Development of a Definition of PASC Infection

Clinical Manifestations and Epidemiologic Characteristics of Long COVID – Signs and Symptoms, Onset and Duration, Attribution to Infection

National Academies of Sciences
Symposium on Long COVID:
Examining the Working Definition

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RECOVER
Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

What is RECOVER?

RECOVER stands for Researching COVID to Enhance Recovery.

It's a research study that aims to learn about the long-term health effects of COVID.

RECOVER is an **observational study**, which means researchers collect information from participants. Participants **will not get treatment** for Long COVID in this study.

RECOVER Components

RECOVER CORES


Clinical Science Core


Data Resource Core


Biorepository Core


Clinical Trial Data Coordination Center

ELEMENTS

1. RECOVER Longitudinal Cohorts
   ~40,000 participants
2. EHR/ Health Systems Studies
   60 million + records; 5.6 million + COVID cases
3. Pathobiology Studies
   Mechanistic studies of pathogenesis
4. Tissue Pathology Studies
   50+ tissue types
5. RECOVER Clinical Trials
   Clinical platform with multi-therapeutic domains

DATA RESOURCES

Clinical

Imaging

Pathology

Mobile & Digital Health

EHR/Other Real-World Data

Study Questions

- How many people are getting Long COVID, or PASC?
- Why do some people get Long COVID or PASC and others do not?
- What symptoms do people feel when they get Long COVID or PASC?
- How long do people feel sick when they get Long COVID or PASC?
- What causes Long COVID or PASC to happen?

RECOVER Enrolling Sites

RECOVER Adult Cohort

- **14,880** participants who are **18 years of age and older** and have reached the age of majority in their state of residence
- **People who have had COVID (12,200):** someone with a positive test showing they had an infection with the virus that causes COVID, or had symptoms that make us think they had COVID
  - **People who never had COVID (2,680)**: someone who never had a positive test for COVID and never had any symptoms that make us think they had COVID

What does the study include?

You may be asked to:

- Answer questions

- Have tests of blood, saliva, stool or urine

- Have simple check-ups or exams

- Send blood to be stored for later research

- Have X-rays and other kinds of body scans

You can decide to do some or all of these, or some parts of each.

It is up to you to decide if you should be in the study or not, and if you want to sign the consent form.

Possible risks may include:

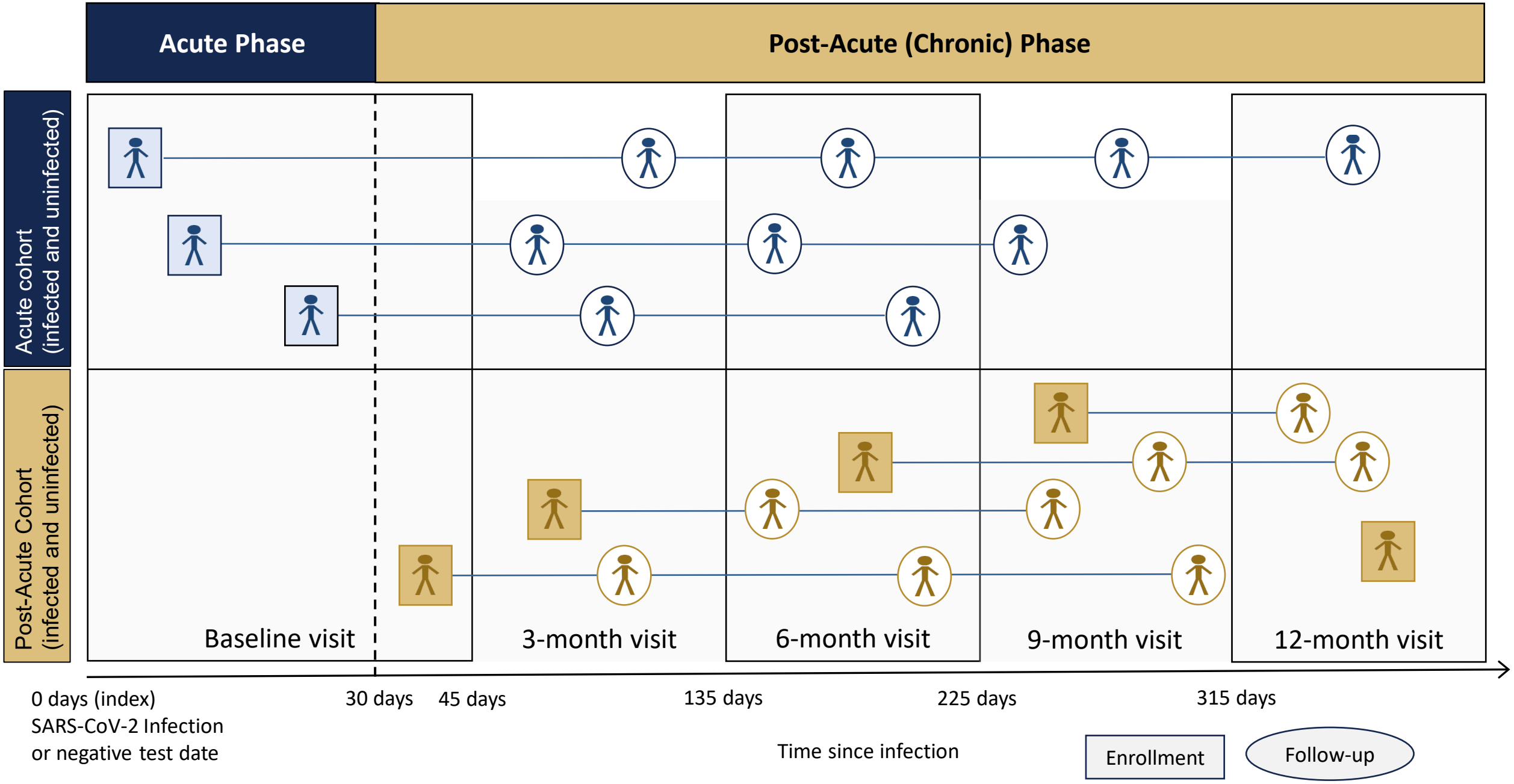
- Loss of private information

- Discomfort from blood tests and check-ups

- Radiation from CT scan (for some people)

You can stop being in the study at any time.

RECOVER Adult Cohort Study Design



RECOVER Adult Cohort Study Design

Acute Phase | **Post-Acute (Chronic) Phase**

Acute cohort (infected and uninfected)

