“Long COVID”

Some unexpected and troubling findings as of early 2022

For NMSR

Alan Zelicoff, MD **3/9/22**

The New York Times

OPINION

Long Covid Is Not Rare. It's a Health Crisis.

Lingering symptoms from the coronavirus may turn out to be one of the largest mass disabling events in modern history.

March 17, 2021

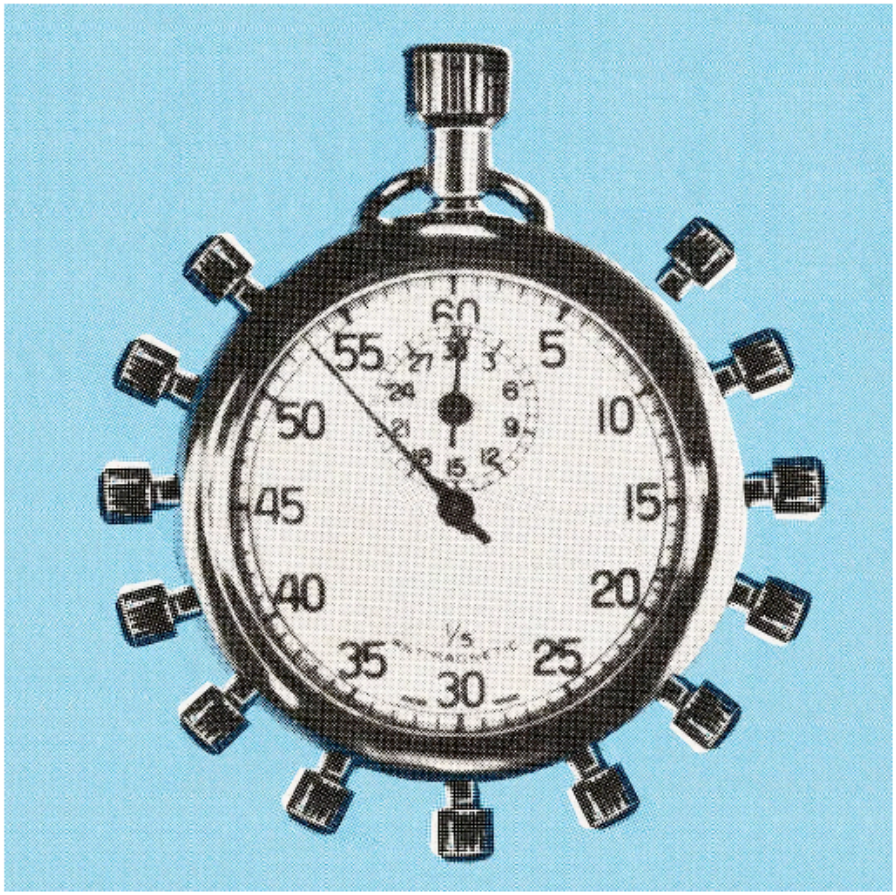

Illustration By Arsh Raziuddin/the New York Times; Photograph By Getty Images

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February 23, 2021

NIH launches new initiative to study "Long COVID"

I write to announce a major new NIH initiative to identify the causes and ultimately the means of prevention and treatment of individuals who have been sickened by COVID-19, but don't recover fully over a period of a few weeks. Large numbers of patients who have been infected with SARS-CoV-2 continue to experience a constellation of symptoms long past the time that they've recovered from the initial stages of COVID-19 illness. Often referred to as "Long COVID", these symptoms, which can include fatigue, shortness of breath, "brain fog", sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and can range from mild to incapacitating. In some cases, new symptoms arise well after the time of infection or evolve over time. In December, NIH held a workshop to summarize what is known about these patients who do not fully recover and identify key gaps in our knowledge about the effects of COVID-19 after the initial stages of infection. In January, I shared the results from the largest global study of these emerging symptoms. While still being defined, these effects can be collectively referred to as Post-Acute Sequelae of SARS-CoV-2 infection (PASC). We do not know yet the magnitude of the problem, but given the number of individuals of all ages who have been or will be infected with SARS-CoV-2, the coronavirus that causes COVID-19, the public health impact could be profound.

What is “Long COVID”?

- A “clinical” defintion to date
- Includes, *inter alia*, the following symptoms:
  - Neurologic
    - Headaches
    - “Brain Fog”
  - Respiratory
    - Shortness of breath
    - Chronic Cough
  - Psychiatric/Psychological
    - Anxiety
    - Depression
  - Non-specific
    - Fatigue
    - Sleep disturbance
    - Rashes
    - Gastro-intestinal “issues"

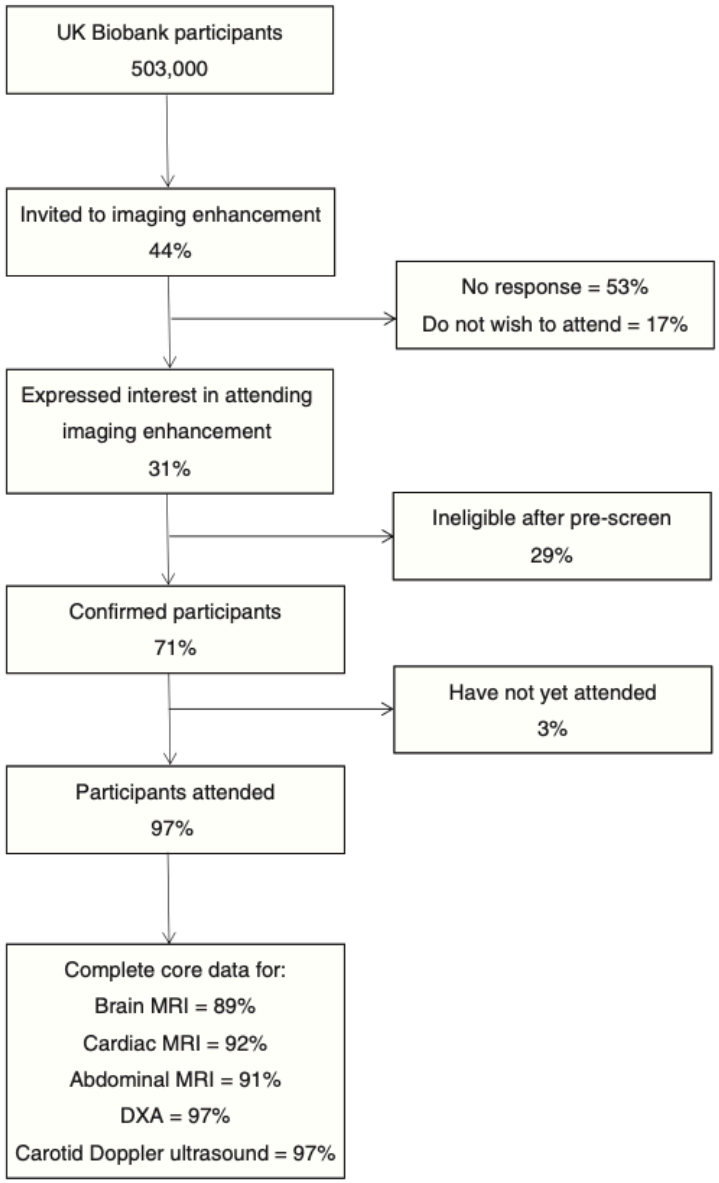
Source: National Institutes of Health
https://tinyurl.com/4bhf36jp

