Long COVID Research: Findings & Recommendations

Hannah Davis
Patient-Led Research

Who we are

- Long COVID patients, all onset in March 2020, all still symptomatic
- Met in Body Politic Support Group's data channel
- Previously researchers:
  - Survey design & participatory design
  - Qualitative research
  - Public policy
  - Research engineering
  - Data science & machine learning
  - Psychiatry (NY Presbyterian/Weill Cornell Medicine)
  - Neuroscience (University College London)
- IRB from University College London

Survey

- First report on Long COVID May 2020
- Second survey (more comprehensive)
- 205 symptoms in total over 7 months
- Impact on work/life, antibody testing, diagnostics, medical support, coping
- 250+ questions, average time 70 minutes
- Translated into 9 languages:
  - **English, French, Spanish, Arabic, Russian, Indonesian, Portuguese, Italian, Dutch**
- Survey questions are open sourced, translations are available for use

Demographics

- 6,100 respondents from 85 countries

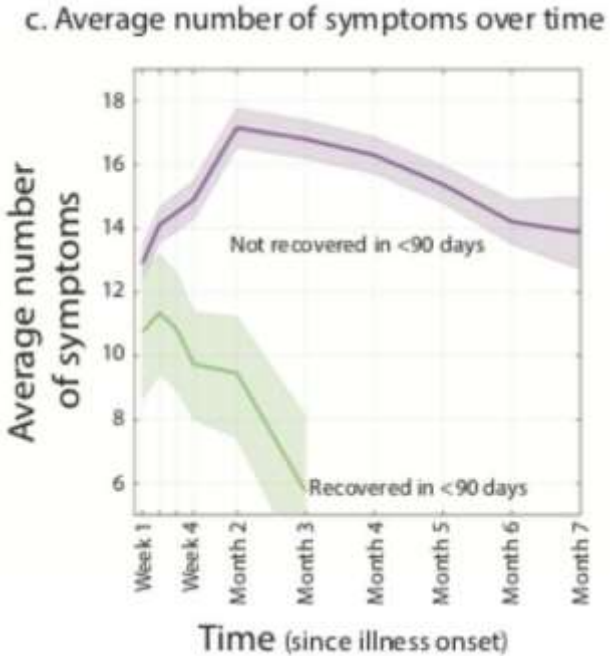
- First paper: 3,762 respondents (include only those with onset between December-May) from 56 countries
- Symptoms >28 days
- 68% with onset in March 2020
- 31.5% **age 18-39**, 31% **age 40-49**, 37.7% **age 50+**

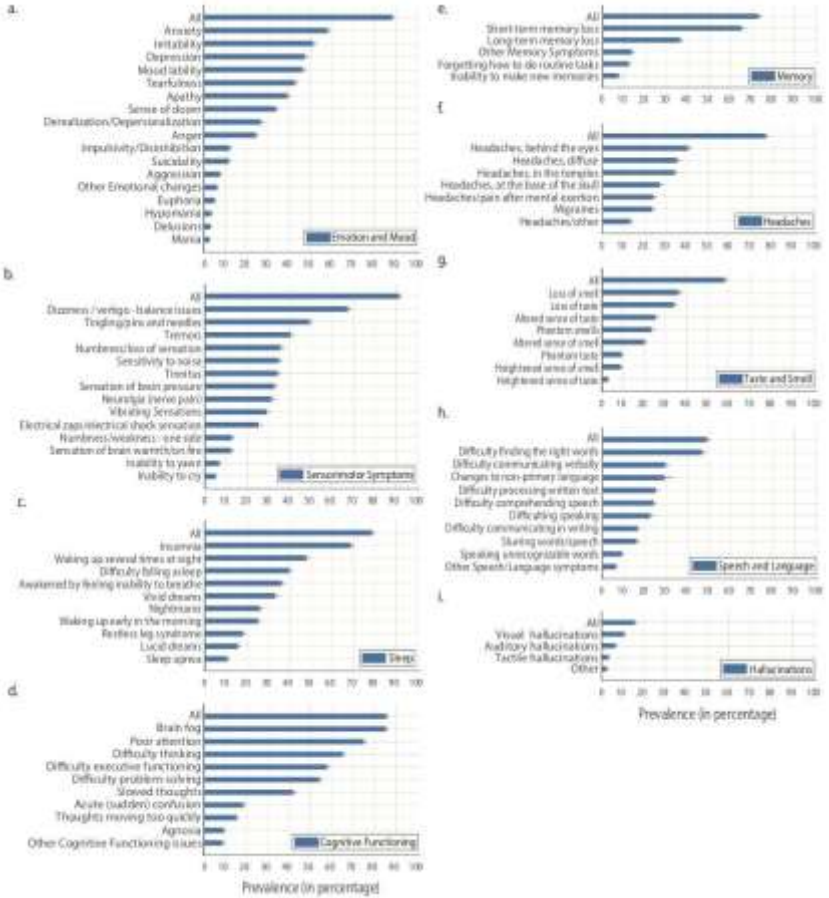
- 8.4% **hospitalized**, 91.6% **not hospitalized**
- 18% **healthcare workers**

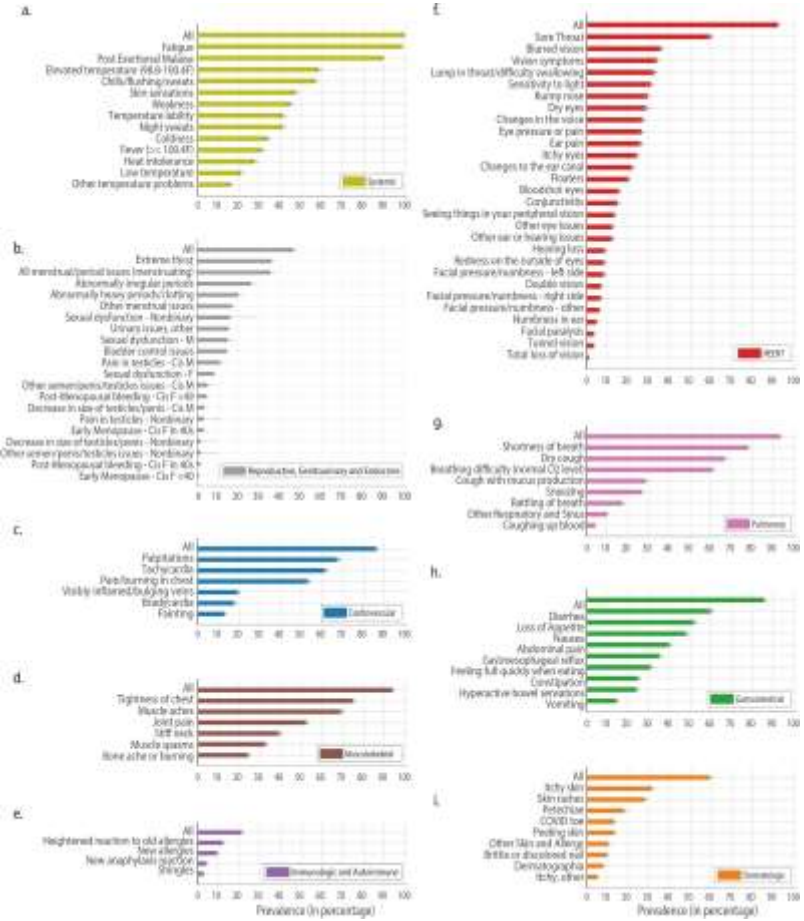
- 6.8% recovered
- 93.2% still having symptoms

