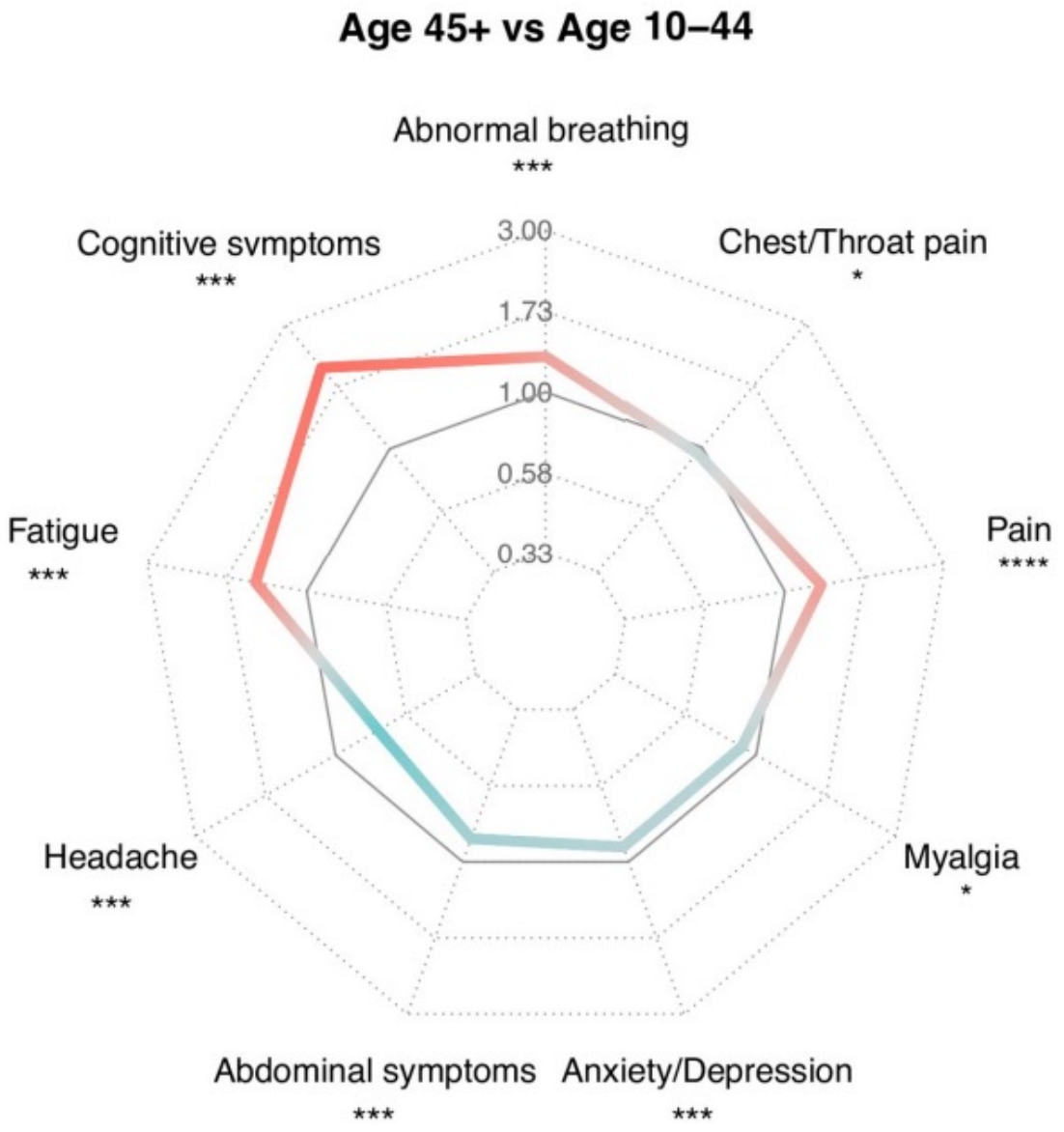

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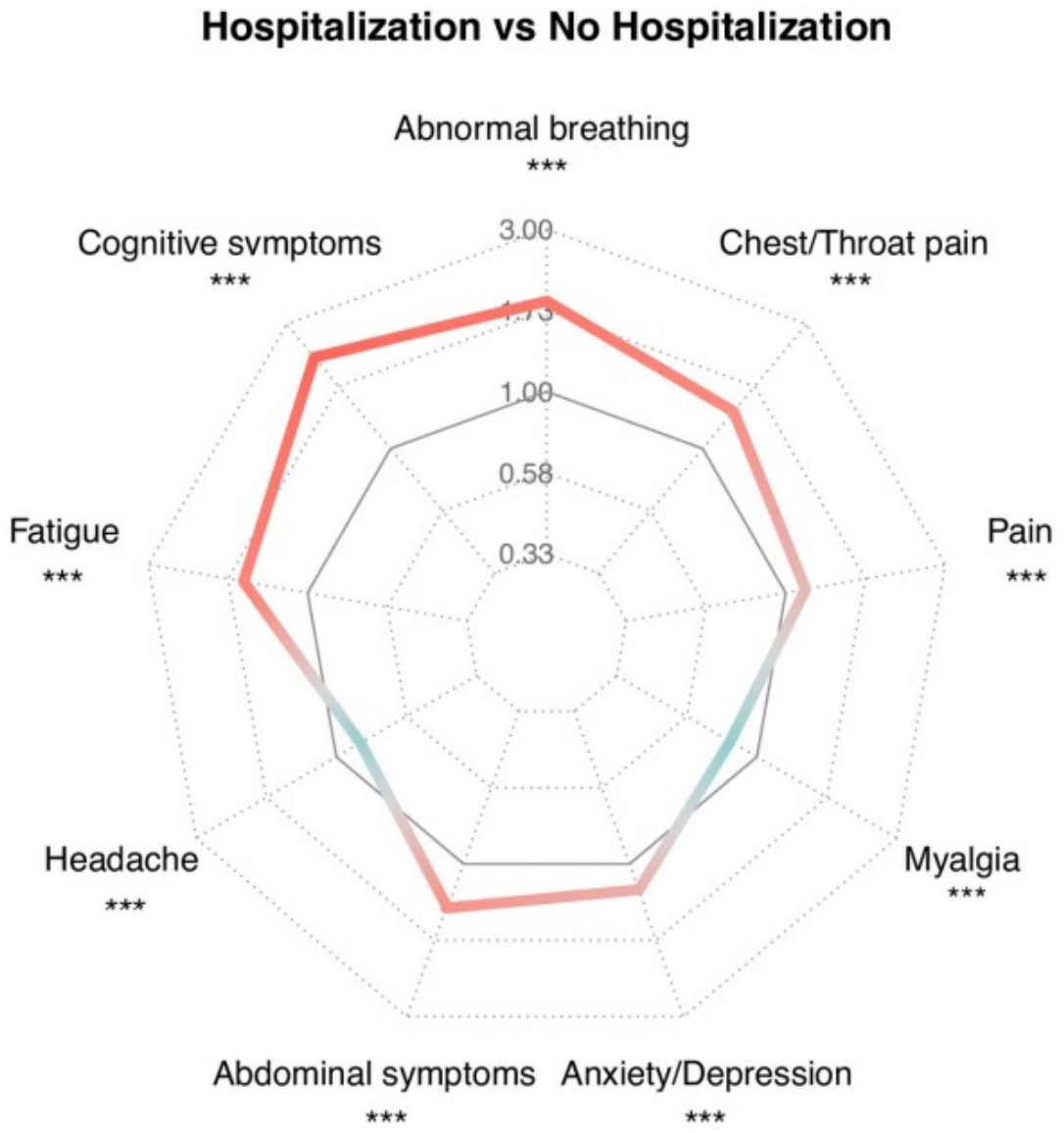