What are the *objective* findings in COVID after acute illness?

- Brain
  - UK BioBank Study, February 2022
  - Liu et al, March 2022
- Heart
  - Xie, et. al. Feb 2022
- Lungs and other tissue
  - Maccio et. al. Feb. 2022

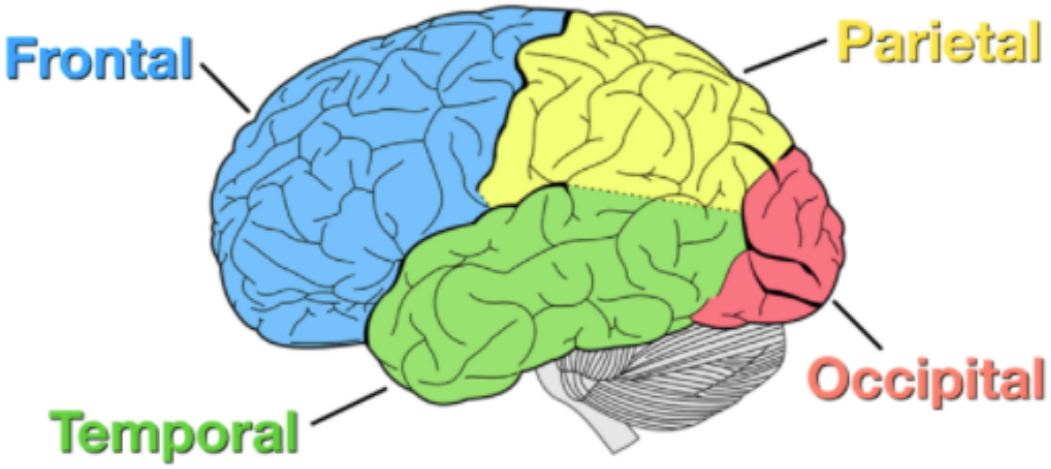
UK BioBank Study

circa 2006 to date



- Between 2006-2010 about 9.2 million adults invited to participate
- About 500,000 participants
- Imaging of 5 body areas
  - Brain (via MRI)
  - Cardia (via MRI)
  - Abdominal (via MRI)
  - Dual X-ray absorption (DXA)
  - Carotid Doppler US
- Baseline assessment
  - Lifestyle
  - Socio-demographic
  - Genotyping
  - Standard screening blood tests
  - Hearing
  - Arterial stiffness
  - Cardiorespiratory fitness
  - Collection of physical activity data over 7 days
  - Dietary
  - Cognitive function
  - Pain

Cerebral Cortex = Outer Grey Matter Layer



Frontal

Executive Functioning - DA

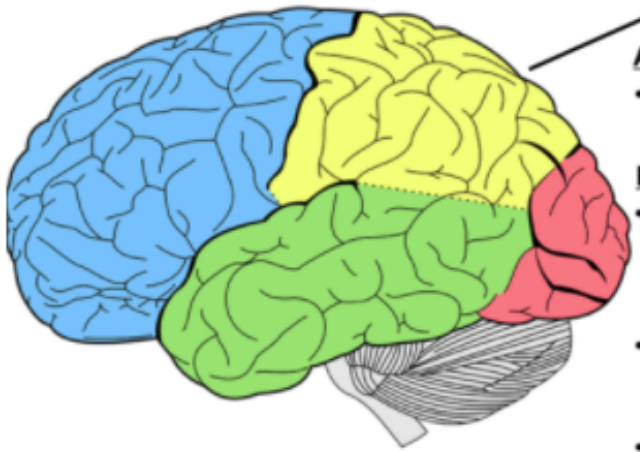
- Planning
- Problem Solving
- Motivation
- Judgement
- Decision Making
- Impulse Control
- Social Behavior
- Personality
- Memory
- Learning
- Reward
- Attention

Frontal

Motor

- Skeletal Muscle Movement
- Ocular Movement
- Speech Control
- Facial Movement

Function: "Somatosensory" Parietal



Awareness of Somatic Sensation

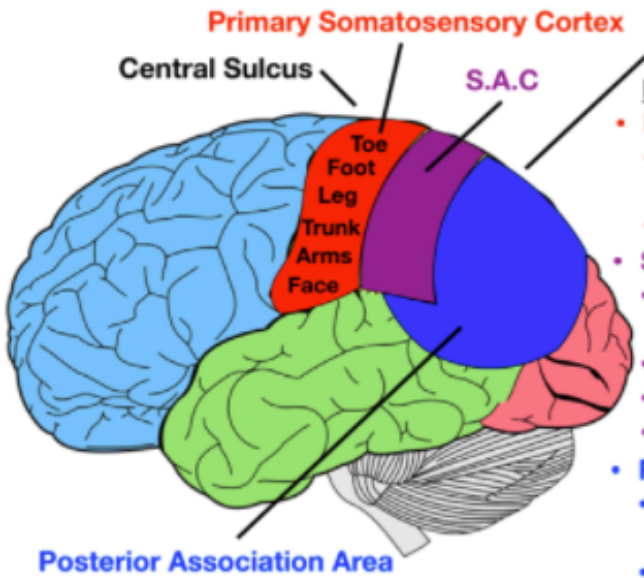
- Touch, Pain,Temperature, Pressure, Vibration

