# Characterizing Long COVID in an International Cohort

Hannah Davis
Patient-Led Research Collaborative

# 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 report December 2020:
  - **“Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact”**
- 205 symptoms in total over 7 months
- Impact on work/life, antibody testing, diagnostics, medical support, coping
- 250+ questions, average time 70 minutes
- 9 languages:
  - **English, French, Spanish, Portuguese, Arabic, Russian, Indonesian, Italian, Dutch**
- Survey questions are open sourced, translations are available at PatientResearchCOVID19.com

# Demographics

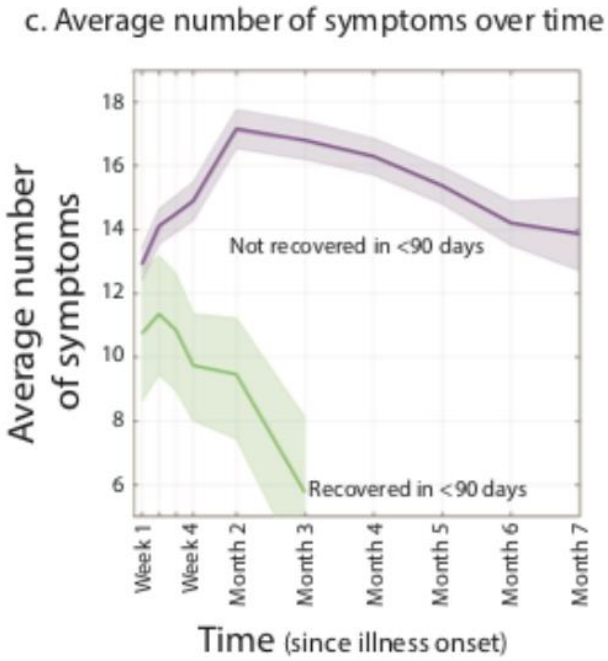
- Total data: 6,500+ respondents from 84 countries
- First paper only on “first wavers” (onset between December-May):
  - 3,762 respondents from 56 countries
  - Symptoms > 28 days
  - 92% not hospitalized!
  - Wide age range:
    - 31.5% age 18-39
    - 31% age 40-49
    - 37.7% age 50+
  - 18% healthcare workers
  - 6.8% recovered

# Recovery

- Recovered: 91 days of symptoms
- Unrecovered: 144 days at time of survey

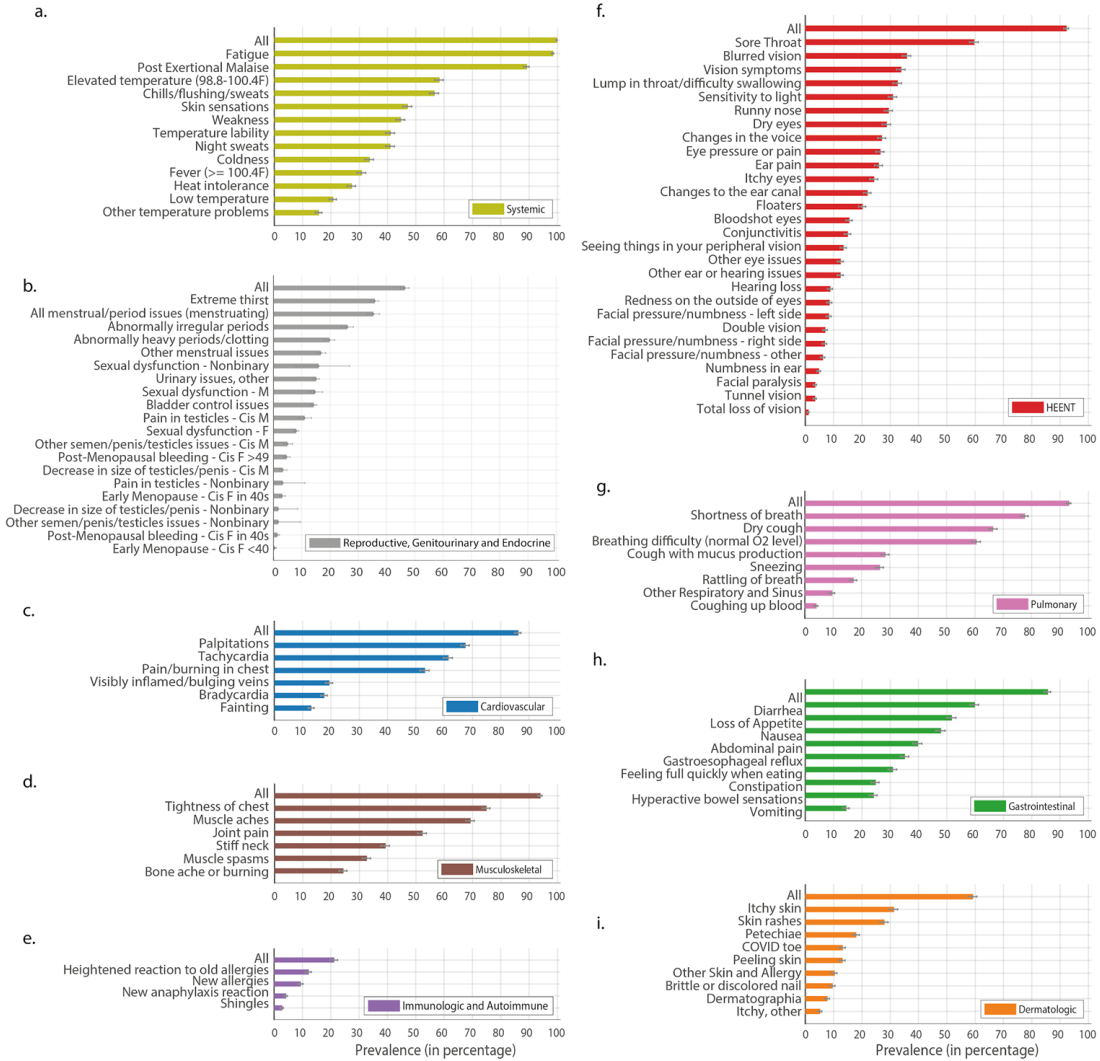
- Recovered <90 days: symptoms peaked in week 2 (11 symptoms)
- Not recovered <90 days: symptoms peaked in month 2 (17 symptoms)

- **Those not recovered by month 7 experienced 14 symptoms on average in month 7**
- 21%: severe or very severe after month 6



# 10 categories

1. Systemic
2. Neurological*
3. Gastrointestinal
4. Pulmonary
5. Dermatologic
6. Immunologic/Autoimmune
7. Cardiovascular
8. Musculoskeletal
9. Reproductive/Genitourinary/Endocrine
10. HEENT (Head, Ears, Eyes, Nose, Throat)



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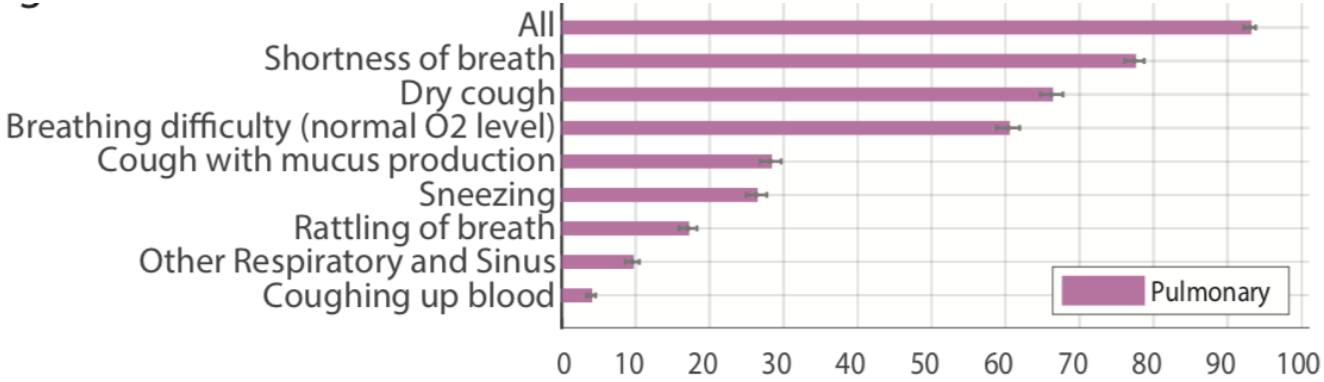