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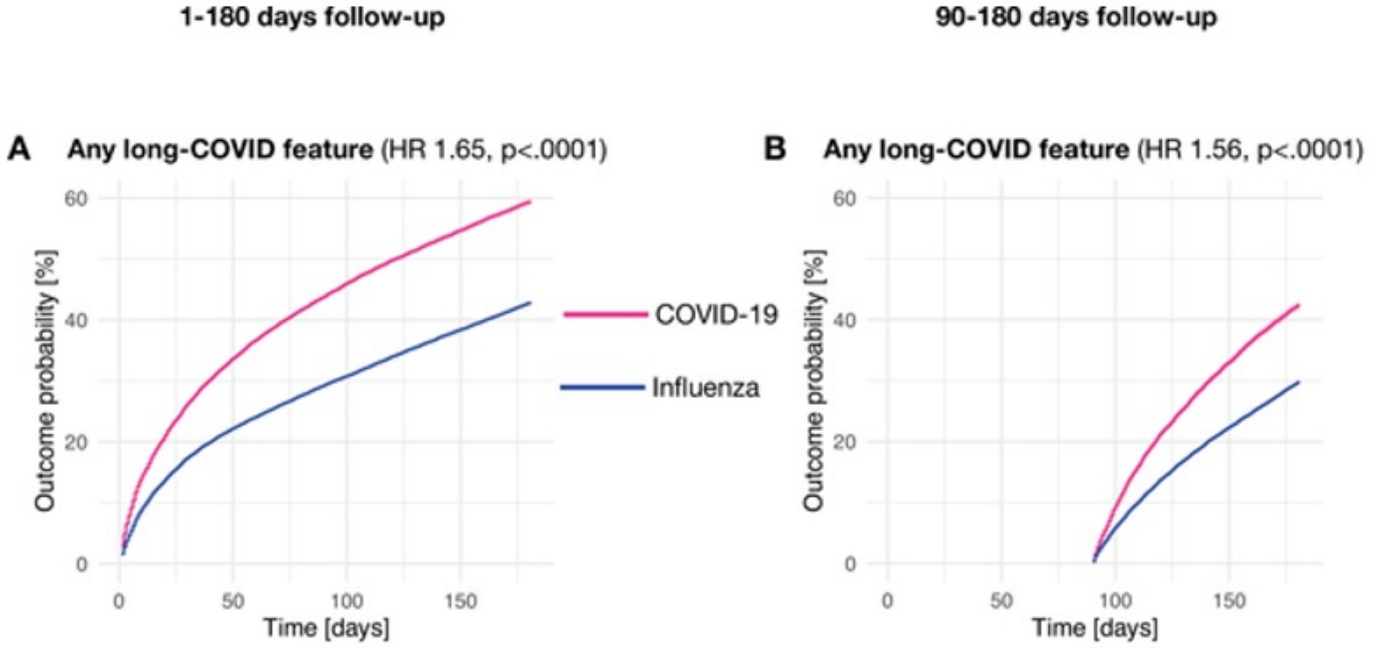
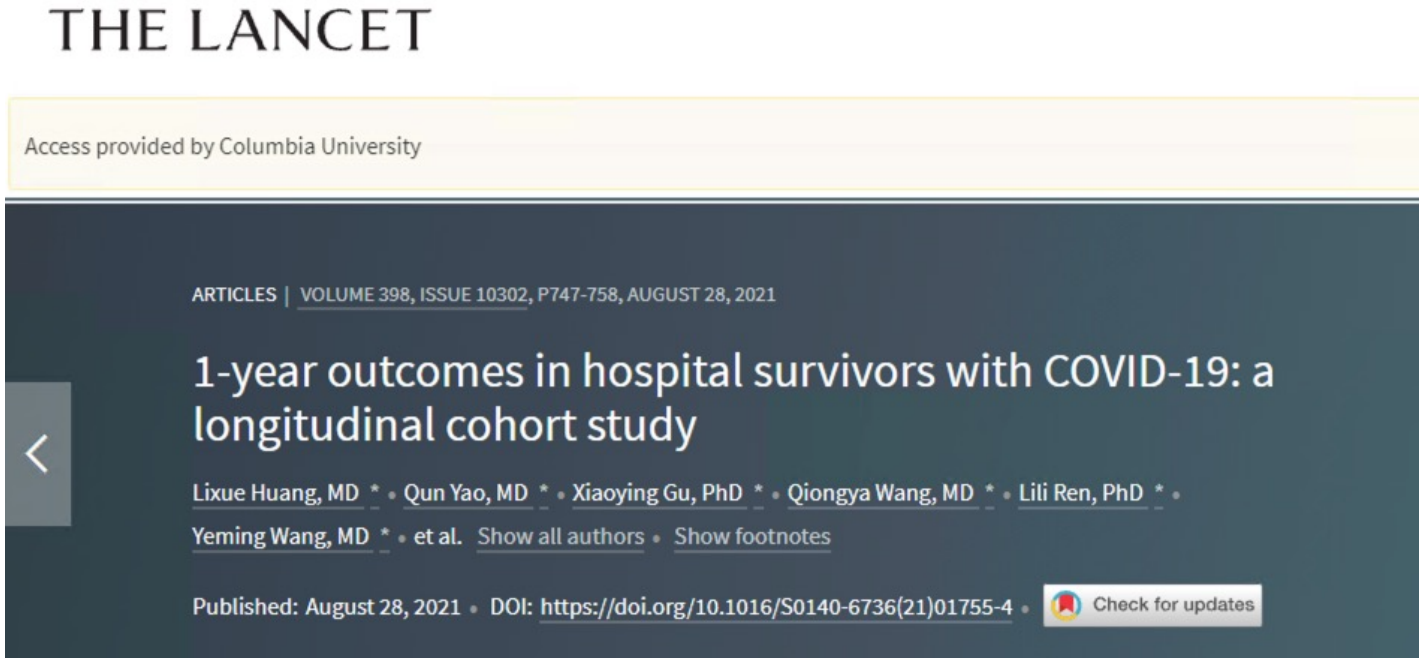
- Higher incidence with COVID-19 than influenza for all symptoms (HR 1.44-2.04, p<0.001)