Processing Somatic Sensation

- Analyzing, Recognizing, Memory of Somatic Sensation

Proprioception

- Coordination of Visual, Auditory, and Somatosensory Stimuli
- Spacial & Body Awareness

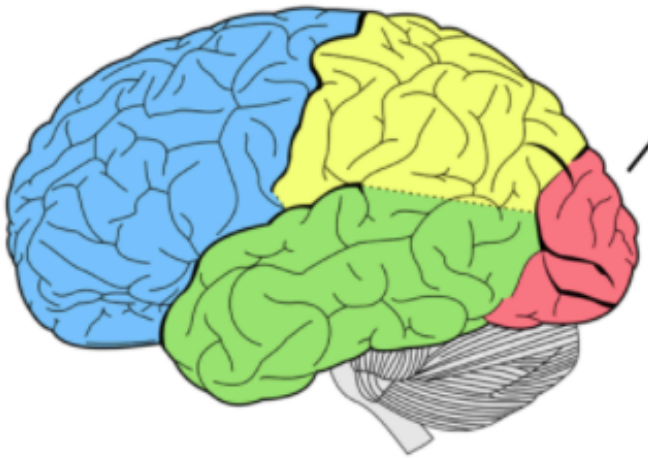


Parietal

Functional Areas

- Primary Somatosensory Cortex
  - Awareness of Somatic Sensations
  - Touch, Pain, Temperature
- Somatosensory Assoc. Cortex
  - Processing/Analyzing Somatic Sensations
  - Memory of Sensations
  - Recognition of Sensations
  - Proprioception
- Posterior Association Area
  - Visual, Auditory, Somatosensory Areas Meet
  - Spacial Awareness of Body

Function: "Visual"



Occipital

Awareness of Visual Stimuli

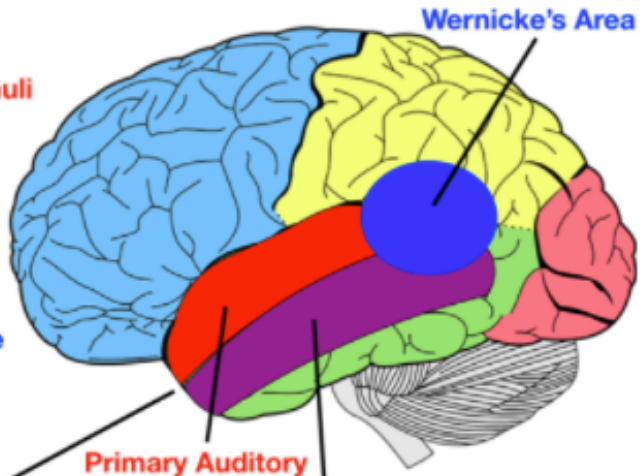
- Seeing Objects/Stimuli

Processing Visual Stimuli

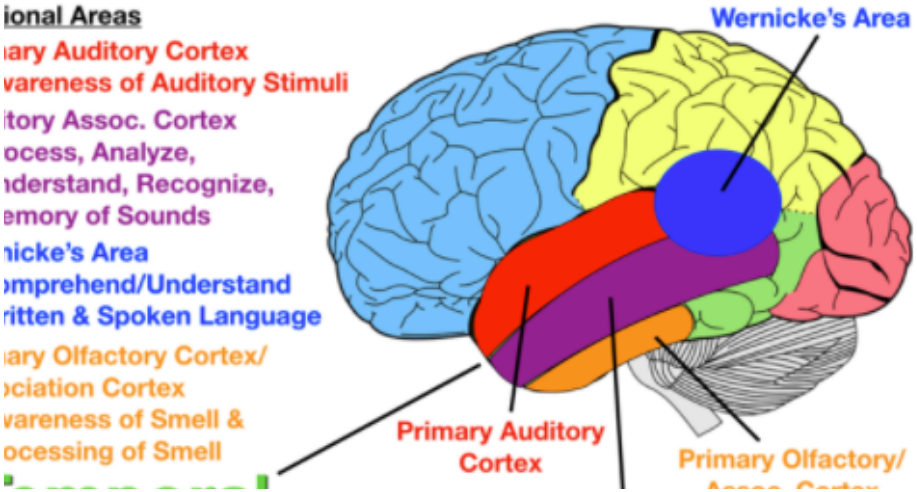
- Analyzing, Recognizing, Memory of Visual Stimuli
- Shapes, Colors, Sizes

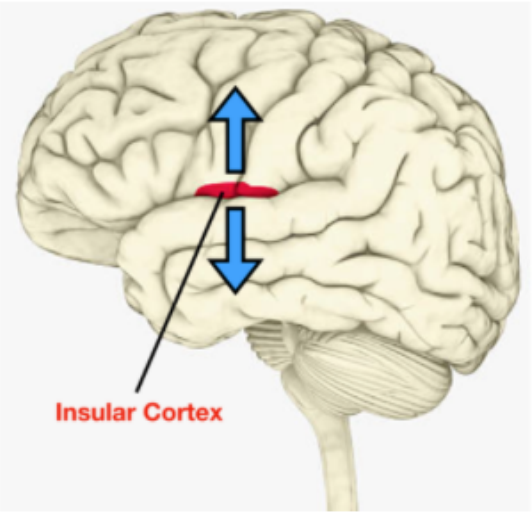
Functional Areas

- Primary Auditory Cortex
  - Awareness of Auditory Stimuli
- Auditory Assoc. Cortex
  - Process, Analyze, Understand, Recognize, Memory of Sounds
- Wernicke's Area
  - Comprehend/Understand Written & Spoken Language



Temporal





Functional Areas

- Deep Within Lateral Sulcus
- Insular Cortex
  - Taste
  - Visceral Sensation
  - Autonomic Control
  - Vestibular Information
  - Equilibrium