Recovery

- Recovered: average 91 days of symptoms
- Unrecovered: average 144 days at time of survey
- Recovered <90 days: symptoms peaked in week 2 (11 symptoms)
- Not recovered <90 days: symptoms peaked in month 2 (17 symptoms)
- **Not recovered by month 7 experienced 14 symptoms on average in month 7**
- 21%: severe or very severe after month 6



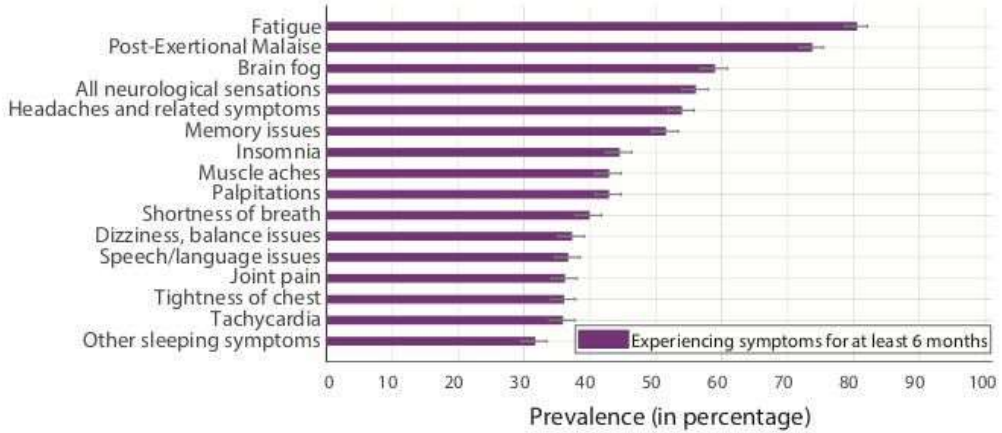

a.
All
Anxiety
Irritability
Depression
Mood lability
Tearfulness
Apathy
Sense of doom
Derealization/Depersonalization
Anger
Impulsivity/Disinhibition
Suicidality
Aggression
Other Emotional changes
Euphoria
Hypochondria
Delusions
Mania
Emotion and Mood
b.
All
Dizziness / vertigo - balance issues
Tingling/pins and needles
Tremor
Numbness/loss of sensation
Sensitivity to noise
Tinnitus
Sensation of brain pressure
Neuralgia (nerve pain)
Vibrating Sensations
Electrical zaps/electrical shock sensation
Numbness/weakness - one side
Sensation of brain warmth/on fire
Inability to yawn
Inability to cry
Sensorimotor Symptoms
c.
All
Insomnia
Waking up several times at night
Difficulty falling asleep
Awakened by feeling inability to breathe
Vivid dreams
Nightmares
Waking up early in the morning
Restless leg syndrome
Lucid dreams
Sleep apnea
Sleep
d.
All
Brain fog
Poor attention
Difficulty thinking
Difficulty executive functioning
Difficulty problem solving
Slowed thoughts
Acute (sudden) confusion
Thoughts moving too quickly
Agnosia
Other Cognitive Functioning issues
Cognitive Functioning
0 10 20 30 40 50 60 70 80 90 100
Prevalence (in percentage)
e.
All
Short term memory loss
Long term memory loss
Other Memory Symptoms
Forgetting how to do routine tasks
Inability to make new memories
Memory
f.
All
Headaches, behind the eyes
Headaches, diffuse
Headaches, in the temples
Headaches, at the base of the skull
Headaches/pain after mental exertion
Migraines
Headaches/other
Headaches
g.
All
Loss of smell
Loss of taste
Altered sense of taste
Phantom smells
Altered sense of smell
Phantom taste
Heightened sense of smell
Heightened sense of taste
Taste and Smell
h.
All
Difficulty finding the right words
Difficulty communicating verbally
Changes to non-primary language
Difficulty processing written text
Difficulty comprehending speech
Difficulting speaking
Difficulty communicating in writing
Stuttering words/speech
Speaking unrecognizable words
Other Speech/Language symptoms
Speech and Language
i.
All
Visual hallucinations
Auditory hallucinations
Tactile hallucinations
Other
Hallucinations
0 10 20 30 40 50 60 70 80 90 100
Prevalence (in percentage)