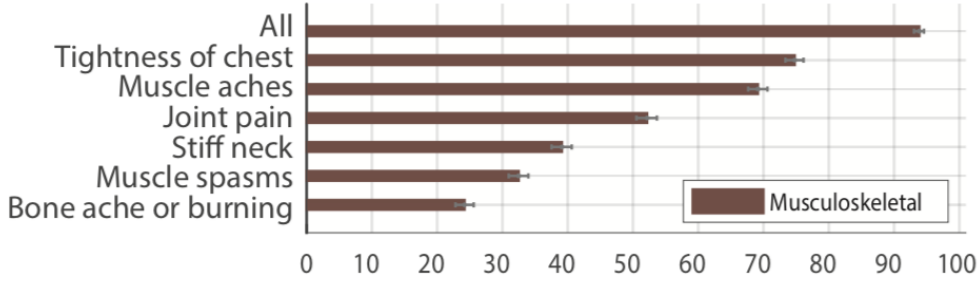

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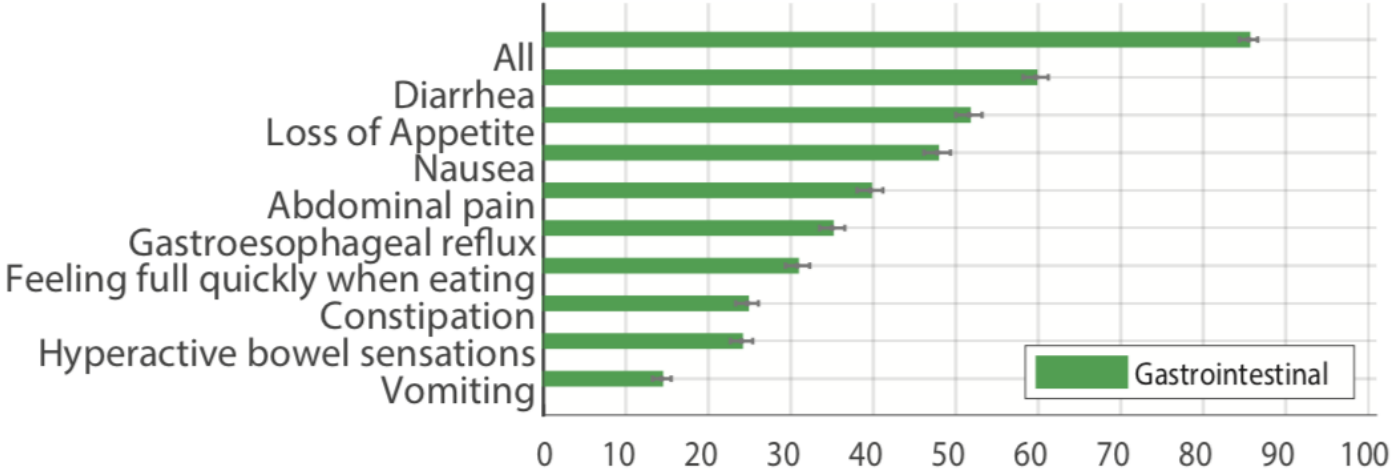


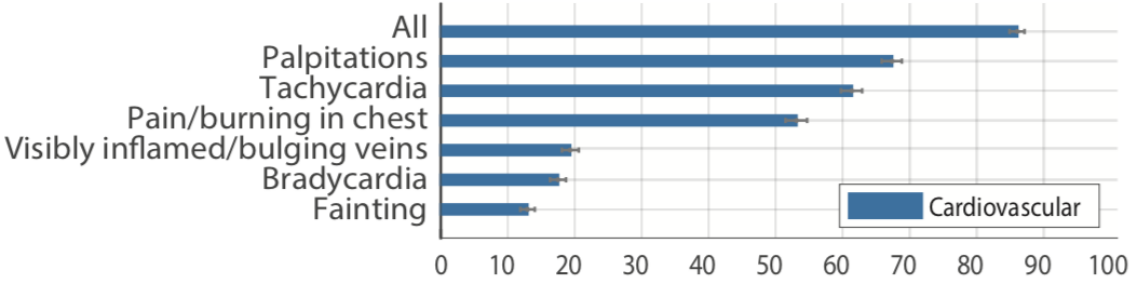

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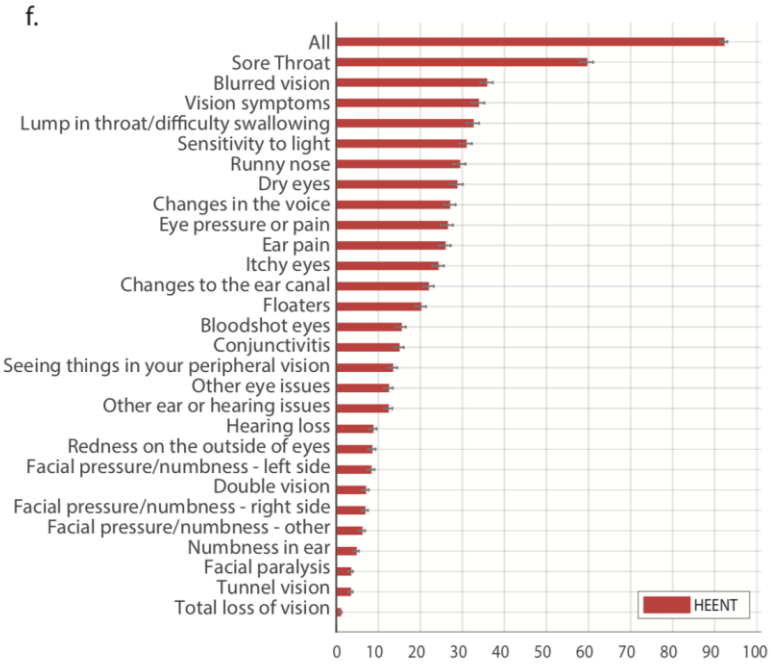


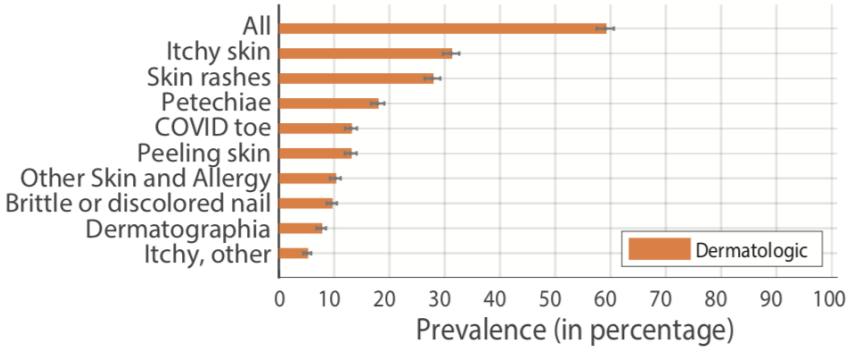

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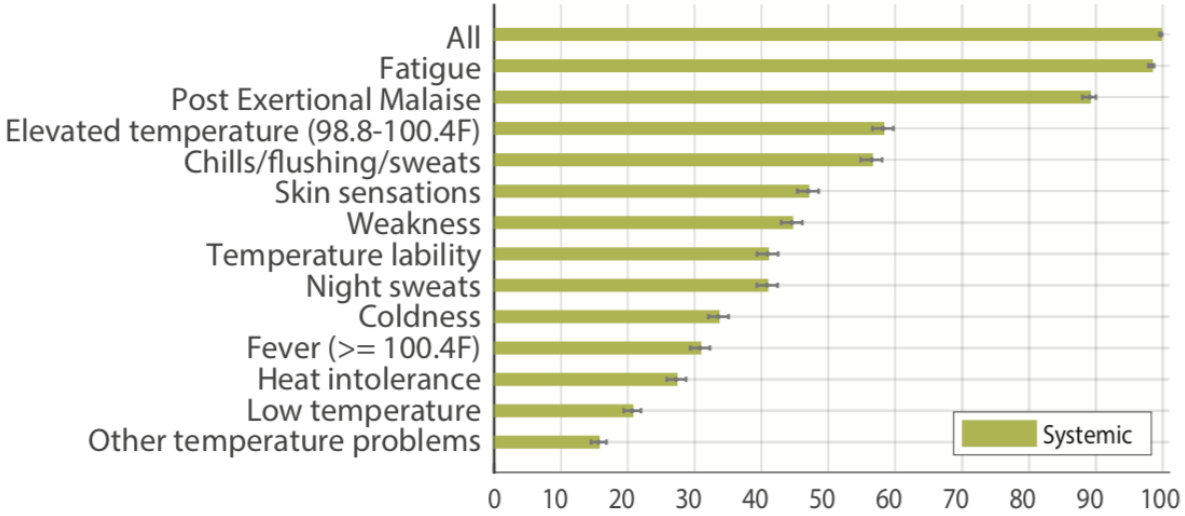
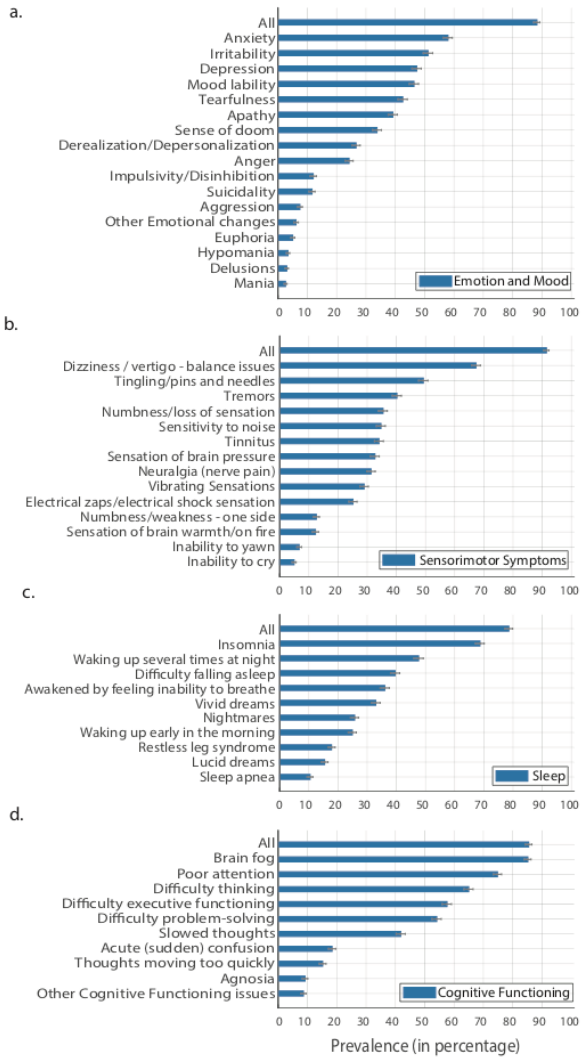