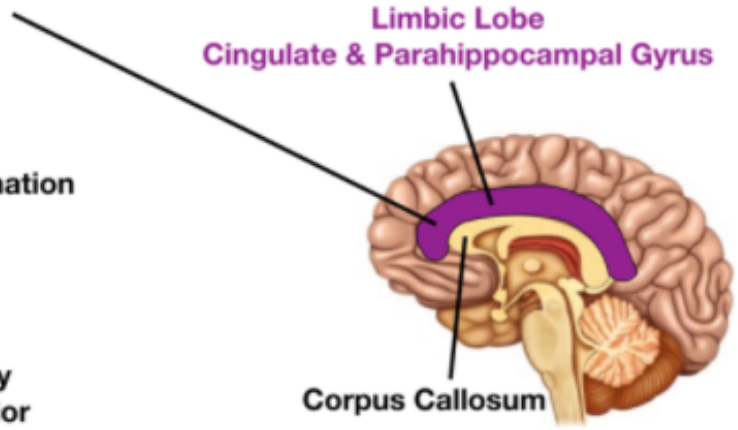
Limbic

Structures:

- Limbic Lobe
- Amygdala
- Hippocampal Formation
- Thalamus
- Hypothalamus

Function:

- Learning & Memory
- Emotions & Behavior
- Smell



Example: Brain MRI scanning

Table 2 Brain MRI protocol parameters.

Modality	Duration (mins)	Resolution (mm^3)	Matrix	Other parameters
T1 MPRAGE	4:54	1.0x1.0x1.0	256x256x208	TI/TR = 880/2000 ms, R = 2
Resting fMRI	6:10	2.4x2.4x2.4	88x88x64	TE/TR = 39/735 ms, α = 51°, MB = 8
T2 FLAIR	5:52	1.0x1.0x1.05	256x256x192	TI/TR = 1800/5000 ms, R = 2
Diffusion MRI[1]	7:08	2.0x2.0x2.0	104x104x72	TR = 3600 ms, 50 directions/shell, b = 0, 1000, 2000 s/mm2, α = 51°, MB = 3
Susceptibility-weighted	2:34	0.8x0.8x3.0	288x256x48	TE1/TE2/TR = 9.4/20/27 ms, R = 2
Task fMRI	4:13	2.4x2.4x2.4	88x88x64	TE/TR = 39/735 ms, α = 51°, MB = 8

FLAIR, fluid-attenuated inversion recovery; MB, multi-band factors; MPRAGE, magnetization-prepared rapid acquisition with gradient echo sequence for T1-weighted contrast; R, parallel imaging acceleration factor

[1]Multi-band excitation and reconstruction protocols were kindly provided by the Center for Magnetic Resonance Research in the Department of Radiology of the University of Minnesota, USA.

- T1 scans allow precise volumetric measures of the whole brain,
- The T2 FLAIR scan identifies changes that might be indicative of inflammation or tissue damage.
- swMRI is sensitive to increased iron content as a result of microbleeds or chronic microglial activation in the context of neurodegeneration
- dMRI reflects structural connectivity and tissue microstructural features describing white matter integrity.
- Resting fMRI is performed on an individual who is not engaged in any particular activity or task and can provide indices related to the functional connectivity between brain regions independent of external stimuli.
- task fMRI is performed on an individual to whom stimuli are repetitively delivered that engage sensory-motor and cognitive processes of interest.

Repeat Scanning

- By early 2020, 50,000 participants had full imaging completed
- Goal is 100,000 by 2023
  - Of this, at least 10,000 will have repeat imaging by 2023
- At least 1,700 separate UKB-related research projects underway

Littlejohns, T. J., Holliday, J., Gibson, L. M., Garratt, S., Oesingmann, N., Alfaro-Almagro, F., Bell, J. D., Boultwood, C., Collins, R., Conroy, M. C., Crabtree, N., Doherty, N., Frangi, A. F., Harvey, N. C., Leeson, P., Miller, K. L., Neubauer, S., Petersen, S. E., Sellors, J., … Allen, N. E. (2020). The UK Biobank imaging enhancement of 100,000 participants: Rationale, data collection, management and future directions. *Nature Communications*, *11*(1), 2624. https://doi.org/10.1038/s41467-020-15948-9

Article

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

https://doi.org/10.1038/s41586-022-04569-5

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Gwenaëlle Douaud[1]✉, Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L. R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Peter Keating[4], Anderson M. Winkler[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Thomas E. Nichols[8] & Stephen M. Smith[1]

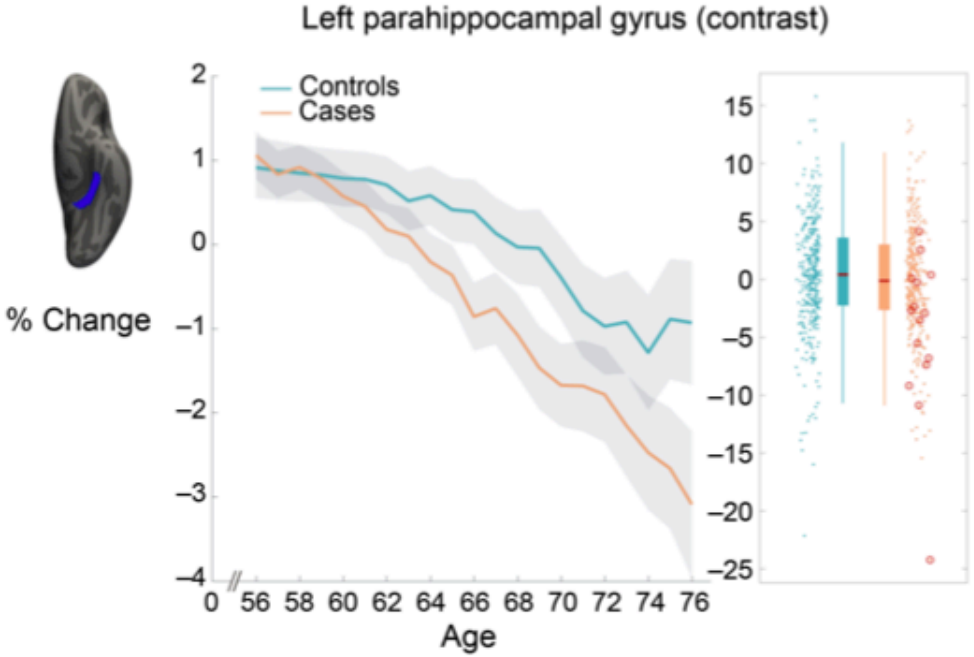
SARS-CoV2 associated brain structure changes