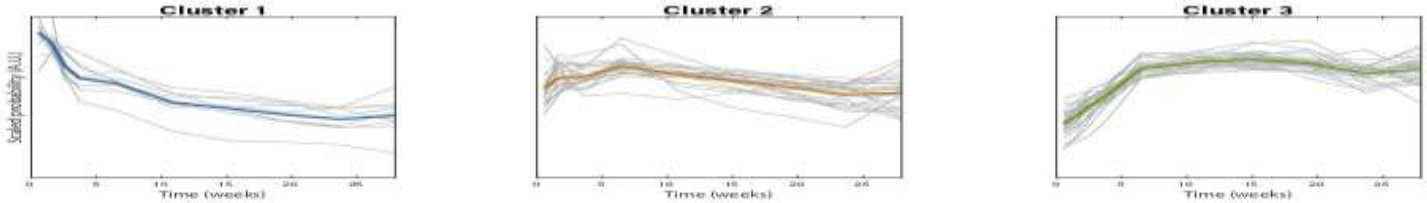

a.
All
Fatigue
Post Exertional Malaise
Elevated temperature (98.9-100.4F)
Chills/flushing/sweats
Skin sensations
Weakness
Temperature lability
Night sweats
Coldness
Fever (>= 100.4F)
Heat intolerance
Low temperature
Other temperature problems
Systemic
0 10 20 30 40 50 60 70 80 90 100
b.
All
Extreme thirst
All menstrual/period issues (menstruating)
Abnormally irregular periods
Abnormally heavy periods/clotting
Other menstrual issues
Sexual dysfunction - Nonbinary
Urinary issues, other
Sexual dysfunction - M
Bladder control issues
Pain in testicles - Cis M
Sexual dysfunction - F
Other semen/penis/testicles issues - Cis M
Post-Menopausal bleeding - Cis F >40
Decrease in size of testicles/penis - Cis M
Pain in testicles - Nonbinary
Early Menopause - Cis F in 40s
Decrease in size of testicles/penis - Nonbinary
Other semen/penis/testicles issues - Nonbinary
Post-Menopausal bleeding - Cis F in 40s
Early Menopause - Cis F >40
Reproductive, Genitourinary and Endocrine
c.
All
Palpitations
Tachycardia
Pain/burning in chest
Visibly inflamed/bulging veins
Bradycardia
Fainting
Cardiovascular
d.
All
Tightness of chest
Muscle aches
Joint pain
Stiff neck
Muscle spasms
Bone ache or burning
Musculoskeletal
e.
All
Heightened reaction to old allergies
New allergies
New anaphylaxis reaction
Shingles
Immunologic and Autoimmune
Prevalence (in percentage)
f.
All
Sore Throat
Blurred vision
Vision symptoms
Lump in throat/difficulty swallowing
Sensitivity to light
Burning nose
Dry eyes
Changes in the voice
Eye pressure or pain
Ear pain
Itchy eyes
Changes to the ear canal
Floaters
Bloodshot eyes
Conjunctivitis
Seeing things in your peripheral vision
Other eye issues
Other ear or hearing issues
Hearing loss
Redness on the outside of eyes
Facial pressure/numbness - left side
Double vision
Facial pressure/numbness - right side
Facial pressure/numbness - other
Numbness in ear
Facial paralysis
Twisted vision
Total loss of vision
HEENT
g.
All
Shortness of breath
Dry cough
Breathing difficulty (normal O2 level)
Cough with mucous production
Sneezing
Rattling of breath
Other Respiratory and Sinus
Coughing up blood
Pulmonary
h.
All
Diarrhea
Loss of Appetite
Nausea
Abdominal pain
Gastroesophageal reflux
Feeling full quickly when eating
Constipation
Hyperactive bowel sensations
Vomiting
Gastrointestinal
i.
All
Itchy skin
Skin rashes
Petechiae
COVID toe
Peeling skin
Other Skin and Allergy
Brittle or discolored nail
Dermatographia
Itchy, other
Dermatologic
Prevalence (in percentage)

#	SYMPTOM	%	CATEGORY
1	Fatigue	98.3	Systemic
2	Post-Exertional Malaise	89.1	Systemic
3	Cognitive Dysfunction ("Brain fog")	85.1	Neuropsychiatric - Cognitive Dysfunction
4	Shortness of Breath	77.4	Pulmonary
5	Poor attention or concentration	74.8	Neuropsychiatric - Cognitive Dysfunction
6	Tightness of Chest	74.8	Musculoskeletal
7	Muscle aches	69.1	Musculoskeletal
8	Insomnia	68.6	Neuropsychiatric - Sleep
9	Heart palpitations	67.4	Cardiovascular
10	Dizziness / vertigo / unsteadiness or balance issues	67.3	Neuropsychiatric - Sensorimotor
11	Dry cough	66.2	Pulmonary
12	Difficulty thinking	65	Neuropsychiatric - Cognitive Dysfunction
13	Short-term memory loss (memory that lasts ~30 seconds, i.e. remembering a phone number before writing it down, or forgetting you're in the middle of a task)	64.8	Neuropsychiatric - Memory
14	Tachycardia	61.4	Cardiovascular
15	Episodes of breathing difficulty/gasping for air with normal oxygen saturation	60.4	Pulmonary
16	Diarrhea	59.7	Gastrointestinal
17	Sore Throat	59.5	HEENT (Head, Ear, Eyes, Nose, Throat)
18	Elevated temperature (98.8-100.4 F)	58.2	Systemic
19	Anxiety	57.9	Neuropsychiatric - Emotion and Mood
20	Difficulty with executive functioning (planning, organizing, figuring out the sequence of actions, abstracting)	57.6	Neuropsychiatric - Cognitive Dysfunction
21	Chills/flushing/sweats	56.5	Systemic
22	Difficulty problem-solving or decision-making	54.1	Neuropsychiatric - Cognitive Dysfunction
23	Pain/burning in chest	53.1	Cardiovascular
24	Joint pain	52.2	Musculoskeletal
25	Loss of Appetite	51.6	Gastrointestinal

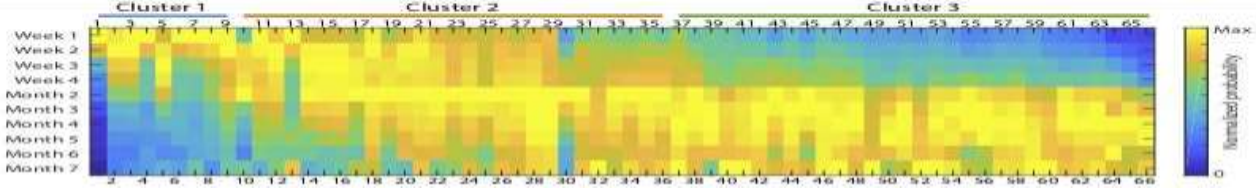
Top symptoms (after month 6

a. Remaining symptoms after month 6 (prevalence > 30%)