# Neuro: 9 subsections

1. Sensorimotor
2. Cognitive Functioning
3. Sleep
4. Taste and Smell
5. Speech and Language
6. Headaches
7. Memory
8. Hallucinations
9. Mood



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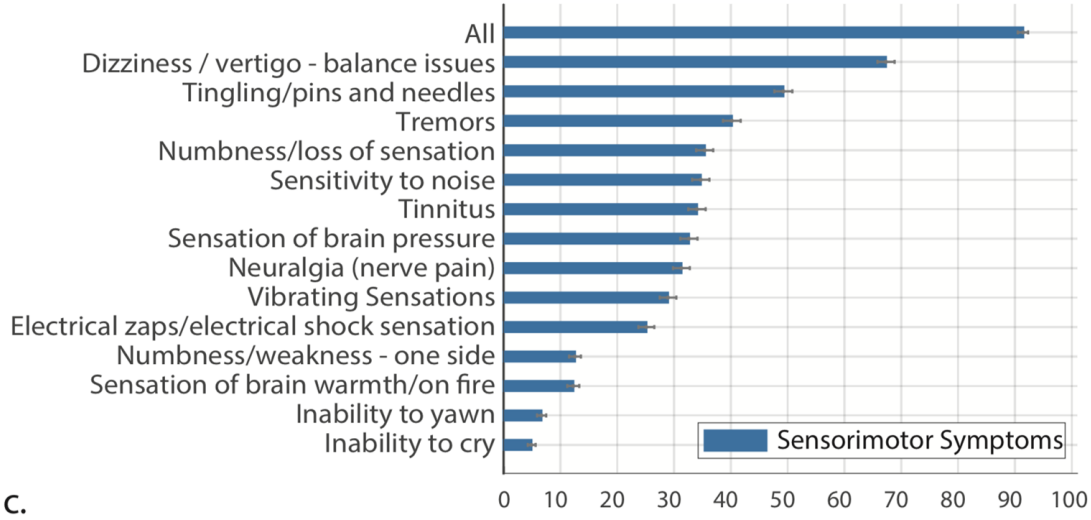


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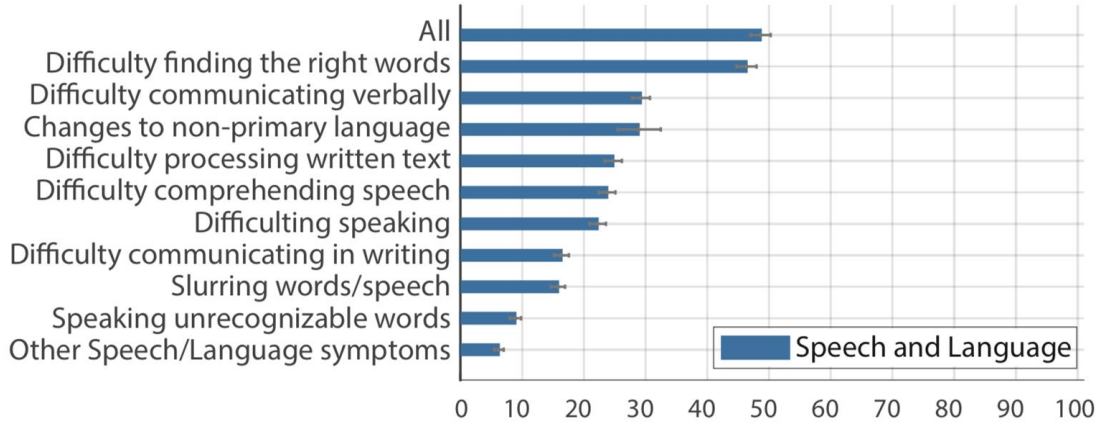