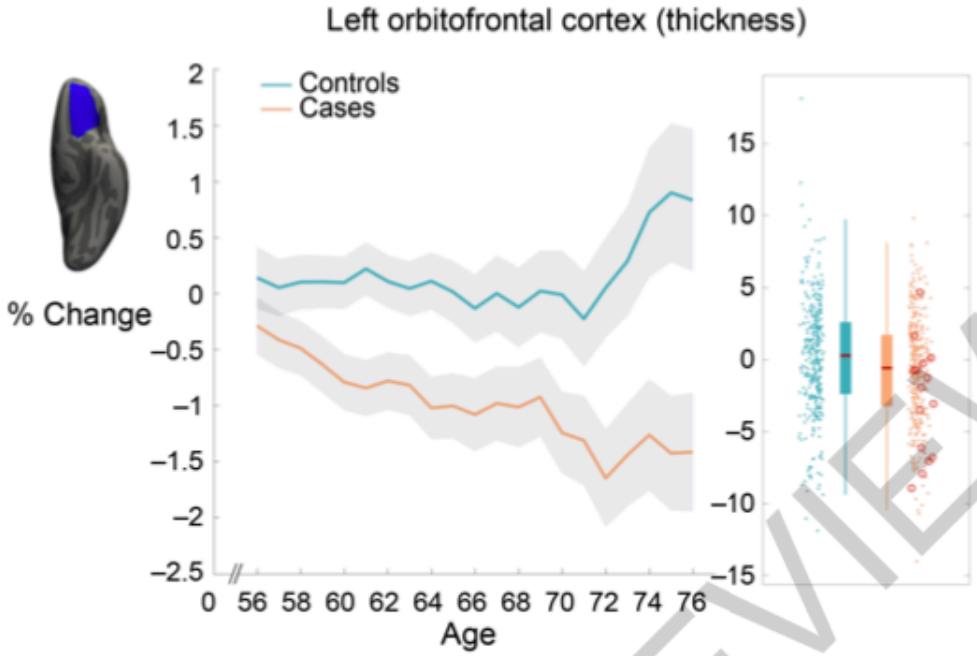
- 785 participants who have been imaged twice
- Age 51-81
- 401 SARS-CoV2 infected people
  - 141 days separating COVID diagnosis and second scan
  - 384 controls (age and sex-matched more or less)

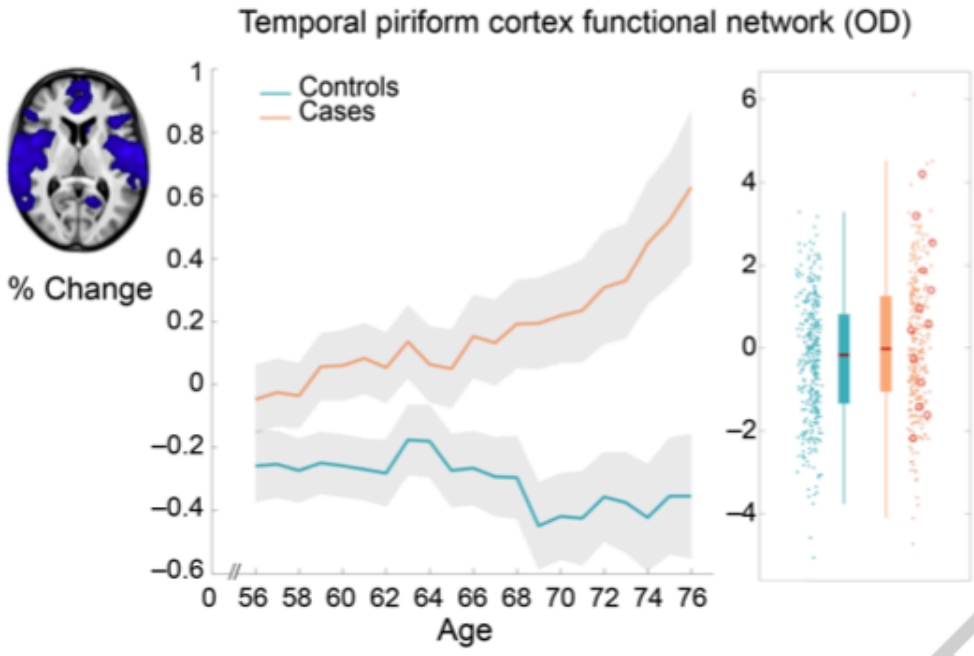
SARS-CoV2 associated brain structure changes

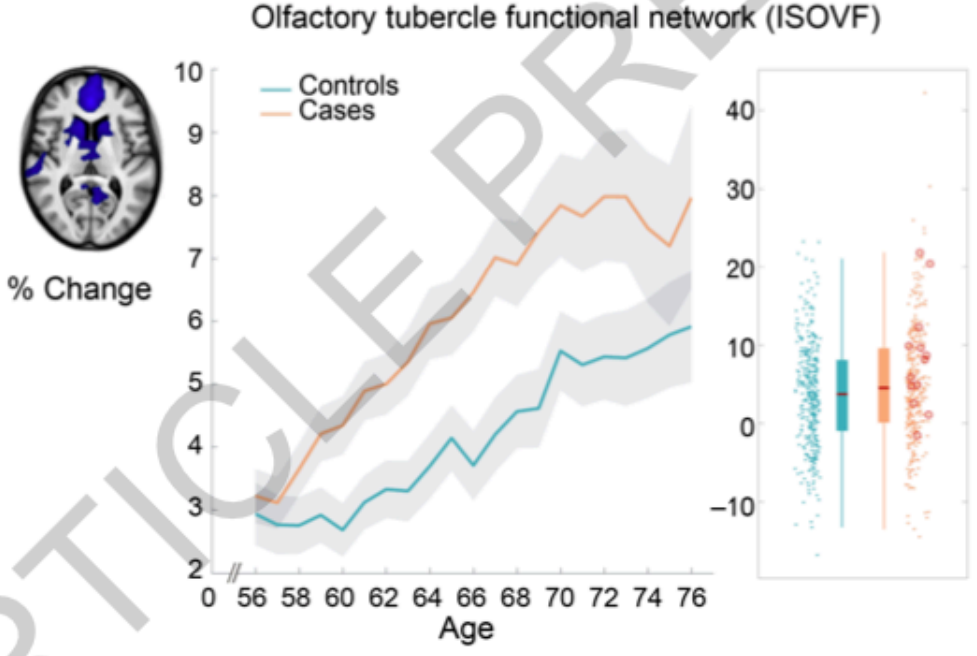
- Primary Findings in COVID patients vs. controls
  - Reduced grey matter thickness in orbitofrontal cortex and parahippocampal gyrus
  - Markers of tissue damage in olfactory cortex
  - Reduction in global brain size
  - Larger cognitive decline