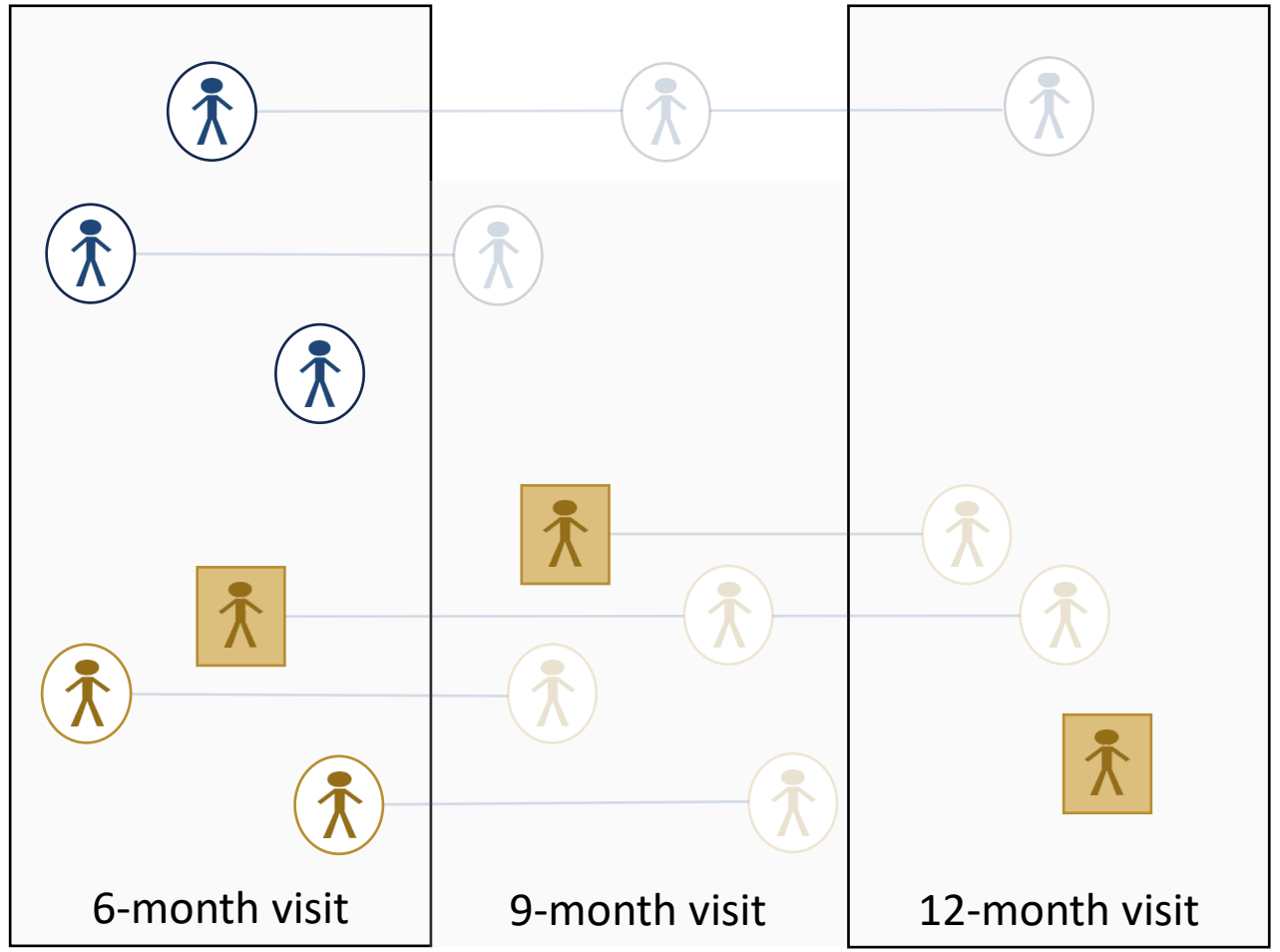
Post-Acute Cohort (infected and uninfected)

Analysis cohort

1. Included participants with at least one visit 6 months or more after index date
2. Used first visit that occurs 6 months or more after index date

Cohort description

- 9,764 participants
- 71% female
- 16% Hispanic/Latino
- 15% non-Hispanic Black
- Median age 47 years
- 55% fully vaccinated before infection
- 41% first infection pre-Omicron



0 days (index)
SARS-CoV-2 Infection
or negative test date

30 days

45 days

135 days

225 days

315 days

Time since infection

Enrollment

Follow-up

RECOVER Adult Self-Reported Symptoms (44)

General
Fatigue
Fever/sweats/chills
PEM
Unspecified pain
Sleep disturbance

Cardiovascular
Chest pain
Palpitations
Swelling of legs

Gastrointestinal
Abdominal pain
GI symptoms
Throat pain

Dermatologic
Hair loss
Skin color
Skin pain
Skin rash

Urinary
Bladder

Reproductive
Pelvic/genital
Sexual capacity

Metabolic
Thirst

Musculoskeletal
Back pain
Foot pain
Joint pain
Muscle pain
Weakness

Respiratory
Chronic cough
Short breadth
Sleep apnea

EENT
Hearing problems
Vision problems
Mouth pain
Teeth
Dry mouth

Neurologic
Abnormal movements
Brain fog
Dizziness
Loss/change smell/taste
Headache
Numbness/tingling
Paralysis
Seizures
Tremor
Unspecified nerve pain