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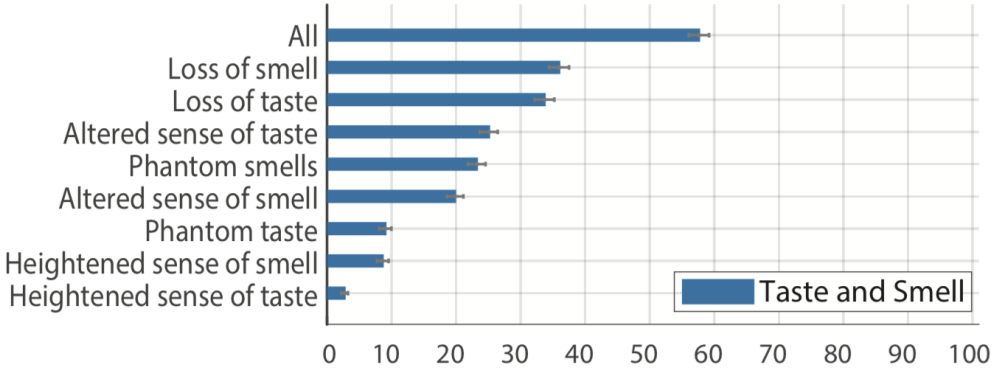
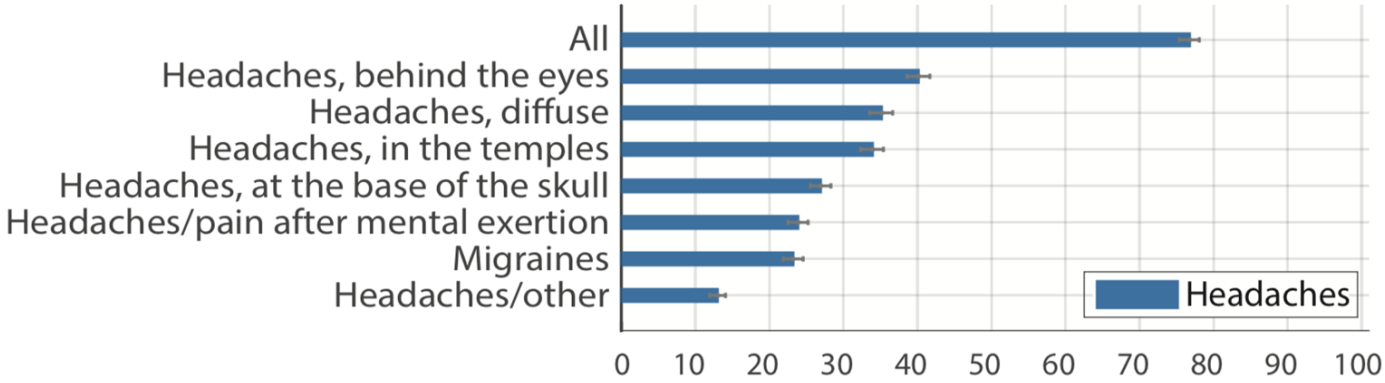
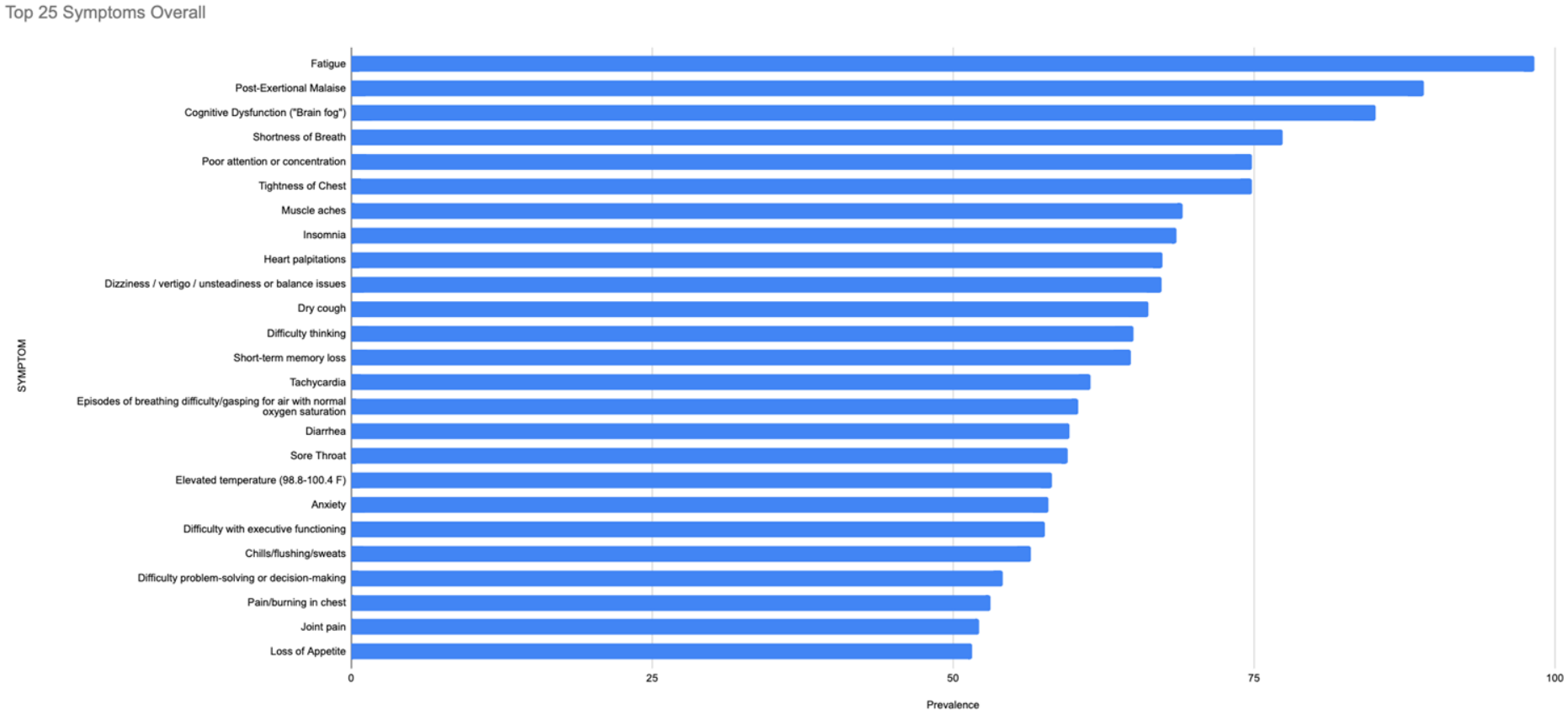
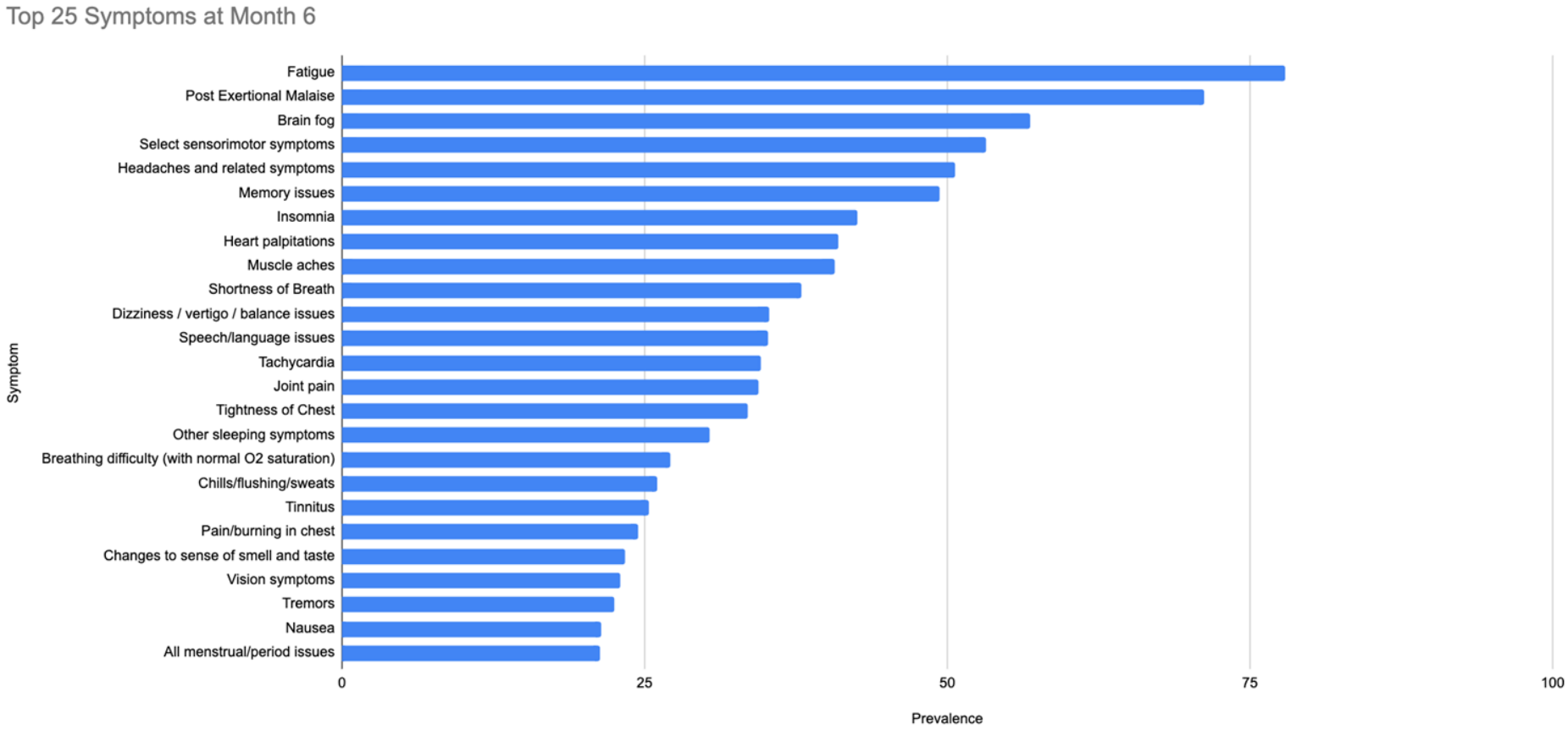


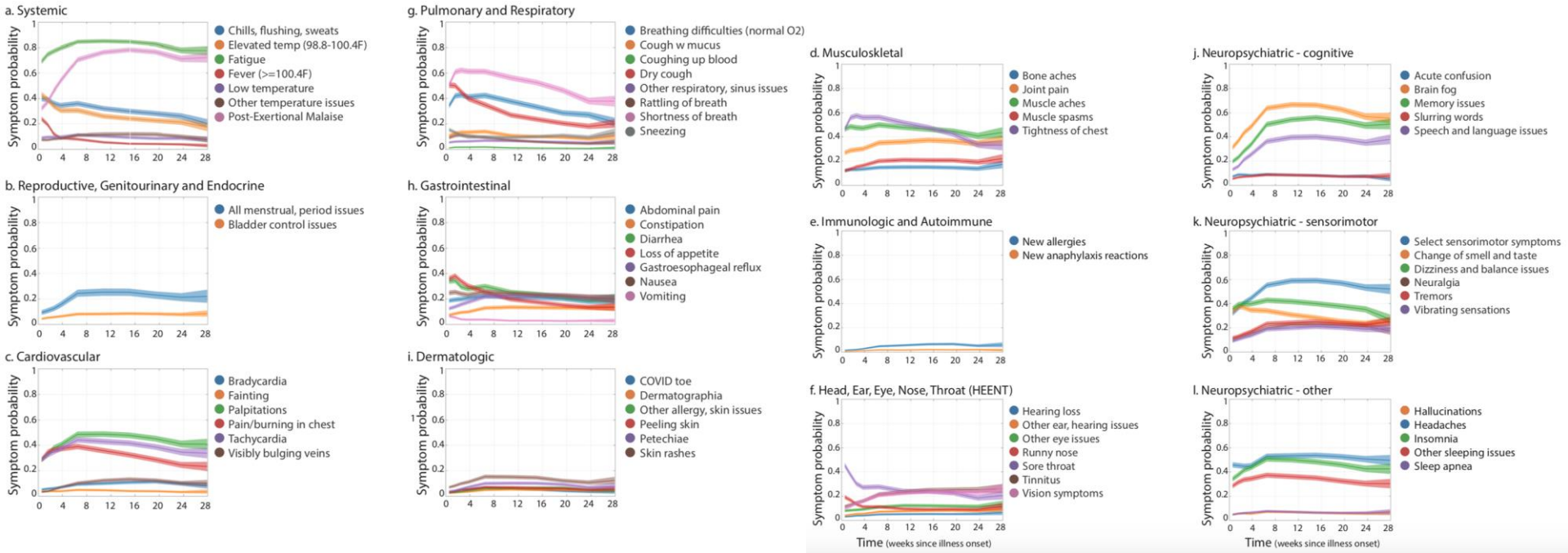
# Top symptoms (at any point)