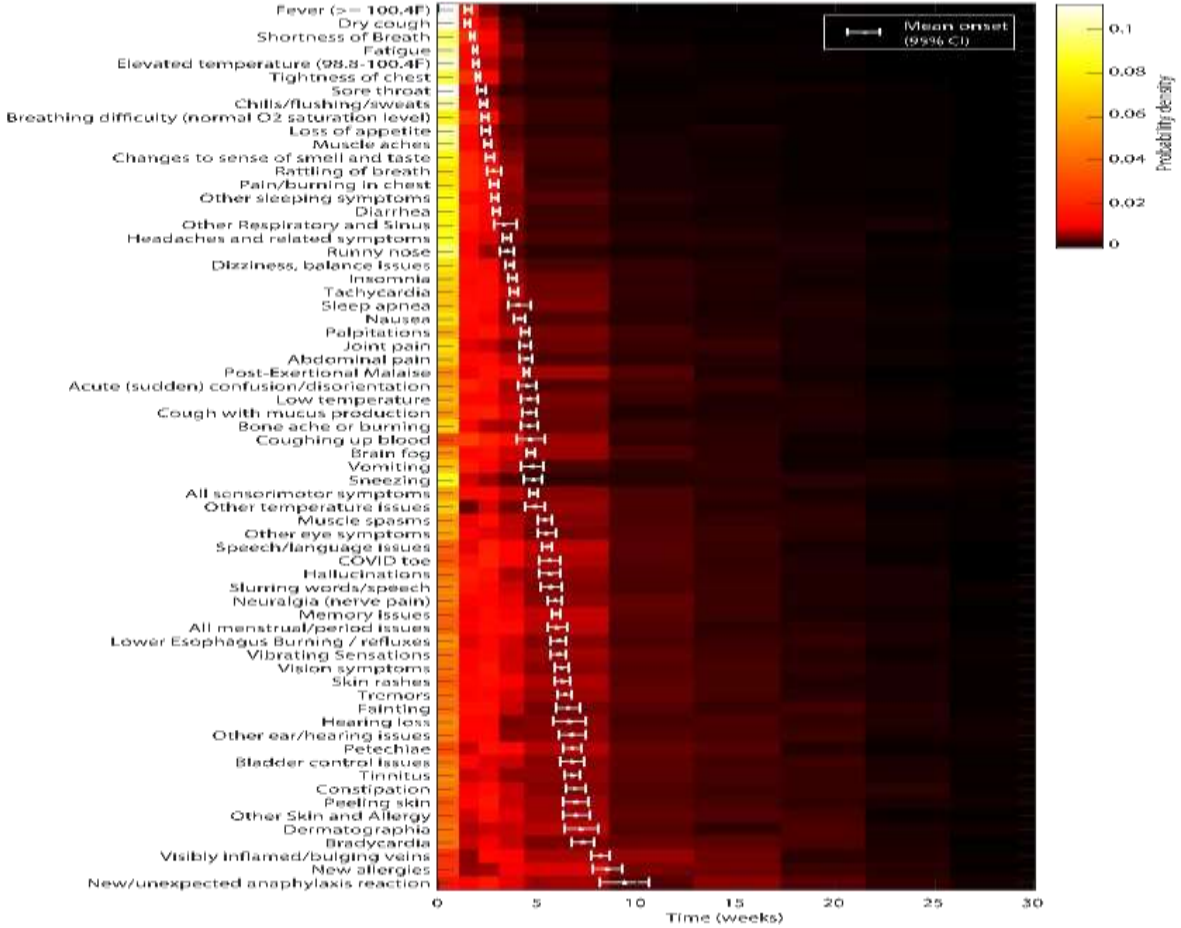




Cardiovascular		25. Fainting 19. Pain/burning in chest 33. Tachycardia	49. Bradycardia 38. Palpitations 64. Visibly inflamed/bulging veins
Dermatologic		30. COVID toe	53. Dermatographia 55. Other Skin and Allergy 42. Peeling skin 54. Petechiae 44. Skin rashes
Gastrointestinal	9. Diarrhea 2. Loss of Appetite 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. Dizzines, 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 (>= 100.4F)	11. Chills/flushing/sweats 28. Fatigue 23. Low temperature	39. Other temperature issues 57. Post Exertional Malaise

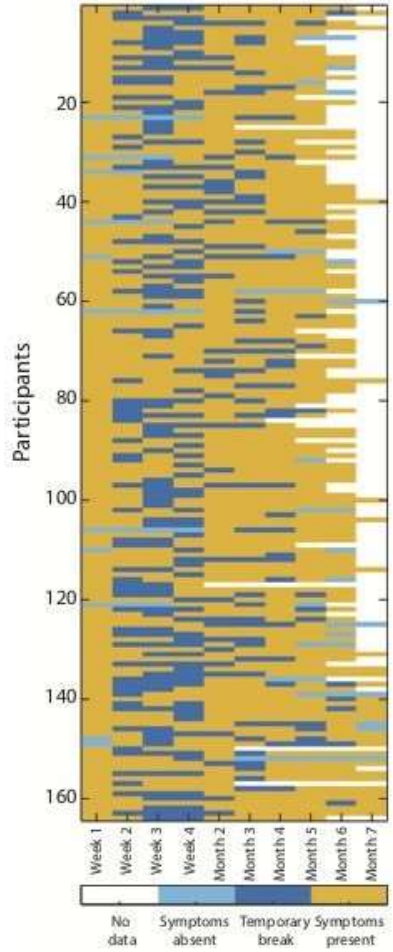


Symptom onset (mean)