- N=1,276 survivors discharged from Jin Yan-tan Hospital in Wuhan, China
- 49% reported at least 1 symptom
  - Fatigue 20%, sleep difficulty 17%, palpitations 9%, joint pain 12%, 26% anxiety or depression
- Women more likely to report:
  - Fatigue or muscle weakness (OR 1.43, CI 1.04-1.96)
  - Anxiety or depression (OR 2.00, CI 1.48-2.69)
  - Diffusion impairment (OR 2.97, CI 1/50-5.88)
- Older age groups more likely to report/have:
  - Anxiety or depression 18% higher (OR 1.18, CI 1.05-1.32)
  - Diffusion impairment 30% higher (OR 1.30, CI 1.01-1.68)

- UK Office for National Statistics:
  - Estimated >970,000 (1.7%) of population with self-reported long-COVID symptoms
    - 37% with COVID <1 year prior
    - 19% report severe impact on day-to-day activities
  - Risk factors: female gender, age 35-69, underserved areas, healthcare or social care employment

EClinicalMedicine
Published by THE LANCET
Volume 38, August 2021, 101019

Research paper

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

Hannah E. Davis [a, 1], Gina S. Assaf [a, 1], Lisa McCorkell [a, 1], Hannah Wei [a, 1], Ryan J. Low [a, b, 1], Yochai Re'em [a, c, 1], Signe Redfield [a], Jared P. Austin [a, d], Athena Akrami [a, b, 1]

- Multinational survey of long-COVID participants conducted by advocacy groups (n=3,762)
  - 86% experienced relapses
  - 87% with fatigue
  - 45% with reduced ability to work

Open access Original research

BMJ Open

Characterising the long-term clinical outcomes of 1190 hospitalised patients with COVID-19 in New York City: a retrospective case series

- Initial 1,190 patients hospitalized with COVID-19 at NYP/CUIMC during the surge in March and April 2020
- Persistent symptoms reported at 6-months
  - 26% cardiac and pulmonary symptoms
  - 24% neuropsychiatric symptoms
  - 21% gastrointestinal symptoms
- Patients with more severe COVID at the time of hospitalization were more likely to have reduced mobility, reduced independence, and need for dialysis

Shoucri et al. BMJ OpenForum. June 2021. PMCID8182750

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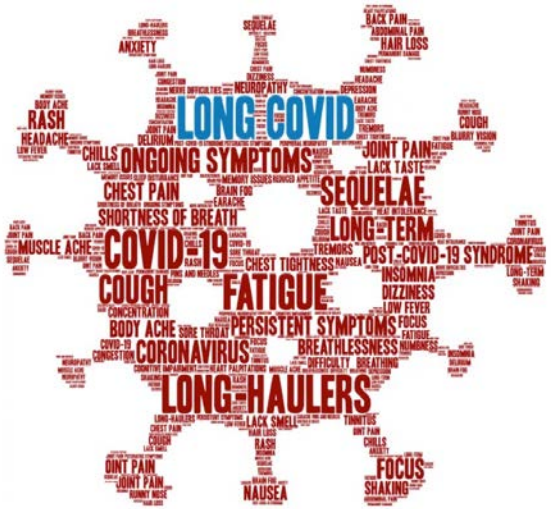
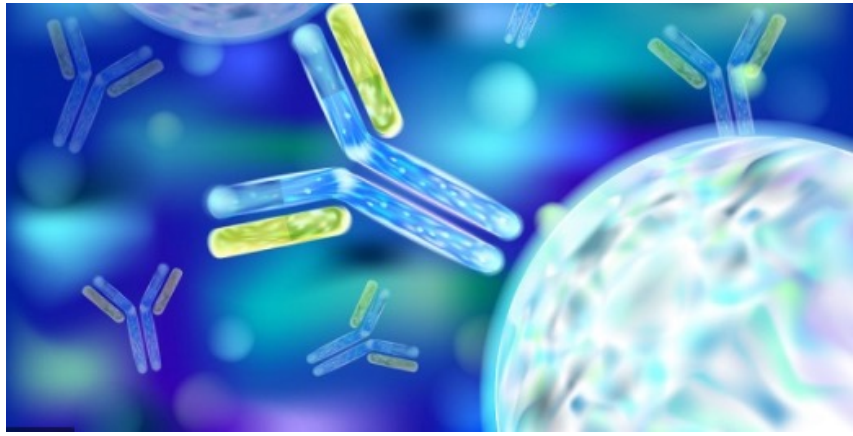
CUIMC COVID-19 Persistence ID Cohort (C-PIC)