# Top symptoms at Month 6



# Symptom timecourse



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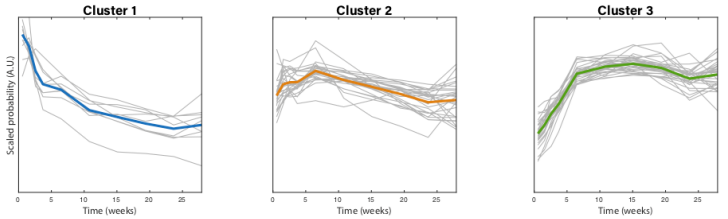
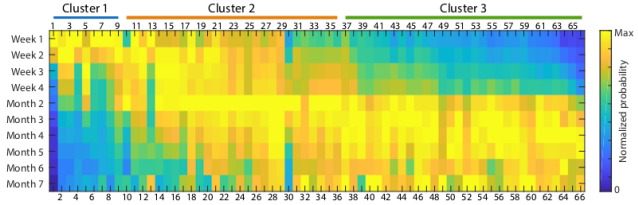
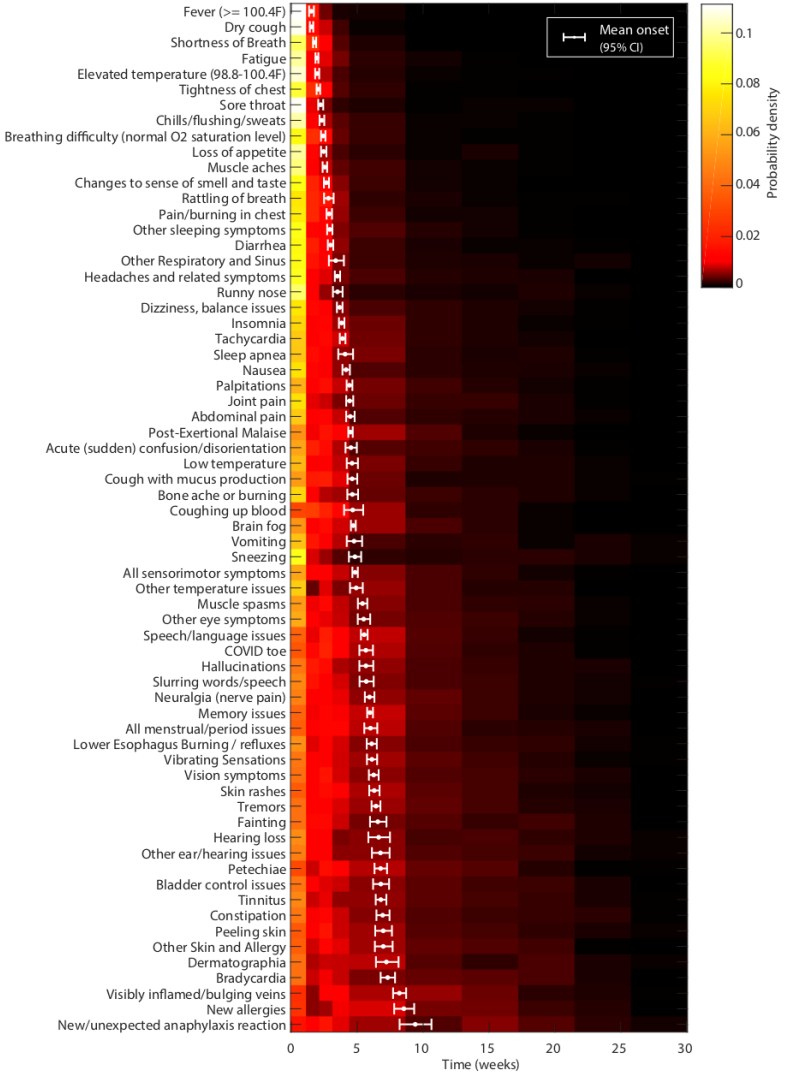


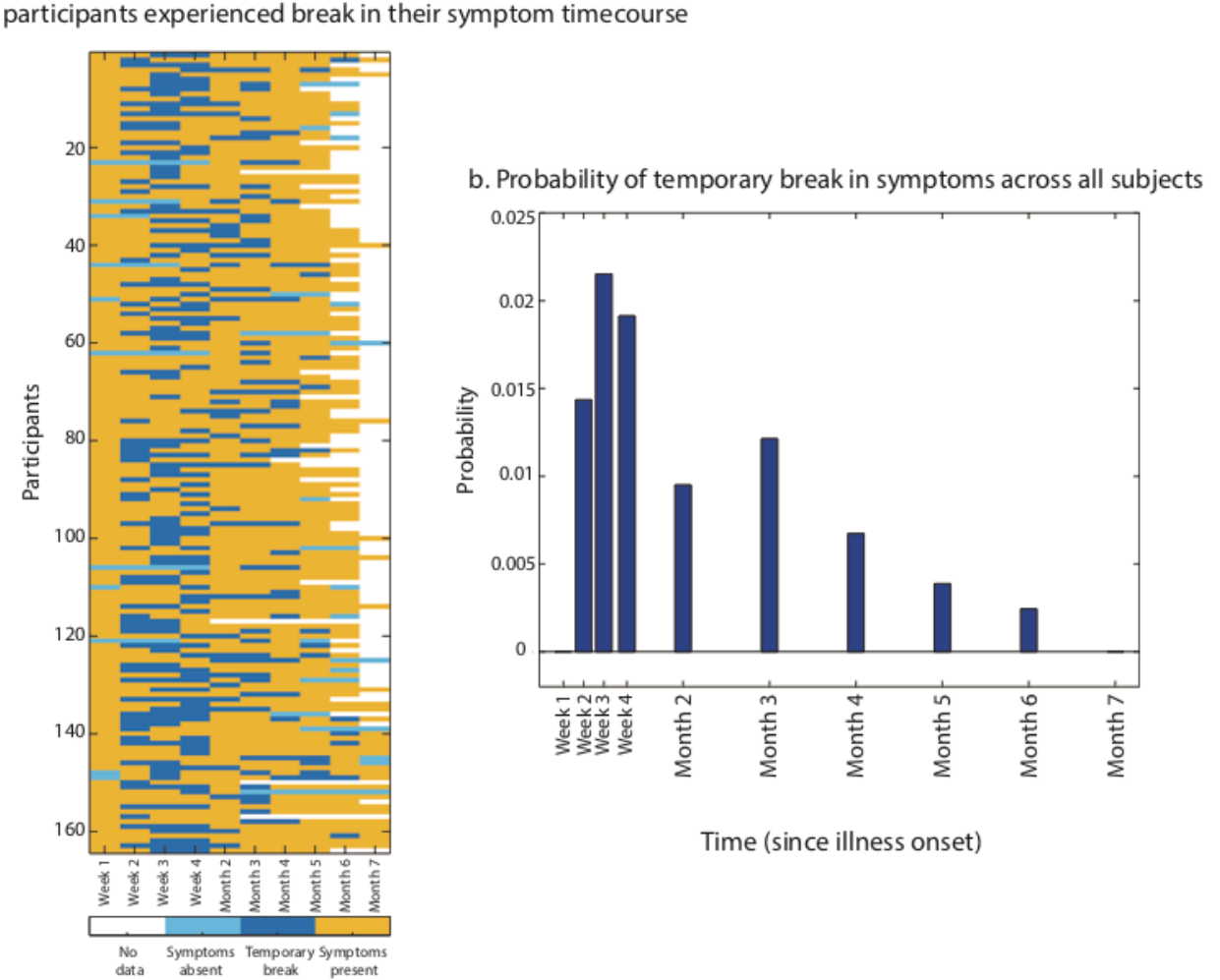

| | | | |
|---|---|---|---|
| **Cardiovascular** | | 25. Fainting<br>19. Pain/burning in chest<br>33. Tachycardia | 49. Bradycardia<br>38. Palpitations<br>64. Visibly inflamed/bulging veins |
| **Dermatologic** | | 30. COVID toe | 53. Dermatographia<br>55. Other Skin and Allergy<br>42. Peeling skin<br>54. Petechiae<br>44. Skin rashes |
| **Gastrointestinal** | 9. Diarrhea<br>2. Loss of Appetite<br>4. Vomiting | 26. Abdominal pain<br>18. Nausea | 45. Constipation<br>43. Gastroesophageal reflux |
| **HEENT (Head, ears, eyes, nose, throat)** | 7. Runny nose<br>6. Sore Throat | | 48. Hearing loss<br>51. Other ear/hearing issues<br>39. Other eye symptoms<br>58. Tinnitus<br>59. Vision symptoms |
| **Immunologic/ Autoimmune** | | | 65. New allergies<br>63. New anaphylaxis reaction |
| **Musculoskeletal** | | 32. Bone ache or burning<br>21. Muscle aches<br>15. Tightness of Chest | 37. Joint pain<br>40. Muscle spasms |
| **Neuropsychiatric** | | 20. Acute (sudden) confusion/disorientation<br>12. Changes to sense of smell and taste<br>22. Dizzines, unsteadiness or balance issues<br>31. Hallucinations<br>29. Headaches and related symptoms<br>35. Insomnia<br>27. Other sleeping symptoms<br>34. Sleep apnea<br>36. Slurring words/speech | 41. All sensorimotor symptoms<br>47. Brain fog<br>61. Memory issues<br>50. Neuralgia (nerve pain)<br>62. Speech/language issues<br>52. Tremors<br>56. Vibrating Sensations |
| **Pulmonary/ Respiratory** | 3. Dry cough<br>5. Rattling of breath | 14. Breathing difficulty (normal O2 saturation level)<br>17. Cough with mucus production<br>10. Coughing up Blood<br>24. Other Respiratory and Sinus<br>16. Shortness of Breath<br>13. Sneezing | |
| **Reproductive/ Genitourinary/ Endocrine** | | | 60. All menstrual/period issues<br>46. Bladder control issues |
| **Systemic** | 8. Elevated temperature (98.8-100.4F)<br>1. Fever (>= 100.4F) | 11. Chills/flushing/sweats<br>28. Fatigue<br>23. Low temperature | 39. Other temperature issues<br>57. Post Exertional Malaise |