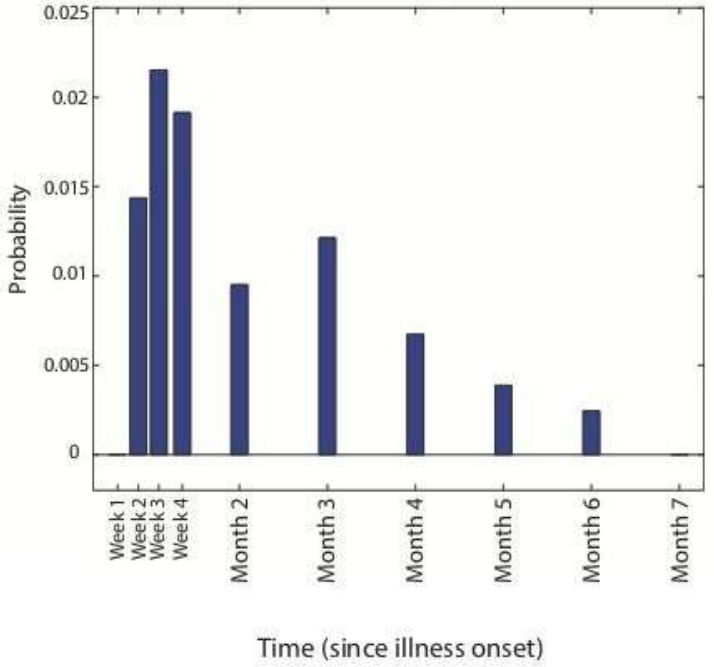


Symptom Breaks

a. 164 participants experienced break in their symptom timecourse

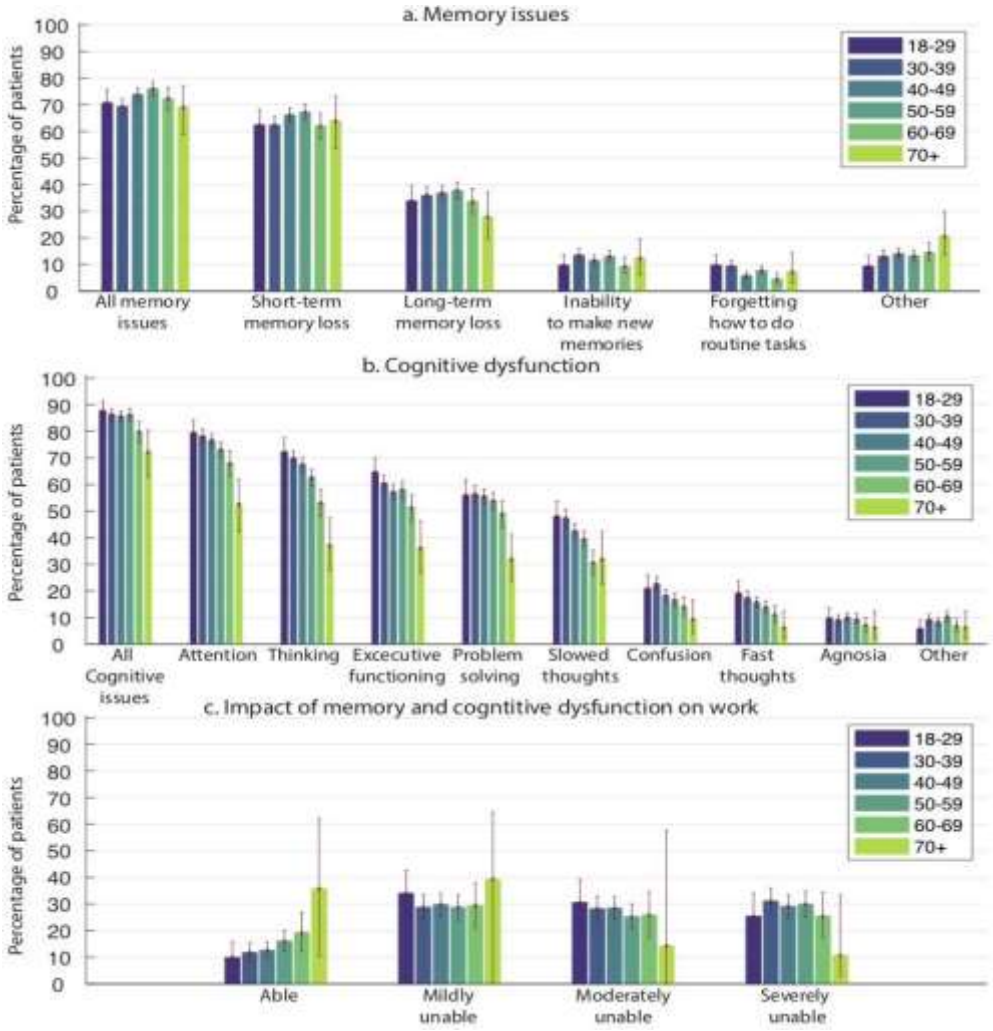


b. Probability of temporary break in symptoms across all subjects

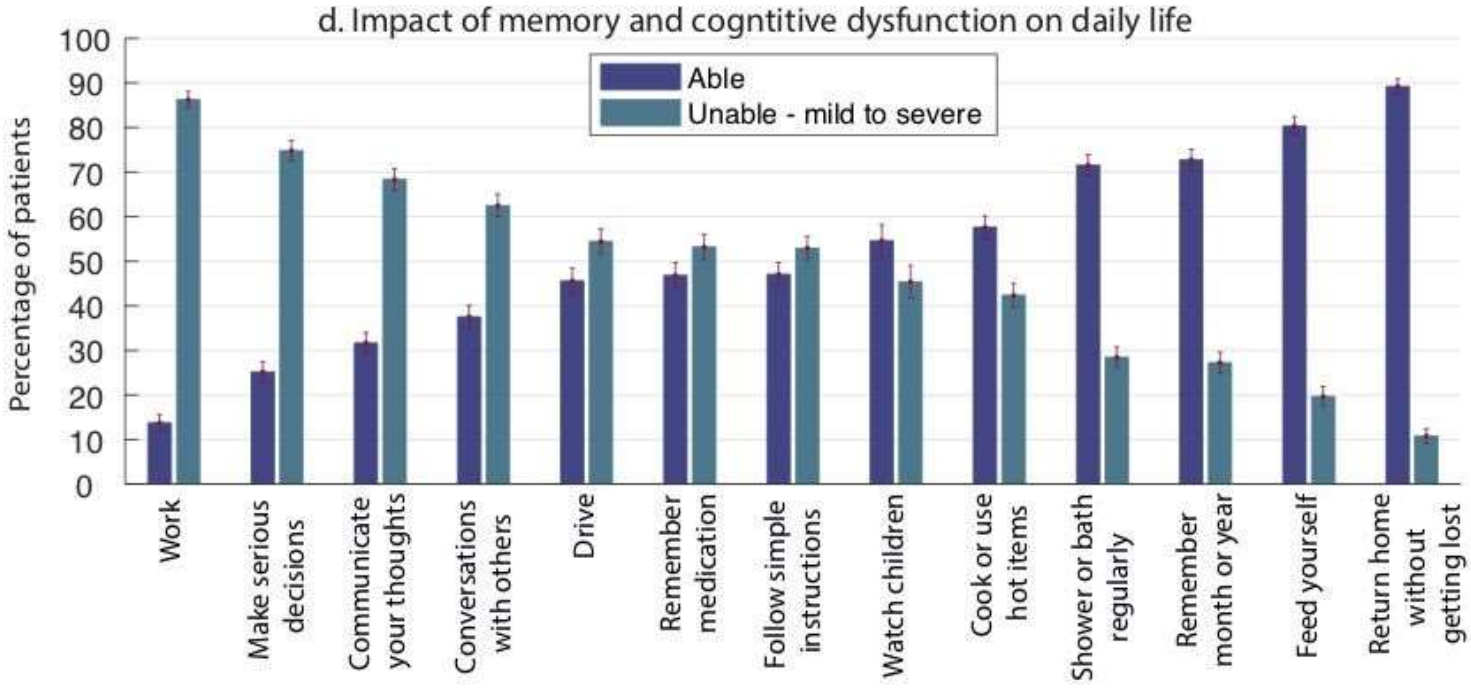


Cognitive Dysfunction & Memory

- No difference in memory by age
- No difference in cognitive dysfunction by age
- No difference in impact on life by age