- Collaboration between CUIMC ID Division and the Aaron Diamond AIDS Research Center
- Aims:
  - Characterize phenotypes of Long COVID
  - Evaluate the host-immune response and viral persistence
- 11 study visits over 2 years
- Study measures
  - Survey data
    - Baseline survey: demographics, acute illness
    - Symptom survey: broad organ system-based questions
    - Mental health surveys: PHQ9, GAD7, PCL-C, ISS
  - Biorepository: PBMC, plasma, saliva, stool, semen
- Current Enrollment: >300 participants





ClinicalTrials.gov Identifier NCT04448145

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NYP/CUIMC ID: COVID-19 PASC Cohort

Table 1. Organ System	Sequelae phenotypes reported at study visits conducted within weekly ranges post-symptom onset				
	≤6 weeks (N=196)	7-18 weeks (N=135)	19-30 weeks (N=116)	31-42 weeks (N=58)	43-54 weeks (N=42)
Neurologic PASC					
Fatigue	31(58%)	37(27%)	38(33%)	22(39%)	17(41%)
Neurocognitive	10(5%)	16(12%)	17(15%)	7(12%)	13(31%)
Dysautonomia	74(38%)	52(39%)	50(43%)	24(41%)	19(45%)
Psychiatric	63(32%)	49(36%)	47(41%)	27(47%)	18(43%)
Any symptom	102(52%)	72(53%)	68(59%)	36(62%)	25(60%)
Non-Neurologic PASC					
Cardiovascular	7(37%)	50(37%)	43(37%)	19(33%)	13(31%)
Pulmonary	90(46%)	50(37%)	37(32%)	16(28%)	18(43%)
GI	64(33%)	40(30%)	24(21%)	13(22%)	15(36%)
Musculoskeletal	63(32%)	5(40%)	37(32%)	18(31%)	16(38%)

Brain, Behavior, & Immunity - Health 16 (2021) 100315

Contents lists available at ScienceDirect

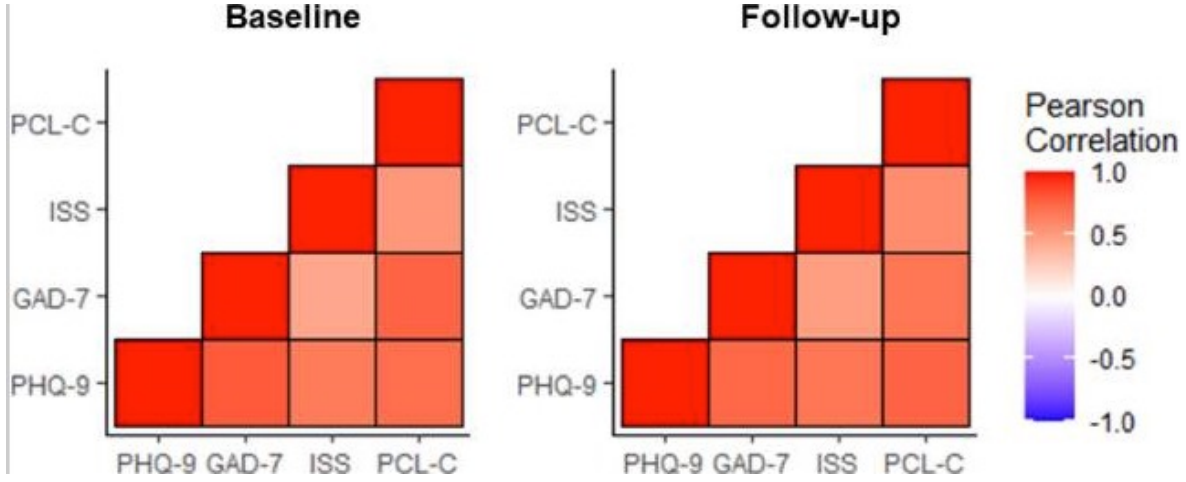
Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Short Communication

Anxiety, depression, insomnia, and trauma-related symptoms following COVID-19 infection at long-term follow-up

	Baseline	6-12 Months
PHQ-9	8/52(15%)	8/52(15%)
GAD-7	2/51(4%)	-
ISS	13/52(25%)	17/52(33%)
PCL-C	6/50(12%)	11/50(22%)



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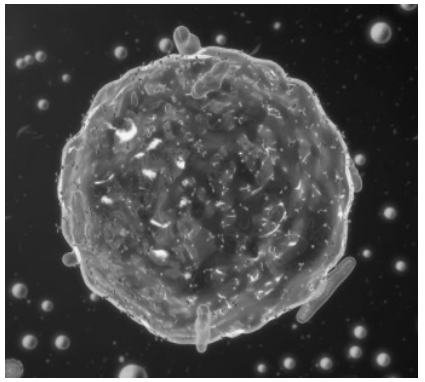
Proposed Long COVID Mechanisms

Autoimmune

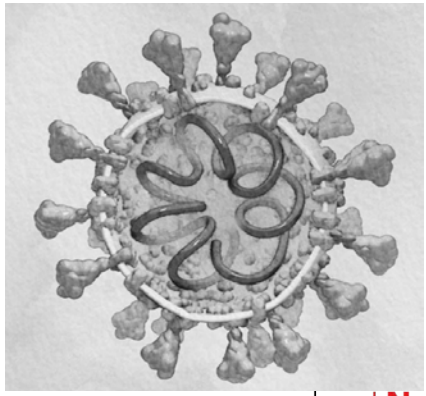
Immune Dysregulation



Host

Organ Damage

Viral Persistence



Viral

Proal, et al. Front Microbiol. June 2021. PMID34248921

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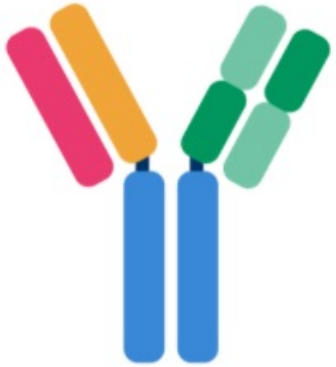
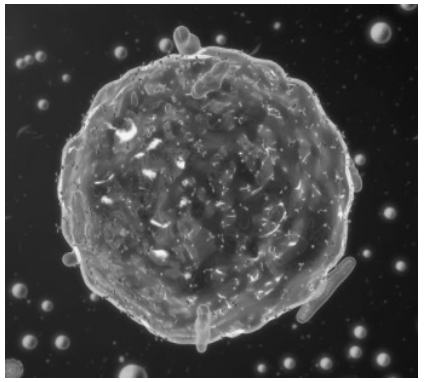