# Symptom onset (mean)



# Symptom Breaks



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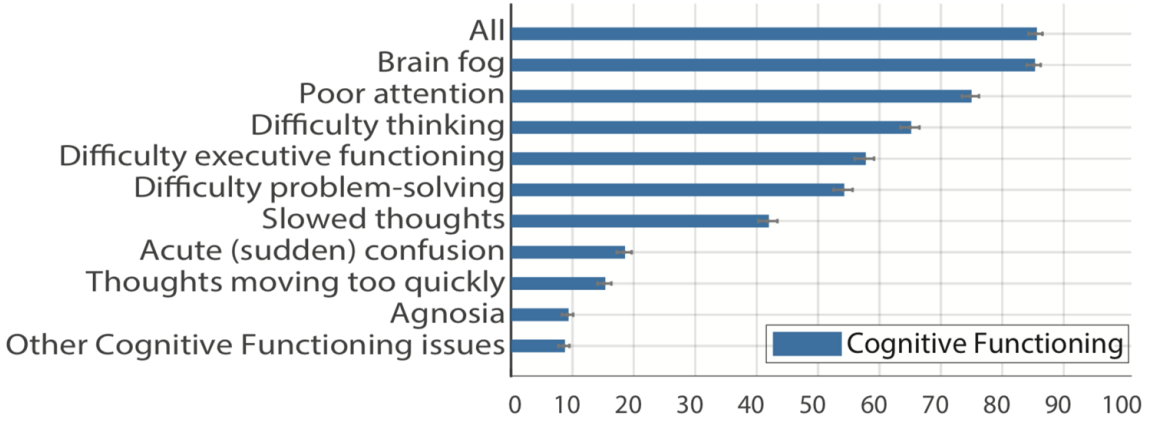


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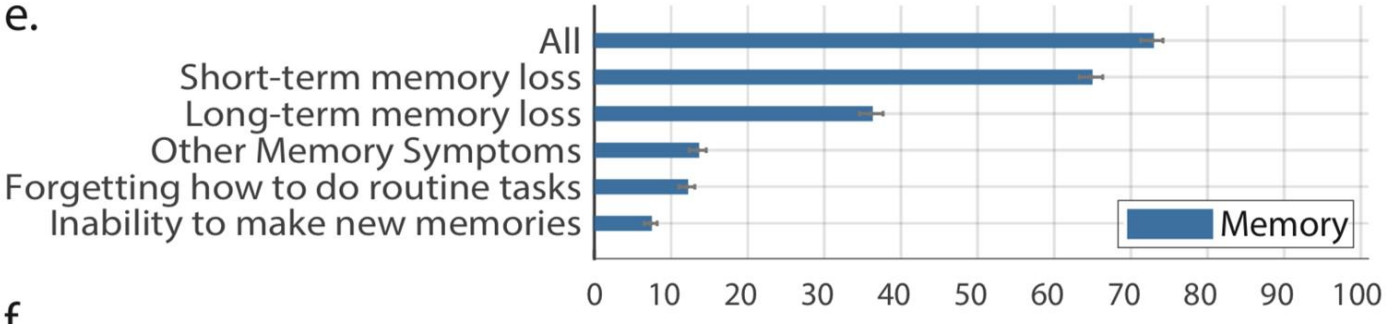


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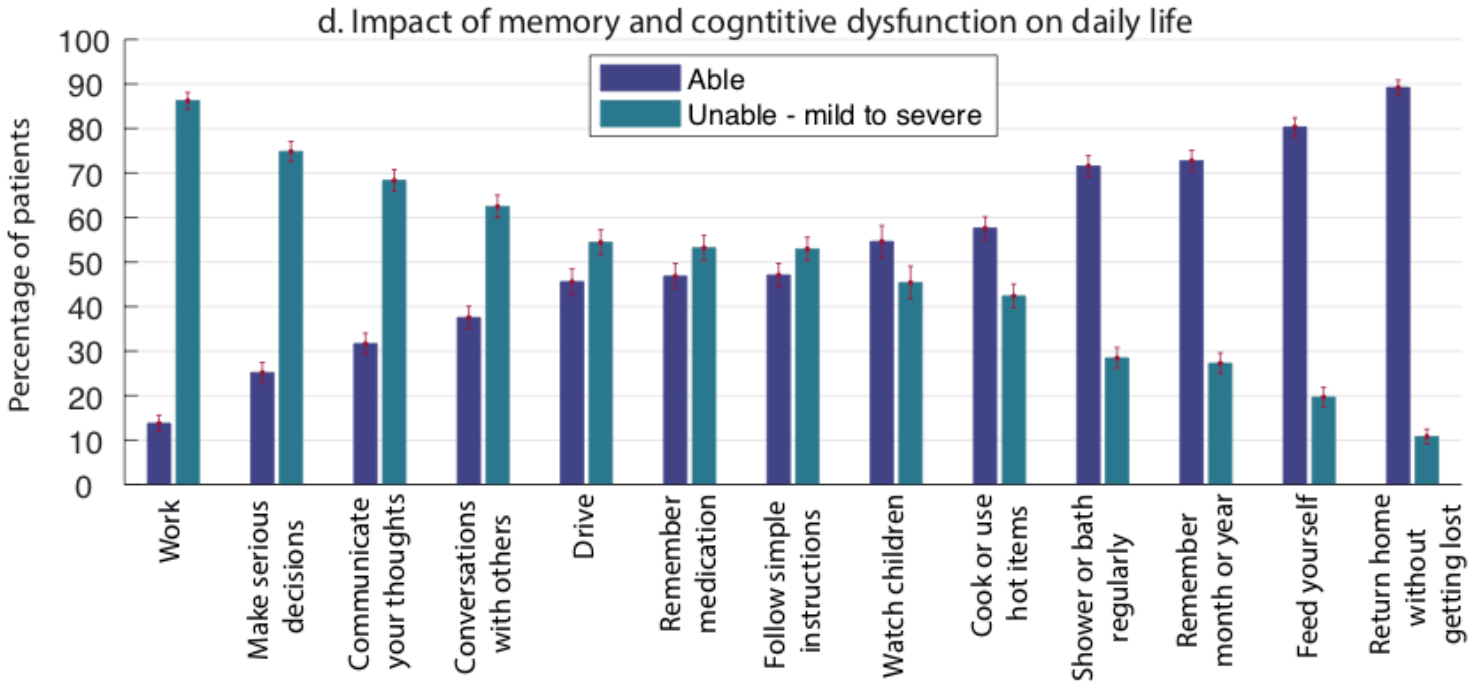
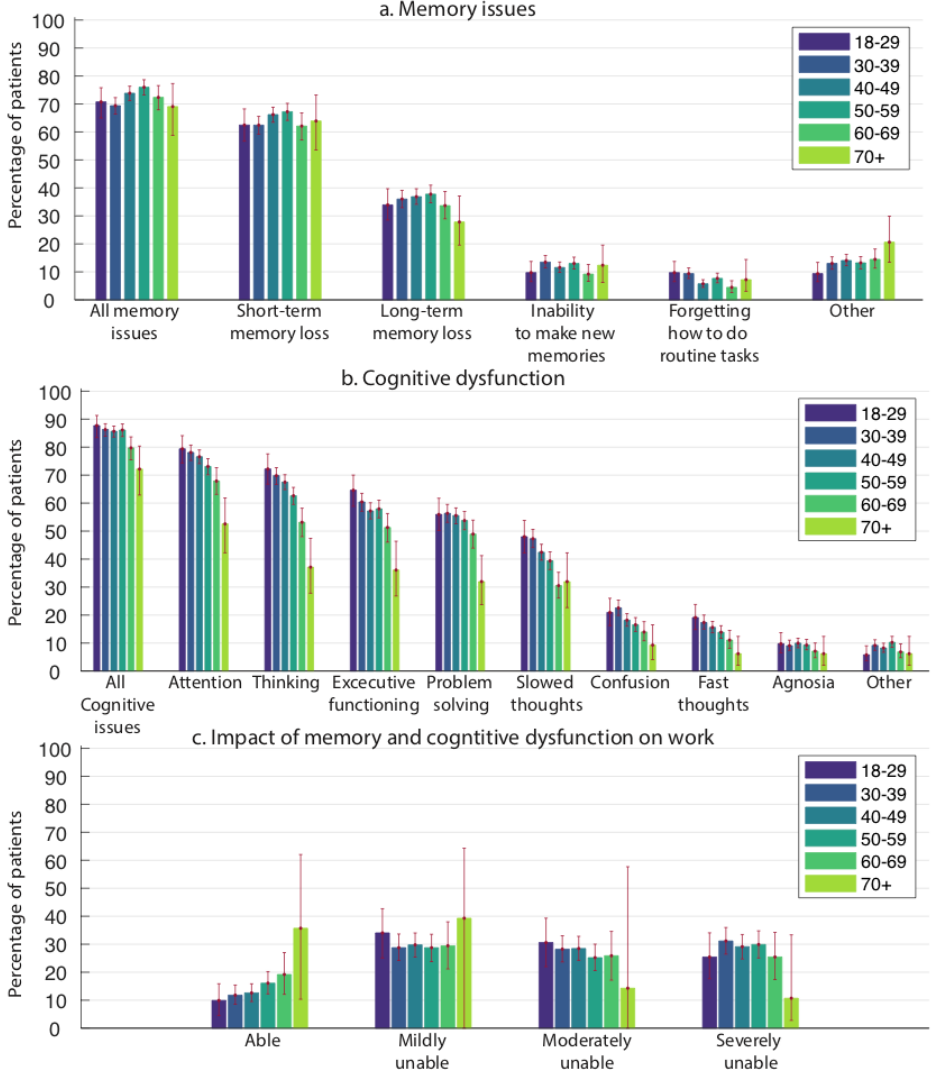
# Cognitive Dysfunction & Memory