Psychiatric
Anxiety
Depression

Analytic overview

Thaweethai et al. (2023) *JAMA*
doi:10.1001/jama.2023.8823

1. Symptom selection (LASSO)
2. Score assignment and calculation
3. Optimal threshold identification

Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

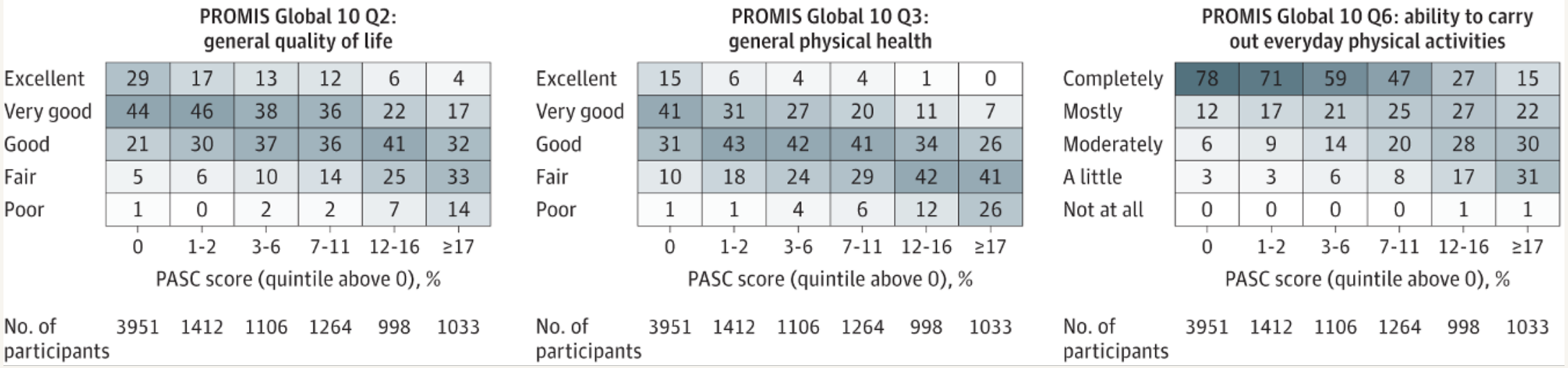
Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072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

[b] Additional severity criteria required (eTables 1 and 2 in Supplement 3).

C Distribution of PROMIS Global 10 responses



PROMIS Global 10 Q2: general quality of life

	0	1-2	3-6	7-11	12-16	≥17
Excellent	29	17	13	12	6	4
Very good	44	46	38	36	22	17
Good	21	30	37	36	41	32
Fair	5	6	10	14	25	33
Poor	1	0	2	2	7	14
No. of participants	3951	1412	1106	1264	998	1033

PASC score (quintile above 0), %

PROMIS Global 10 Q3: general physical health

	0	1-2	3-6	7-11	12-16	≥17
Excellent	15	6	4	4	1	0
Very good	41	31	27	20	11	7
Good	31	43	42	41	34	26
Fair	10	18	24	29	42	41
Poor	1	1	4	6	12	26
No. of participants	3951	1412	1106	1264	998	1033

PASC score (quintile above 0), %

PROMIS Global 10 Q6: ability to carry out everyday physical activities

	0	1-2	3-6	7-11	12-16	≥17
Completely	78	71	59	47	27	15
Mostly	12	17	21	25	27	22
Moderately	6	9	14	20	28	30
A little	3	3	6	8	17	31
Not at all	0	0	0	0	1	1
No. of participants	3951	1412	1106	1264	998	1033