Host

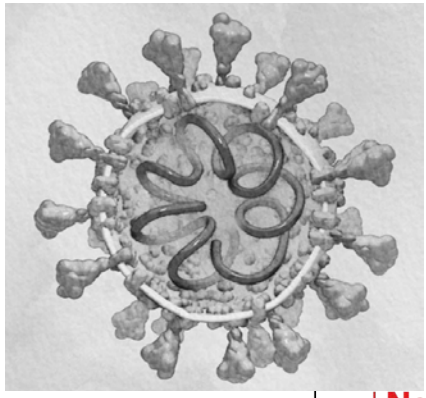
Immune Dysregulation



Organ Damage

Viral

Viral Persistence



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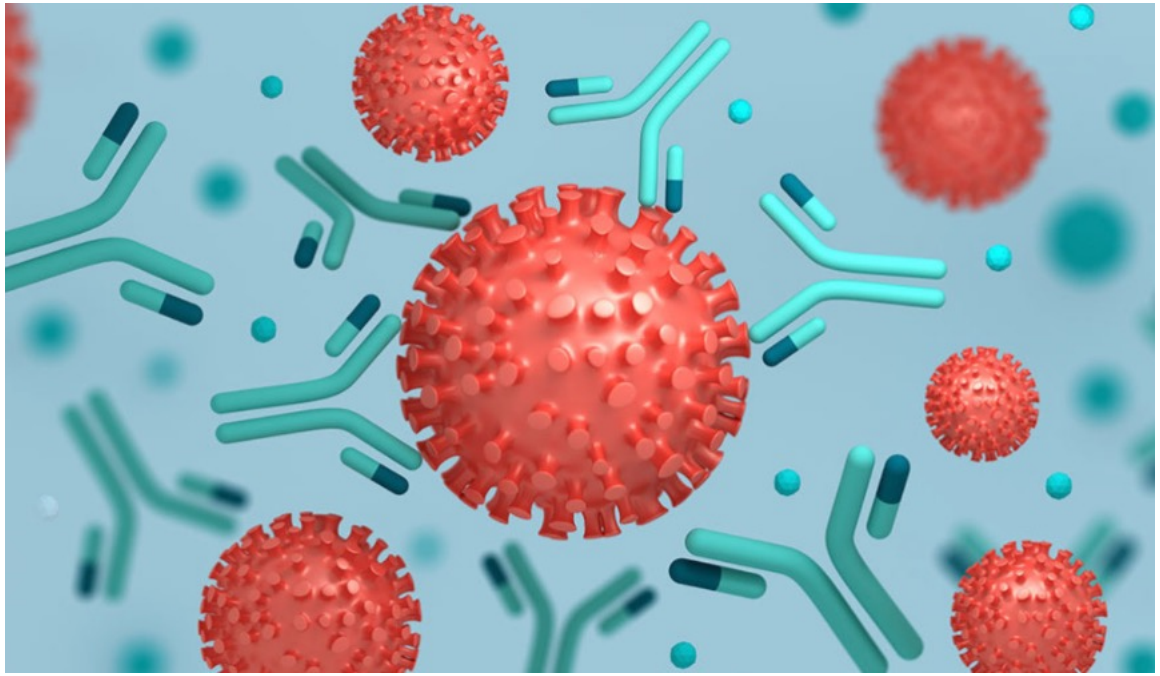
Autoantibodies in Acute COVID-19

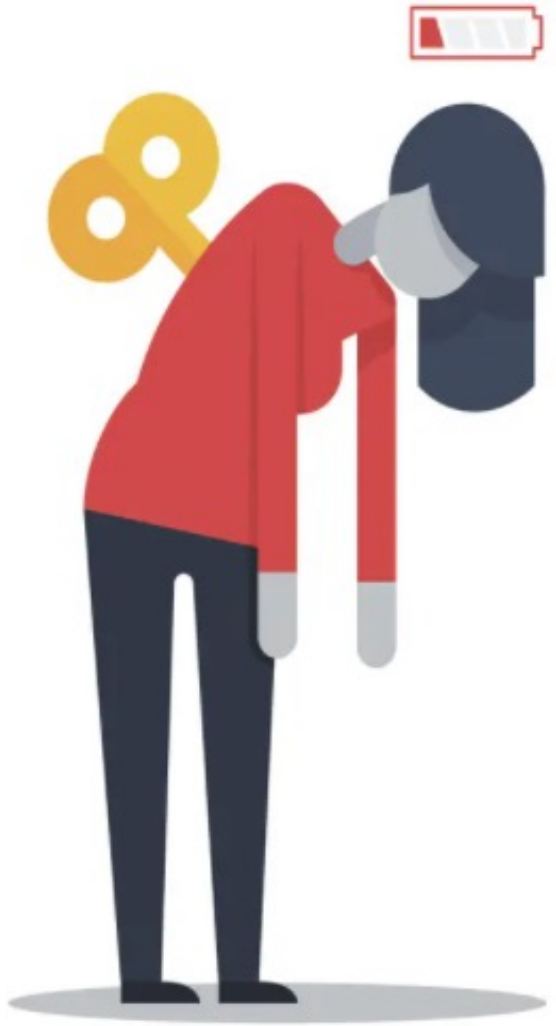
- Acute autoantibodies
  - Anti-SSA/Ro, ANA[1]
  - Anti-type 1 interferon[2]
  - Autoantibodies against immunomodulatory proteins (cytokines, chemokines, complement, cell-surface proteins)[3]