# 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 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”*

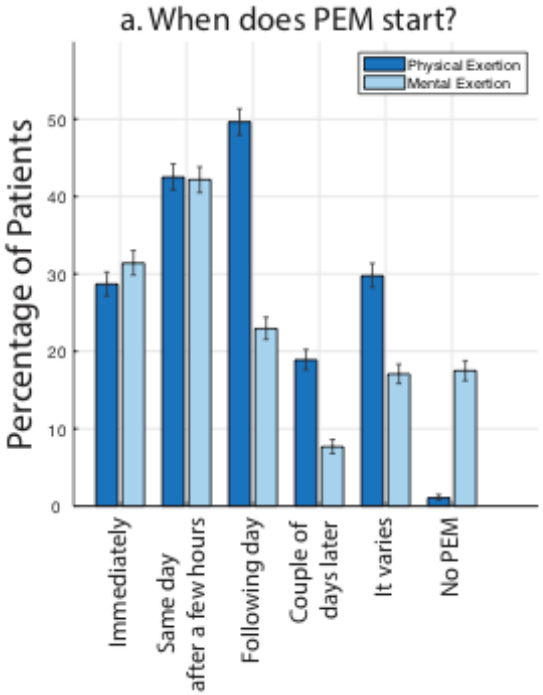
*“had to terminate many phone calls because I **could no longer comprehend the speakers nor communicate clearly** with them”*

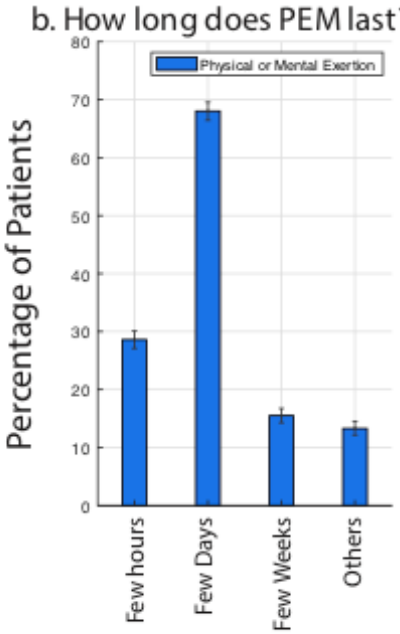
*“used to do the New York Times crossword puzzle every single day and I **can't even manage the mini ones** now”*

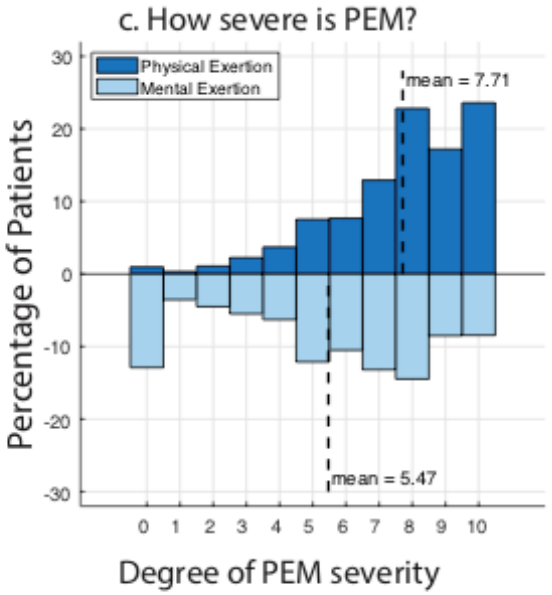
***"can't focus on reading complex texts**, and it makes me feel very tired to do that"*

*“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, Lyme reported
    - Occipital and trigeminal neuralgias

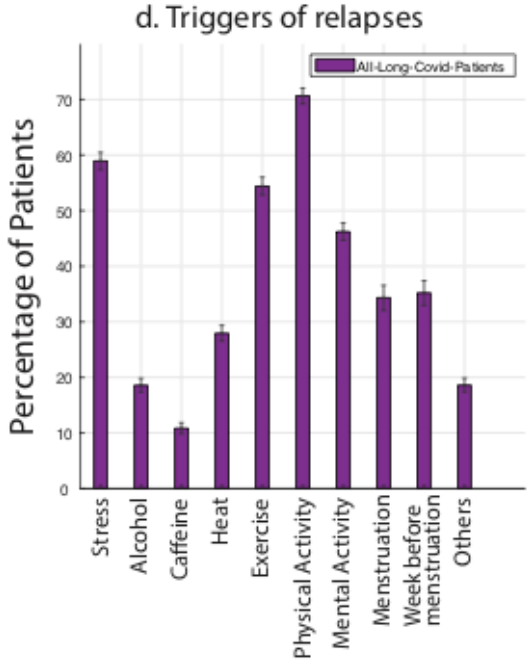
# Other serious symptoms

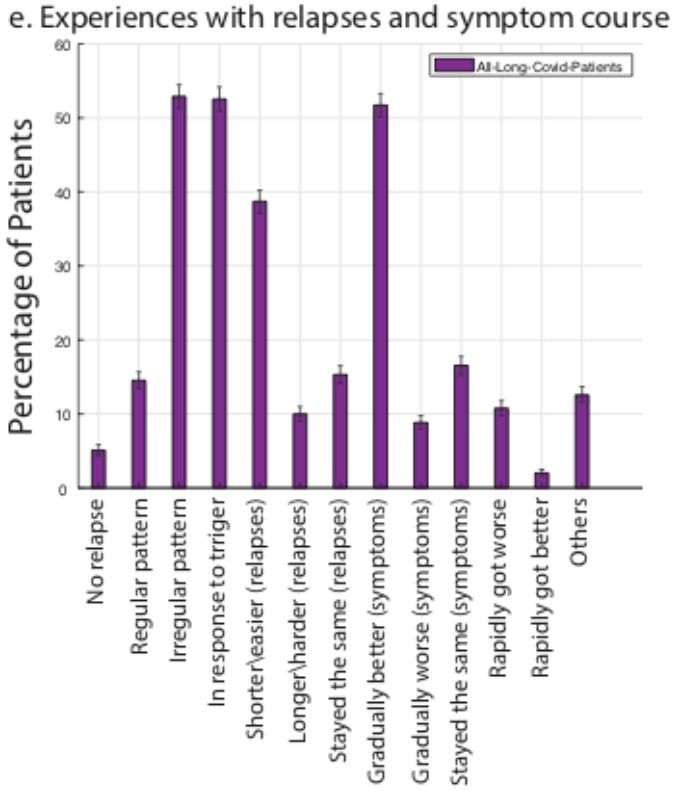
- 1% vision loss
- 9% hearing loss
- 3% facial paralysis
- 12% suicidality