Imaging results in selected brain areas





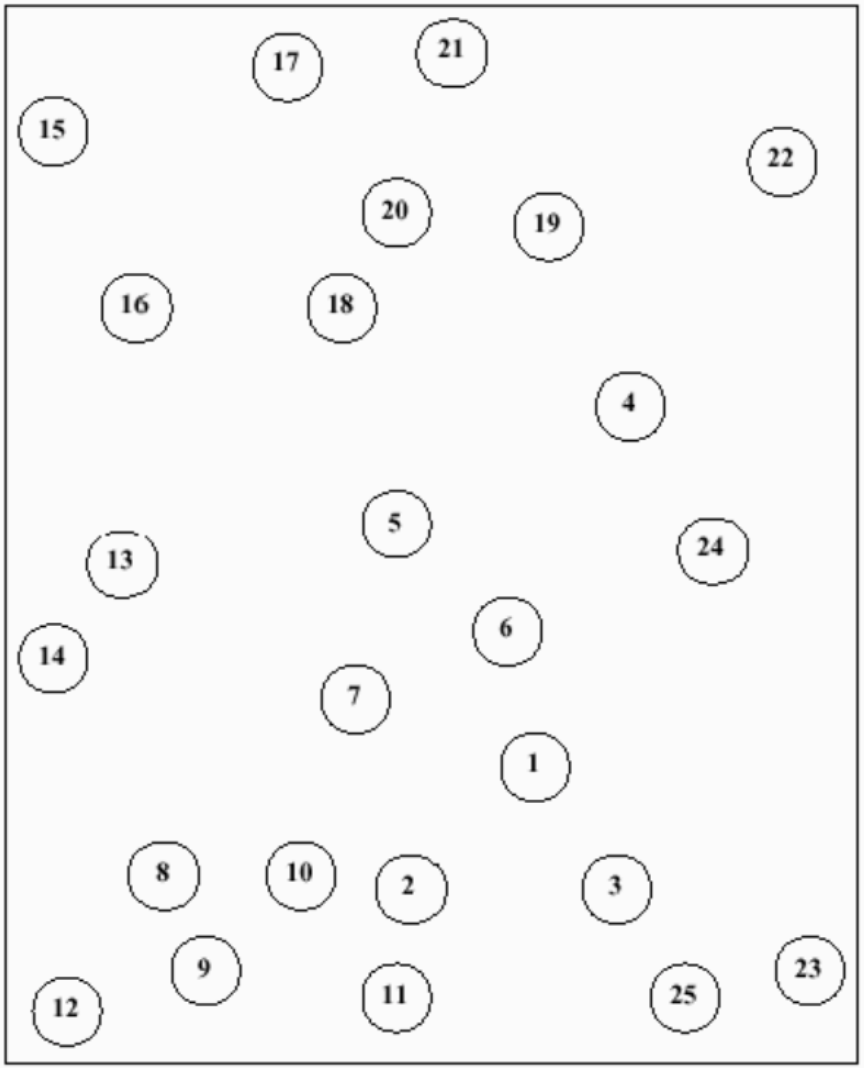




Cognitive Testing: The Trail Making tests

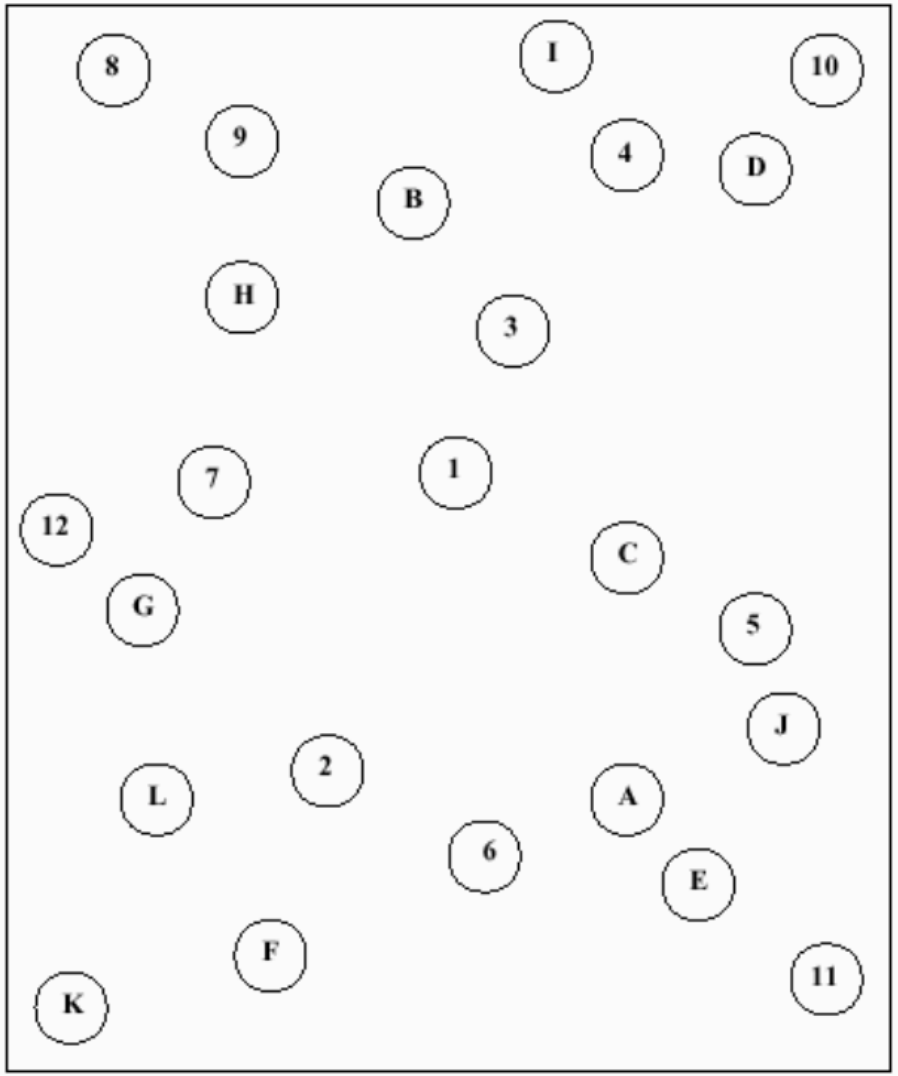
Trail Making Test Part A