[1]Zhou, et al. Clin Trans Sci. 2020. PMCID 7264560
[2]Bastard, et al. Science. October 2020. PMCID 7857397
[3]Wang, et al. Nature. May 2021. PMCID 7743105

Long COVID: Autoantibodies

- G-protein coupled receptor (GPCR) autoantibodies
  - ME/CFS:
    - Elevations in beta adrenergic and muscarinic acetylcholine autoantibodies in chronic fatigue syndrome[1]
  - COVID-19:
    - All 31 with PASC enrolled had 2 to 7 GPCR-autoantibodies detected[2]
- Anti-ACE2 autoantibody[3]
  - 26/32 (81%) of convalescent inpatients
  - 14/15(93%) of acute inpatients
  - 1/20(5%) of outpatients
  - 0/13 controls



[1]Loebel, et al. Brain Behav Immun. 2016. PMID 26399744
[2]Wallukat, et al. J Transl Autoimmun. Apr 2021. PMCID 8049853
[3]Arthur et al. PLOS One. Sept, 2021. DOI: 10.1371/journal.pone.0257016

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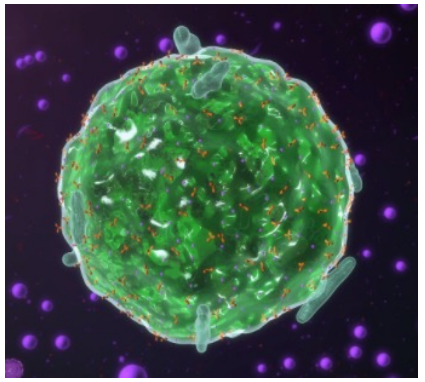
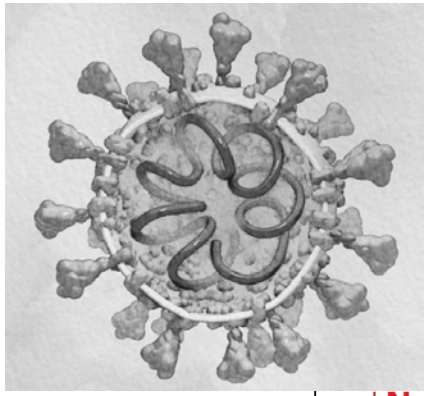


Host

Organ Damage

Viral Persistence



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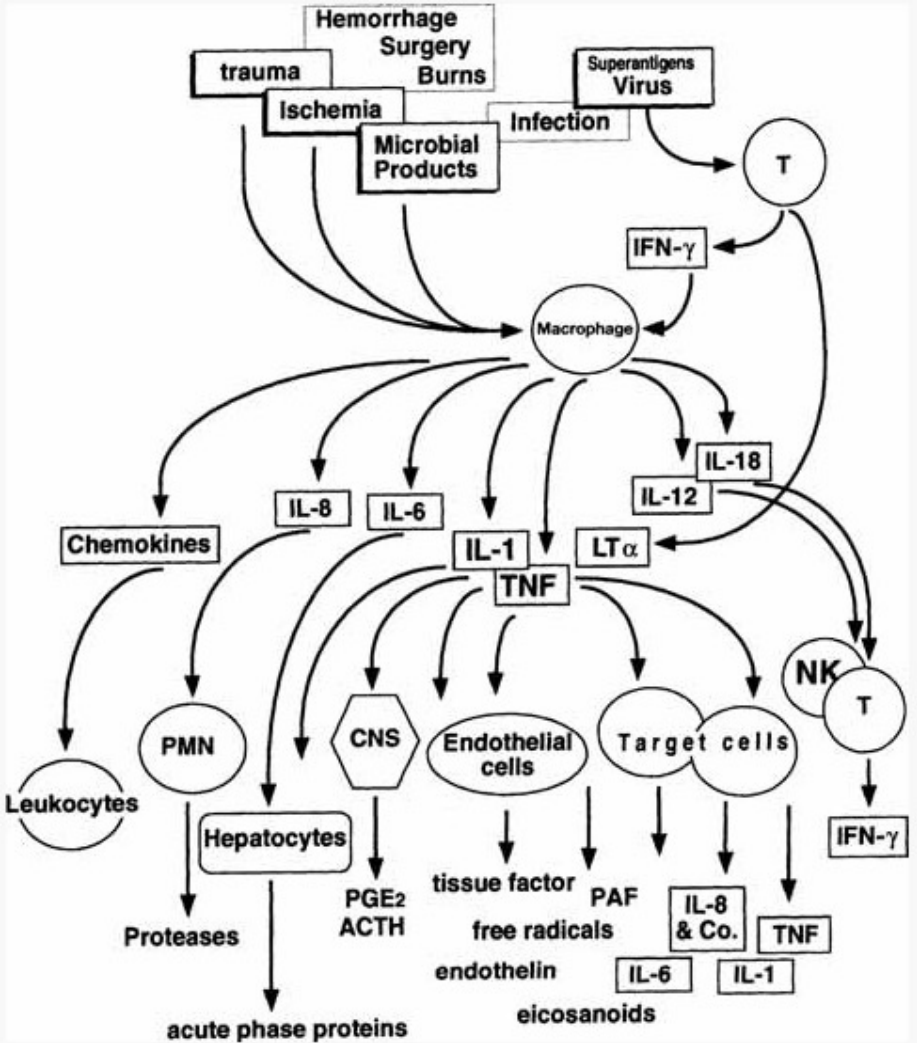
PASC: General Immune Dysregulation

- Compared with healthy controls, Long COVID patients had[1]:
  - Monocyte activation: CD14, CD16, and CCR5
  - Decreased PD-1 expressing T cells: CD4 and CD8
  - Cytokine elevation: CCL5/RANTES, IL-2, IL-4, CCL3, IL-6, IL-10, IFN-gamma, VEGF
  - Cytokine decrease: GM-CSF, CCL4
- Neurologic Long COVID[2]
  - Cytokine elevation: IL-4 and IL-6
  - Neuronal dysfunction: amyloid beta, neurofilament light, neurogranin, p-T181-tau