Cognitive Dysfunction & Memory



Cognitive Dysfunction and Memory Loss

*"mother has started to help me take the medications I'm on because I **can't remember** if I've taken them immediately after having the bottle in my hand"*

*"was trying to fill out a mortgage application form and couldn't remember our rent. I put £3750 a month. My partner said, no it's £1375. So I put £13750. My partner said no, so I tried several more times - I **was just guessing numbers**"*

*"sitting on the toilet to pee and **had to stop for a second to think** if I was really there and not about to pee myself or the bed"*

***"don't remember what I did** in March or April up until the last week of April. I had almost nothing on my schedule. I don't know what I did"*

*"put food on the gas stove and walked away for over an hour, **only noticing when they were smoking/burning**"*

***"forget how to do normal routines** like running a meeting at work"*

*"**felt lost driving** and had to stop and find my position in a GPS to be able to drive back home. It's a route I have done hundreds of times"*

*"have trouble **comprehending new ideas**"*

***"can't hold multiple trains of thought** [...] If I tell myself I have to water my plants, I must do it before another thought comes into my mind because otherwise I will forget"*

*"**can't follow plots** in movies or tv shows, **have to write everything down**, have to remember to look at notes"*

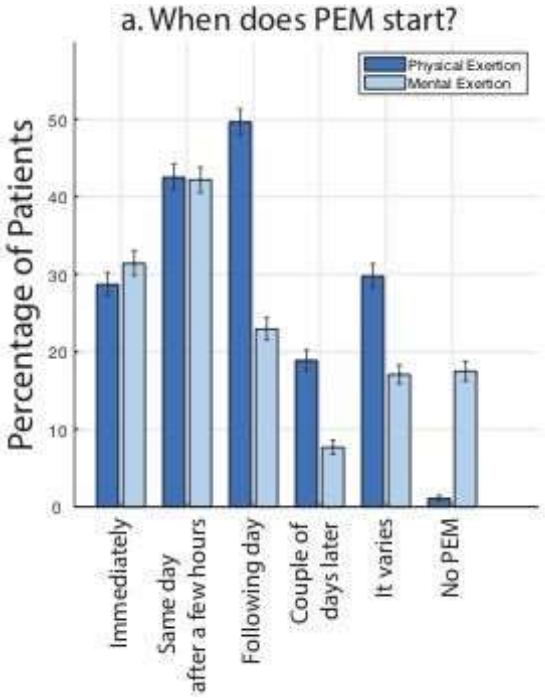
*"had to terminate many phone calls because I **could no longer comprehend the speakers nor communicate clearly** with them"*

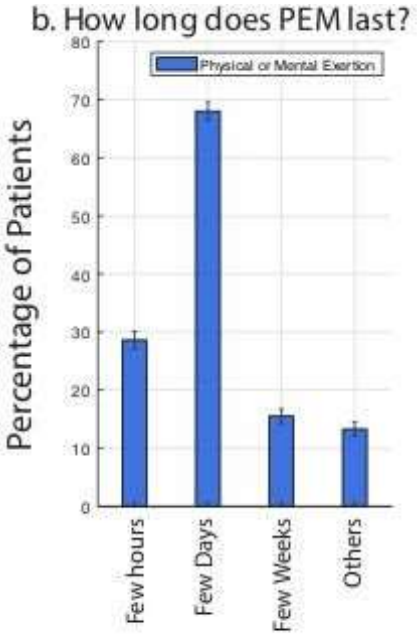
*"used to do the New York Times crossword puzzle every single day and I **can't even manage the mini ones** now"*

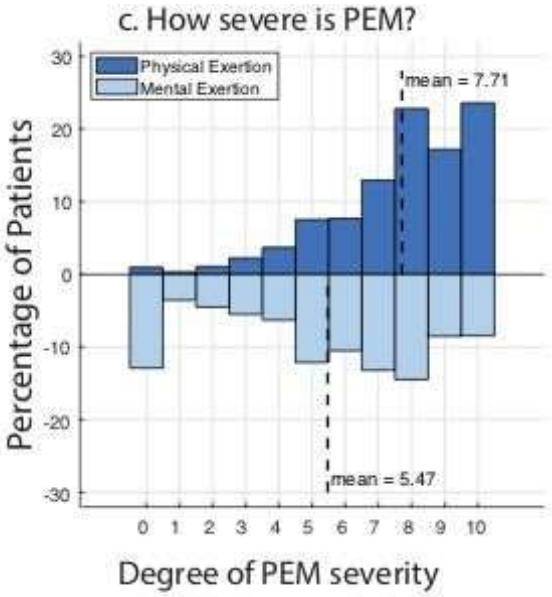
***"can't focus on reading complex texts**, and it makes me feel very tired to do that"*

*"Found that I had become dyslexic - and knew it was happening at the time, **could not remember how to spell words** - also found I was missing words from sentences and sometimes writing things that did not make sense"*

Post-Exertional Malaise







Immunologic/Allergies

- 20%: change in sensitivity (in both directions) to medications
- 12.1%: heightened reaction to old allergies
- 9.3%: new allergies
- 4%: new/unexpected anaphylaxis reactions
- Disappearing allergies (shellfish, medications, seasonal allergies)
- Post-COVID Reactivations of EBV, CMV, Shingles, and Lyme reported in <10%