PASC score (quintile above 0), %

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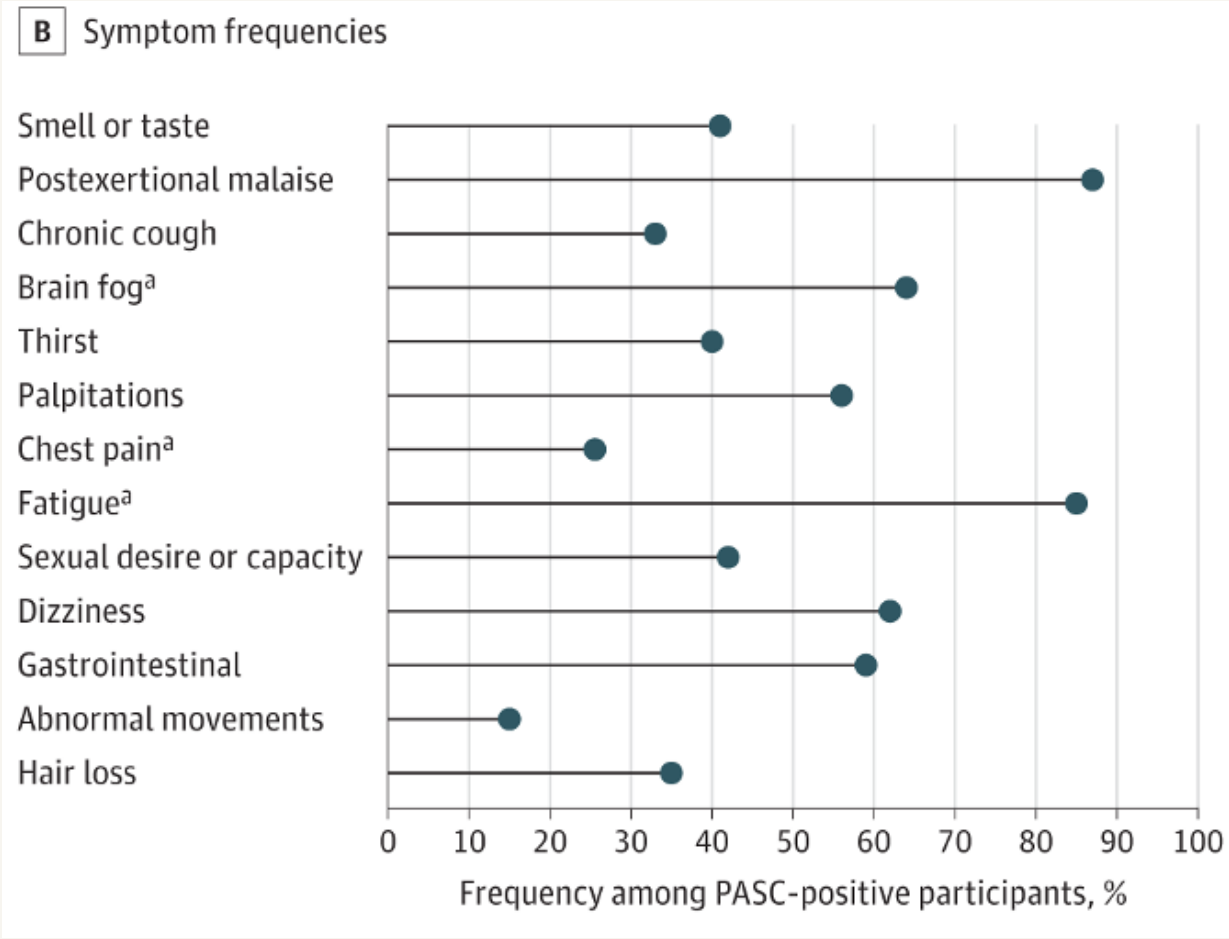
- The PASC score is calculated by adding up the scores for each symptom an individual has.

  Score < 12 ⇨ PASC-indeterminate

  Score ≥ 12 ⇨ PASC-positive

- Many other symptoms were highly correlated with these symptoms, including
  - dry mouth
  - weakness
  - headaches
  - tremor
  - muscle and abdominal pain
  - fever/sweats/chills
  - sleep disturbance



Among participants with scores ≥ 12

Study strengths

- These are early findings from a large, prospective cohort-based study based on patient-reported symptoms.
- We included an uninfected contemporaneous comparator group.
- Survey instruments were designed by a large group of stakeholders, including patient and community representatives, clinical scientists, epidemiologists, and biostatisticians.
- As such, some symptoms we asked about were not included in prior studies or are not available in other data sources.
- Some symptoms included severity measures.

Implications for a working definition

- This is a symptom-based definition that is not intended for immediate clinical use for individuals, but rather is intended for research use for populations
- It should not be used to rule out long COVID
- Individuals who do not meet the threshold may still have long COVID
- Conversely, individuals above the threshold may not have long COVID
- The symptoms included in the score are not necessarily the most common, burdensome or severe long COVID symptoms; they are the most distinctive
- Note that anxiety and depression were not distinctive enough to be in the score: this is a not a syndrome primarily characterized by mental health problems

ACKNOWLEDGEMENTS

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