Patient's Name: _____ Date: _____



Trail Making Test Part B

Patient's Name: _____ Date: _____



Cognitive Testing Results

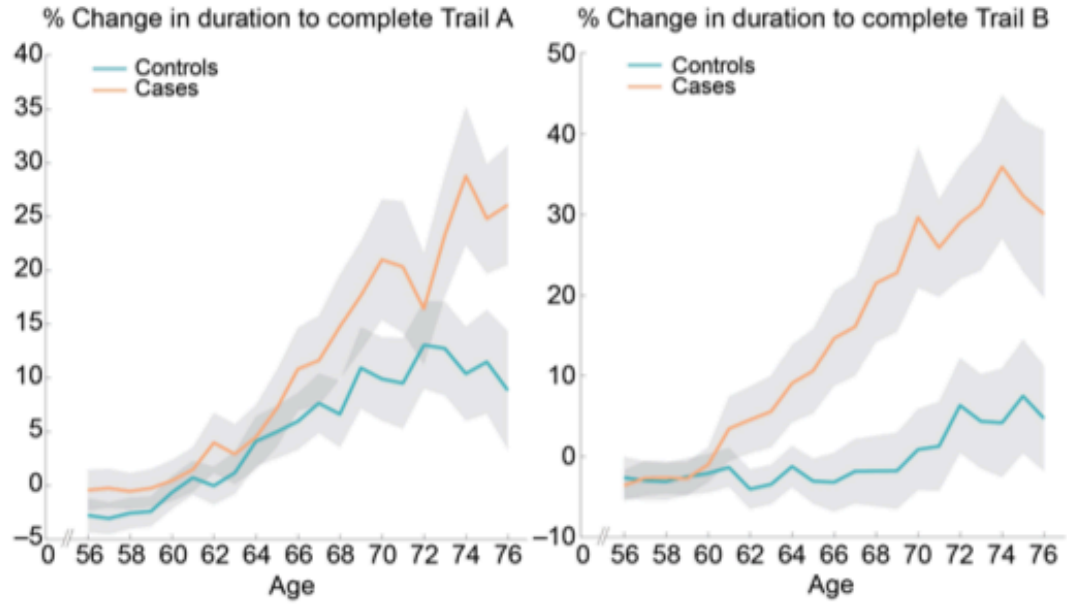
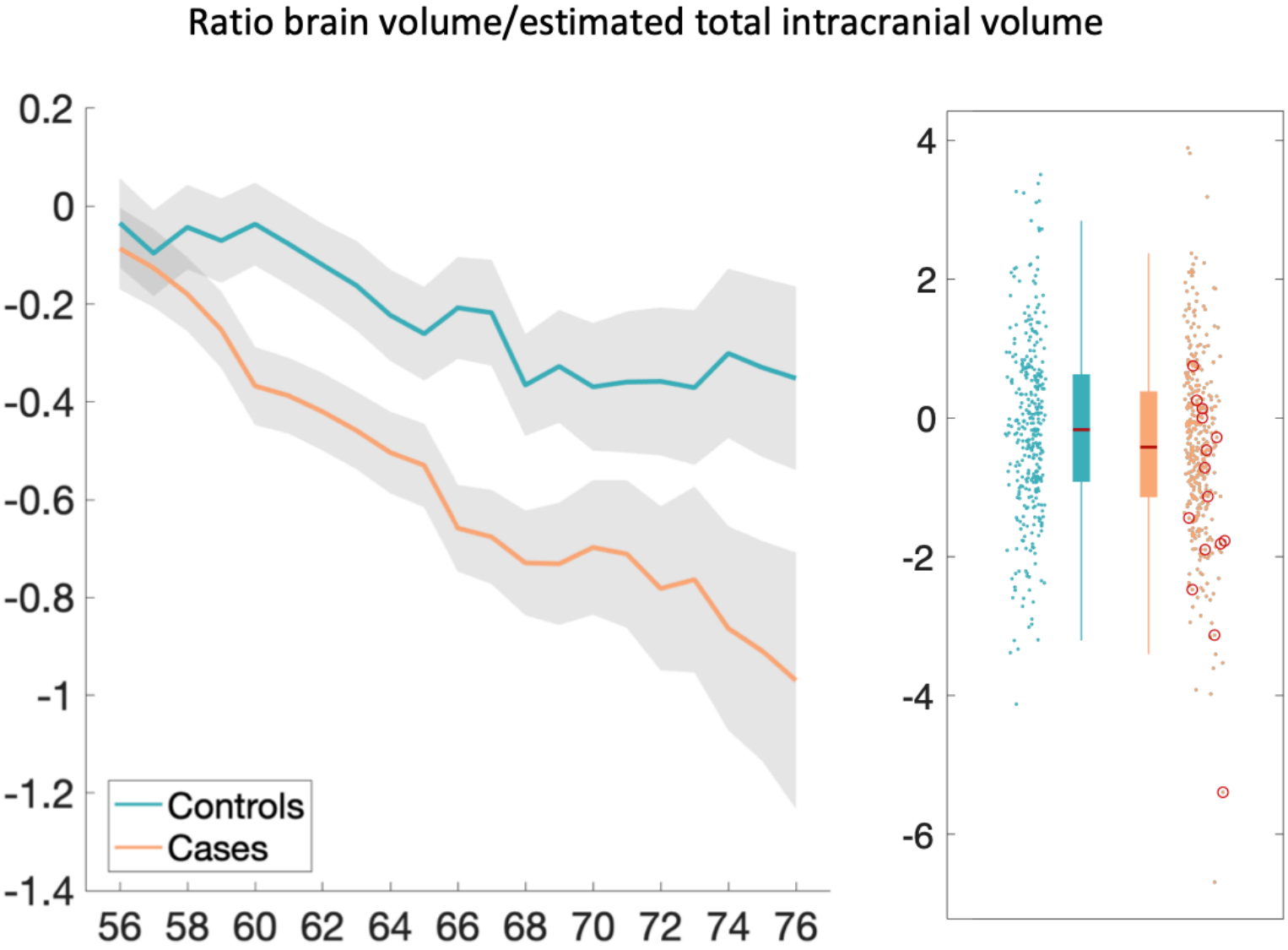