# 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

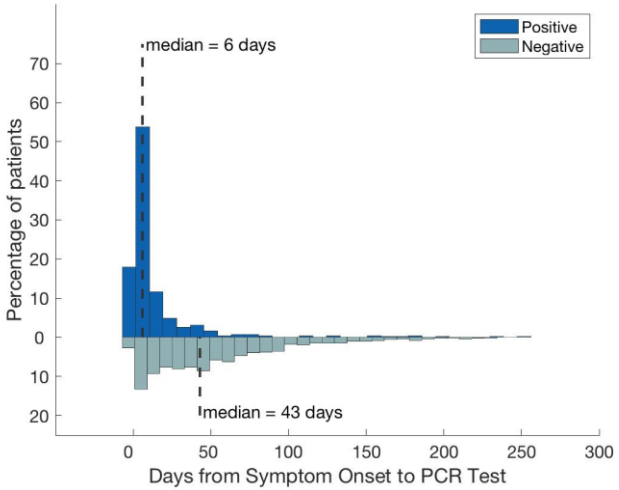


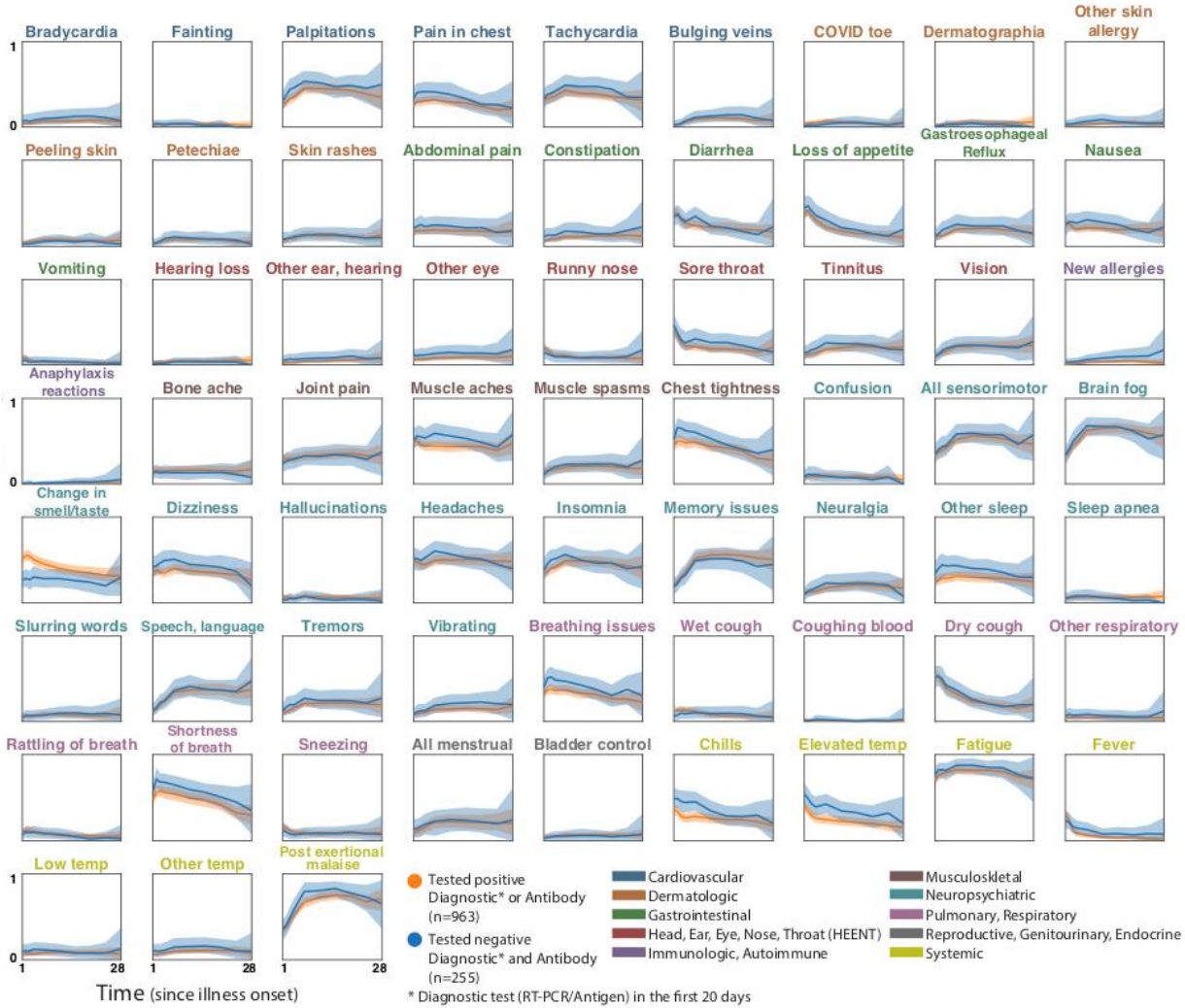



# Impact on work

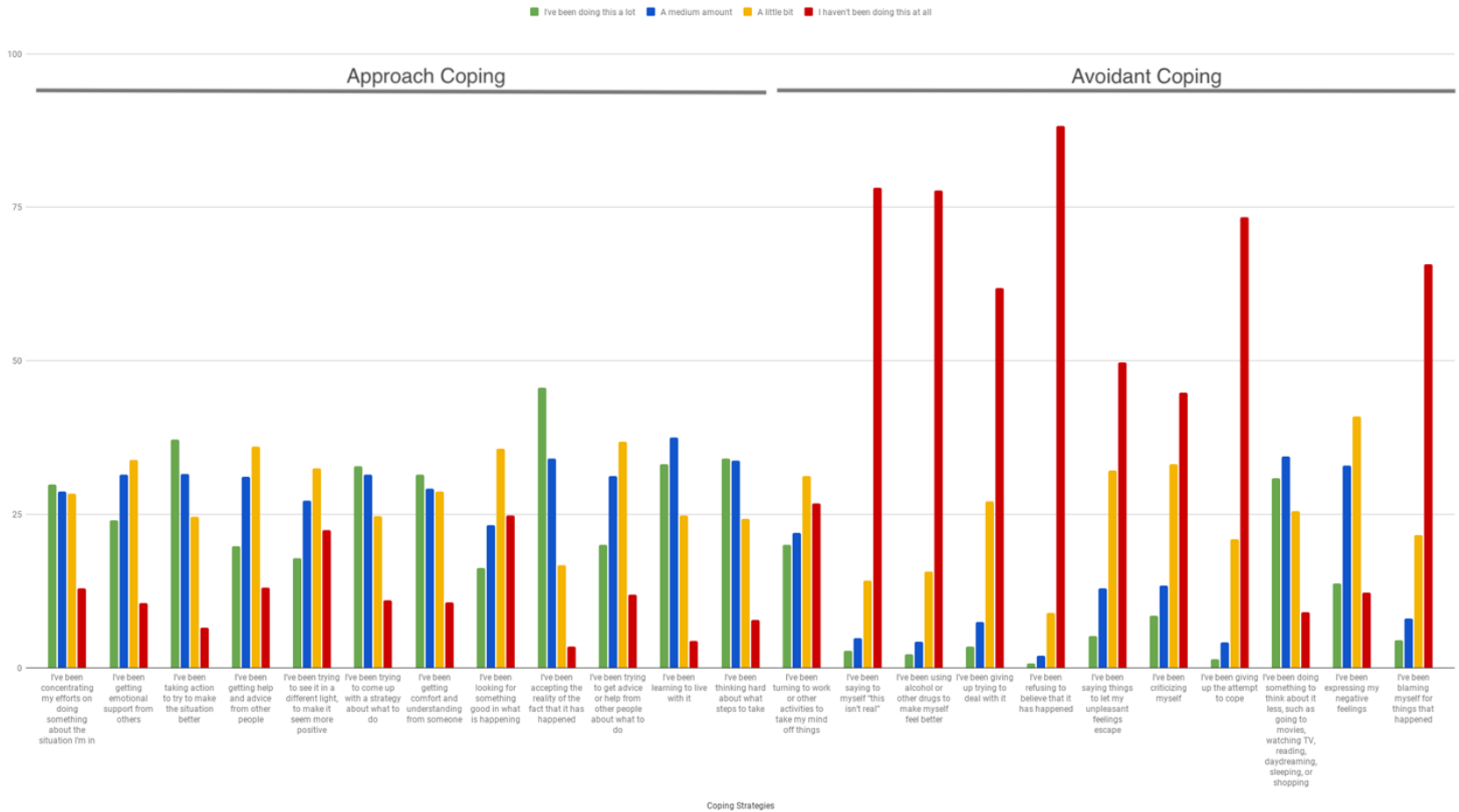
- 67.5% had their work affected due to their illness
  - 45.2% required a reduced work schedule
  - 22.3% were not working at all
  - Remaining respondents were retired, volunteers, or did not provide enough information.
- Of patients with brain fog, 86.2% are mildly to severely unable to work because of brain fog.

# Comparing Positive & Negative Cohorts



Long COVID Coping Strategies (Brief COPE, n=3762)



# 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)
  - **Neuroimmunology** (Dr. Avindra Nath, NIH)
  - **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)
  - **Reactivations, difference in early vs late post-viral years** (Dr. Nancy Klimas)

# Treatment Options

- Pacing Regiment!
  - no exercise for people with post-exertional malaise
- Dysautonomia
  - Test for POTS
  - Compression garments (leggings, abdominal binders)
  - Salt and electrolyte tablets
- Mast Cell Activation Syndrome
  - H1 and H2 histamine antagonists (famotidine, loratadine)
  - Quercetin
- Many symptoms don’t currently have treatments

# @patientled (Twitter)
# PatientResearchCovid19.com

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

Thank you!