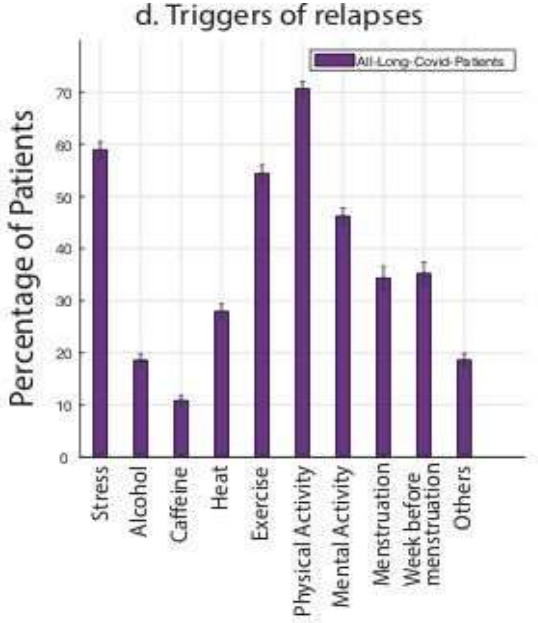
Other serious symptoms

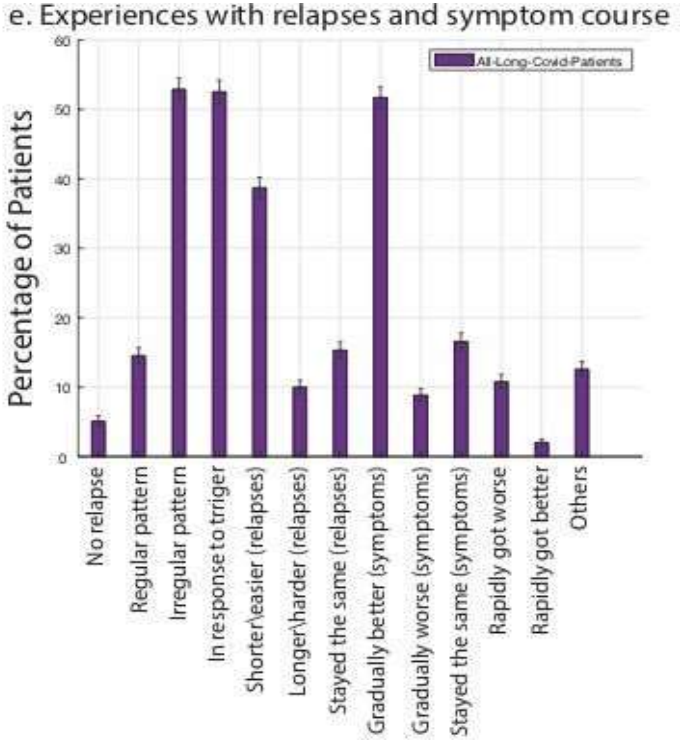
- 1% vision loss
- 9% hearing loss
- 3% facial paralysis
- 12% suicidality

Reproductive Health

- 15% of men, 8% of women: sexual dysfunction
- 11% of cis men: pain in testicles
- 3% of cis men: decrease in genital size
- Post-menopausal bleeding/spotting: 4.5% of cis women over age 49
- Early menopause: 3% of cis women in their 40s
- Abnormal periods: 26%