Patterson, et al. Frontiers in Immunology. June 2021. PMID 34262570
Sun, et al. Cells. February 2021. PMID 33668514

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Proposed Long COVID Mechanisms

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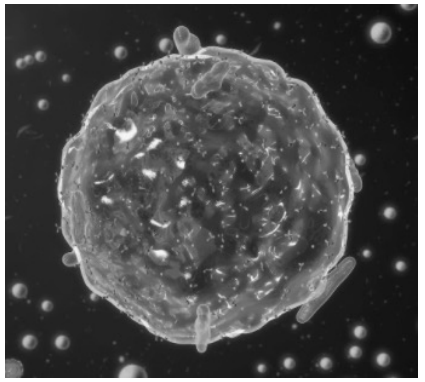

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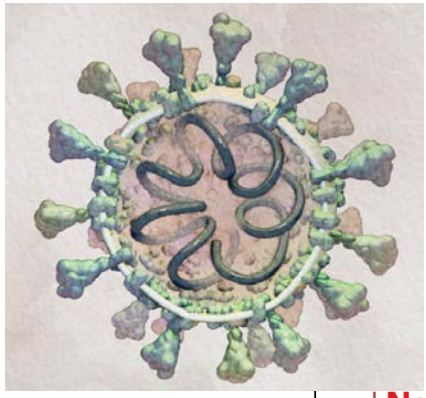

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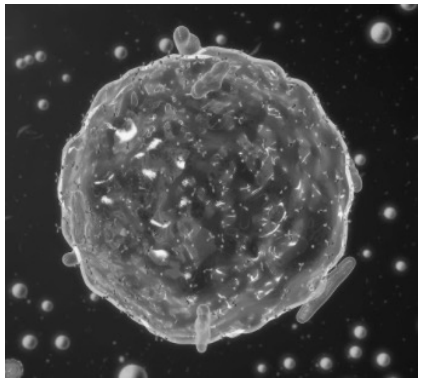

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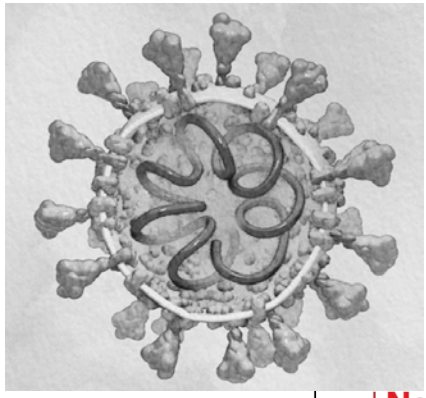

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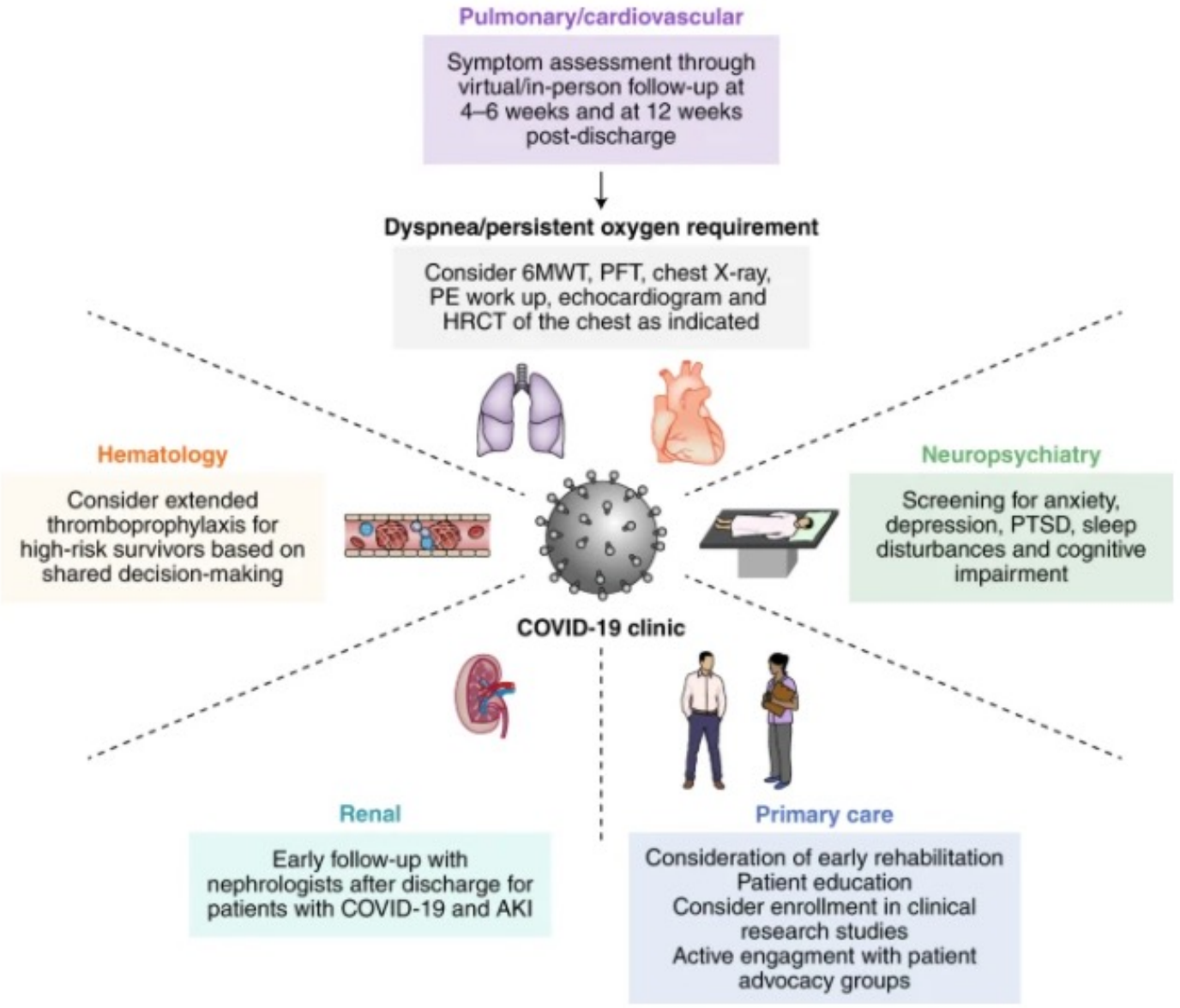
NYP-CUIMC Care

- Neurology/ID/Primary Care
  - ME/CFS[1]:
    - Pacing: identify mental and physical activity limits
    - Pharmacologic therapy
    - Diet modification
  - Insomnia:
    - Sleep optimization
    - Pharmacologic therapy
- Neurology/cardiology
  - Dysautonomia:
    - Compression stalkings, hydration, salt intake
    - Pharmacologic therapy
- Rehabilitation services
  - Pulmonary
  - Cardiovascular
  - Physical Medicine and Rehabilitation
- Mental health services

Fig. 2: Interdisciplinary management in COVID-19 clinics.



[1]https://www.cdc.gov/me-cfs/treatment/index.html

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Long COVID & Stigma

Long Covid Doubles Burden of Mystery Illness Few Doctors Treat

Oct. 14, 2021, 5:36 AM

Listen

- No lab test for chronic fatigue syndrome
- Condition is often misdiagnosed, doctors say

Lydia Wheeler
Senior Reporter

STAT

FIRST OPINION

Don't give Covid-19 long-haulers the silent treatment

By E. Wesley Ely Oct. 22, 2021

FIRST OPINION

Needed for long Covid: a less authoritarian approach to understanding, treatment

By Diane O'Leary April 22, 2021

Reprints

SONYA CHOWDHURY

Long Covid and ME patients deserve a better approach

Sonya Chowdhury | Monday October 18 2021, 9.00pm BST, The Times

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WORLD

Coronavirus Stigma Lingers Long After Disease Fades

Some people have recovered from Covid-19 only to find friends and colleagues shunning them, which can make it harder to fight outbreaks

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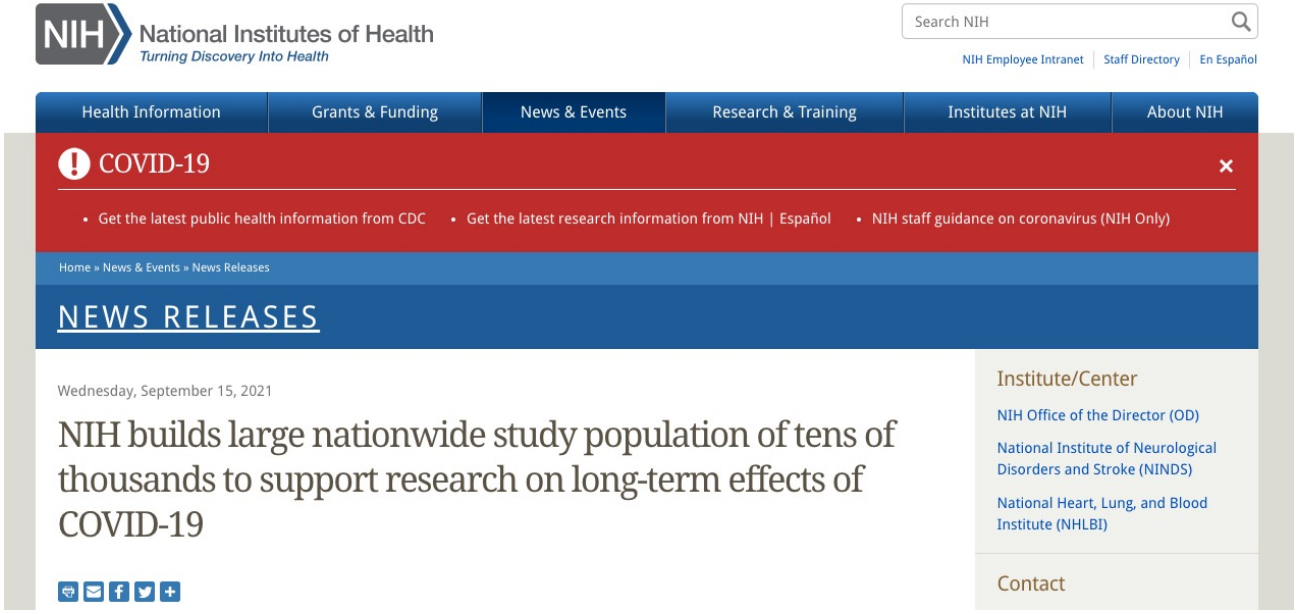
Recent PASC updates



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

6 October 2021

World Health Organization

ICD-10-CM Official Guidelines for Coding and Reporting
FY 2022
(October 1, 2021 - September 30, 2022)

(m) Post COVID-19 Condition

For sequela of COVID-19, or associated symptoms or conditions that develop following a previous COVID-19 infection, assign a code(s) for the specific symptom(s) or condition(s) related to the previous COVID-19 infection, if known, and code U09.9, Post COVID-19 condition, unspecified.

Code U09.9 should not be assigned for manifestations of an active (current) COVID-19 infection.

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

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PASC Resources

- Clinical resources
  - **CDC**: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html
  - **IDSA**: https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/post-covid-syndrome/
  - **AAPMR**: https://www.aapmr.org/members-publications/covid-19/physiatrist-resource-center/long-covid-pasc-resources
  - **AMA**: https://www.ama-assn.org/topics/covid-19-long-haulers
  - **WHO**: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
  - **UpToDate**: COVID-19: Evaluation and management of adults following acute viral illness
- Long-COVID advocacy groups
  - Body Politic COVID-19 support group
  - Survivor Corps
  - Patient-led Research for COVID-19
  - Long COVID Alliance
  - Long COVID Support Group
  - Long Haul COVID Fighters

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Thank you

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A very special thanks to all of the patients, participants, and advocates contributing to our long-COVID clinical care and research.

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