Relapses, Triggers, Recovery

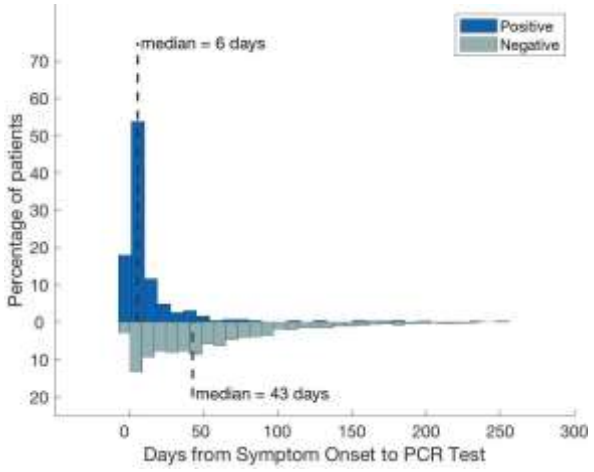


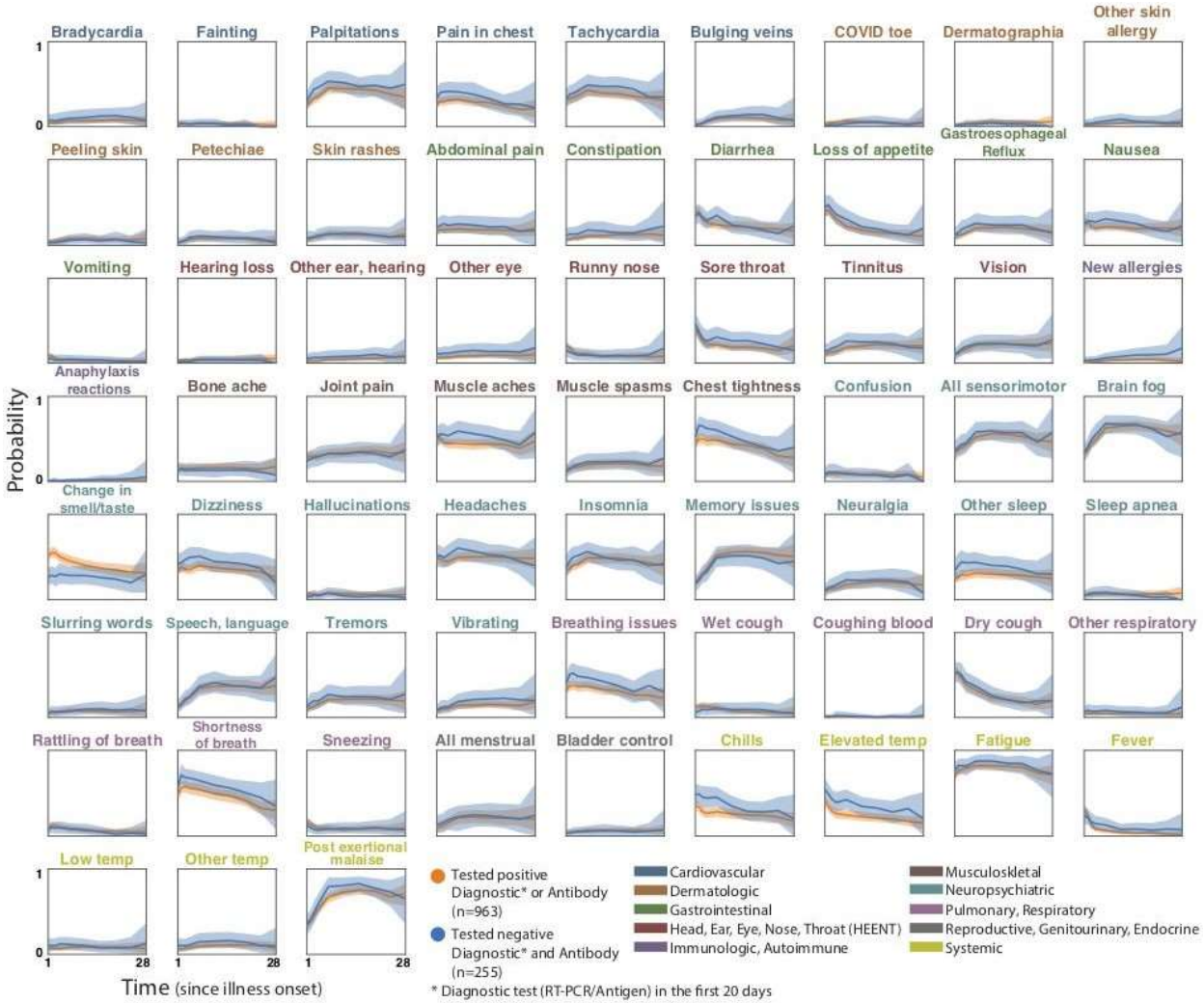


Impact on work

- 67.5% required reduced work schedule or were no longer working due to their illness
  - 45.2% required a reduced work schedule
  - 22.3% were not working at all
  - Remaining respondents were retired, volunteers, or did not provide enough information about their working status.
- Of those with brain fog, 86.2% are mildly to severely unable to work because of brain fog specifically.

Comparing Positive & Negative Cohorts





Priority Research Questions and Methods

- Need comprehensive selection of patients:
  - Many/most LC patients were not hospitalized
  - Many didn't experience respiratory symptoms
  - Many were not PCR positive/antibody positive (must include clinical diagnosis subset)
  - Many had mild acute cases
  - Many never had low oxygen levels
- Ask about right symptoms!
  - Often missing neurological, especially cognitive, and post-exertional malaise
  - Often missing questions on relapses
- Particularly when using machine learning!
  - Algorithms will be biased without representative patient and symptom dataset

Long COVID-specific research:

1. **F-FDG brain PET hypometabolism in patients with long COVID, Guedj et al**
   a. MRIs are normal, but hypometabolism found in PET scans w' 100% classification between patients & controls
   b. Symptom severity correlates w' metabolic PET severity
   c. Results: decrease in brain activity in olfactory bulb, limbic regions (memory/emotion regulation), brainstem (autonomic functions, breathing/sleeping), cerebellum (motor skills/balance)
2. **Early immune pathology and persistent dysregulation characterise severe COVID-19, Bergamaschi et al**
   a. Immunometabolic inflammatory changes & unresolved immune cell defects may contribute to Long COVID
3. **Neurologic manifestations of nonhospitalized patients with COVID-19 in Wuhan, China, Ding et al**
   a. Non-hospitalized patients more likely to have neurological symptoms
   b. Non-hospitalized patients more likely to test negative on antibody tests
   c. Non-hospitalized patients have symptoms for longer
4. **CDC study "Decline in SARS-CoV-2 Antibodies"**
   a. 28% seroreverted by 60 days
   b. 2 %of PCR-positive patients seroreverted compared to 27% of PCR-negative
   c. 65% of patients with low antibody levels seroreverted (low levels more likely in women)
   d. Seroreversion more likely in 1) younger patients, 2) patients with underlying conditions
   e. Non-Hispanic Black patients and Hispanic patients less likely to serorevert

Priority Research Questions and Methods

- Validate & further investigate past post-viral research, interdisciplinarily:
  - **Brain inflammation, brainstem inflammation, appropriate neuroimaging techniques** (Dr.Jarred Younger, Dr. Michael VanElzakker, Dr. David Systrom, Harvard)
  - **Metabolic profiling** (Dr. Oystein Fluge, Dr. Ron Davis, Dr. Jarred Younger)
  - **Impaired endothelial function in POTS** (Dr. Alfred Gamboa, Vanderbilt)
  - **Mitochondrial fragmentation, antiviral & metabolic phenotypes in ME** (Dr. Bhupesh Prustry)
  - **Hypoperfusion/cerebral blood flow** (Dr. Peter Rowe, Johns Hopkins)
  - **Two-day exercise testing & other PEM research** (Workwell foundation, Dr. Leonard Jason)
  - **Nanoneedle diagnostic test** (Dr. Ron Davis, Stanford)
  - **Overlaps with connective tissue disorders, including Ehlers-Danlos Syndrome** (PolyBio Research, Dr. Peter Rowe, Johns Hopkins, Dr. Bjorn Bragee, Karolinska Institutet)
  - **Autoimmunity, autoantibodies** (Dr. Franziska Sotzny)
  - **Viral/microbial persistence** (Dr. Amy Proal, Dr. Bhupesh Prusty)
  - **Intracranial hypertension, hypermobility, craniocervical obstructions** (Karolinska Institutet, Dr. Bjorn Bragee, Dr. Nicolas Higgins)
  - **Altered T cells and B cells, Metabolomics and Proteomics** (Dr. Maureen Hanson, Cornell University)
  - **Elevated blood lactate** (Dr. Alaa Ghali)

Research questions

1. Are those with Long COVID more likely to serorevert, serorevert earlier, or never seroconvert?
2. Is there viral persistence in places like the gut or elsewhere in Long COVID patients?
3. How is the immune response in non-hospitalized Long COVID patients different than those with mild cases and those who are hospitalized?
4. What causes the hypometabolism found in the brains of Long COVID patients?
5. What causes post-exertional malaise?
6. What is the mechanism behind relapses?
7. What imaging or diagnostic tools can identify persisting neurological symptoms, particularly in patients with normal MRIs?

@patientled

PatientResearchCovid19.com

Resources for Long COVID researchers:
https://patientresearchcovid19.com/resources-for-long-covid-researchers/

Thank you!