Fig. 3 | Percentage longitudinal change for SARS-CoV-2 positive participants and controls, in the duration to complete Trails A and B of the UK Biobank Trail Making Test. Absolute baseline (used to convert longitudinal change into percent change) estimated across the 785 participants. These curves were created using a 10-year sliding window across cases and controls (standard errors in grey).

Total Brain Volume



Cognitive Changes post-COVID in adults >=60 years

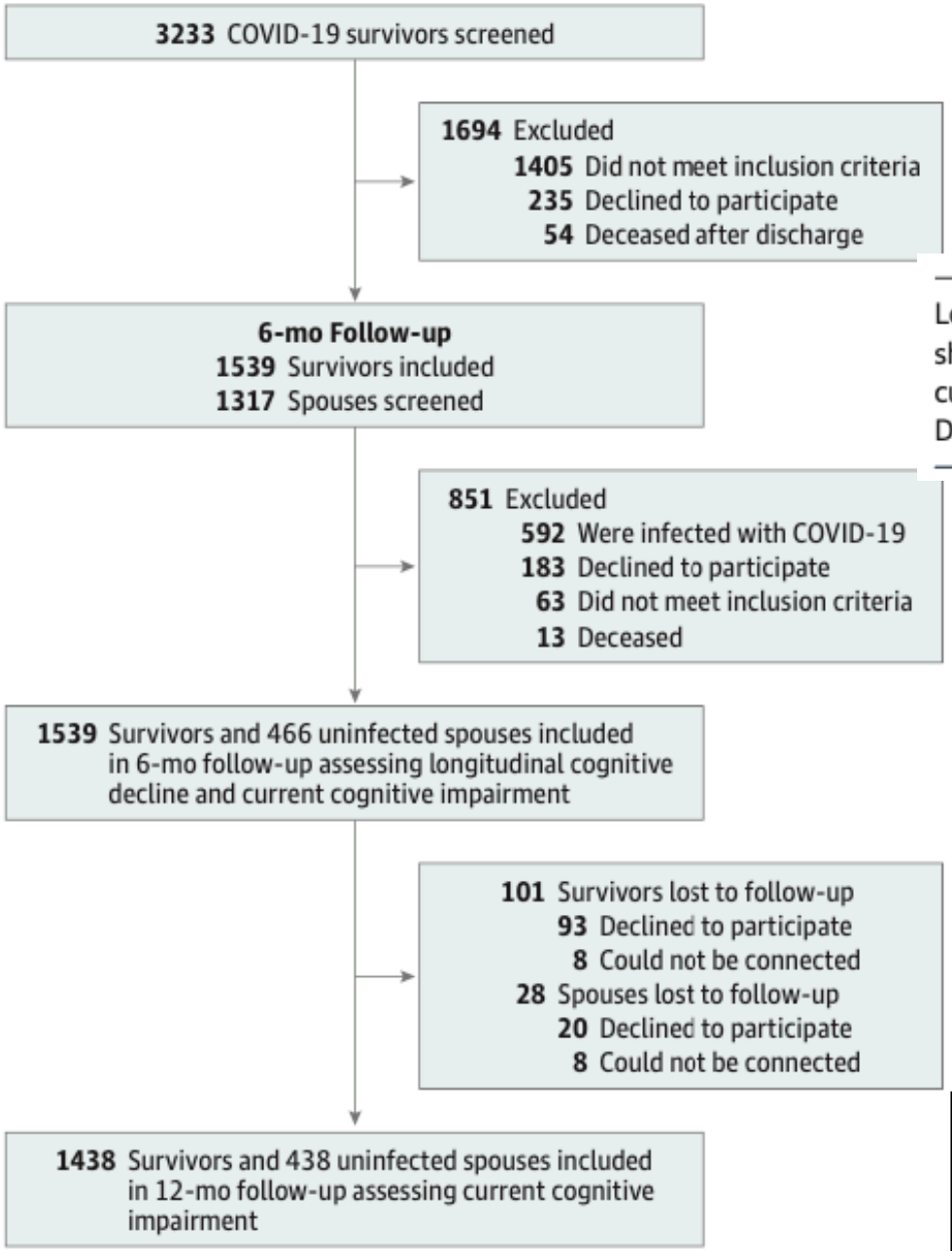
JAMA Neurology | Original Investigation

One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China

A Longitudinal Cohort Study

Liu, Y.-H., Chen, Y., Wang, Q.-H., Wang, L.-R., Jiang, L., Yang, Y., Chen, X., Li, Y., Cen, Y., Xu, C., Zhu, J., Li, W., Wang, Y.-R., Zhang, L.-L., Liu, J., Xu, Z.-Q., & Wang, Y.-J. (2022). One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. *JAMA Neurology*. https://doi.org/10.1001/jamaneurol.2022.0461

Figure 1. Screening Flowchart

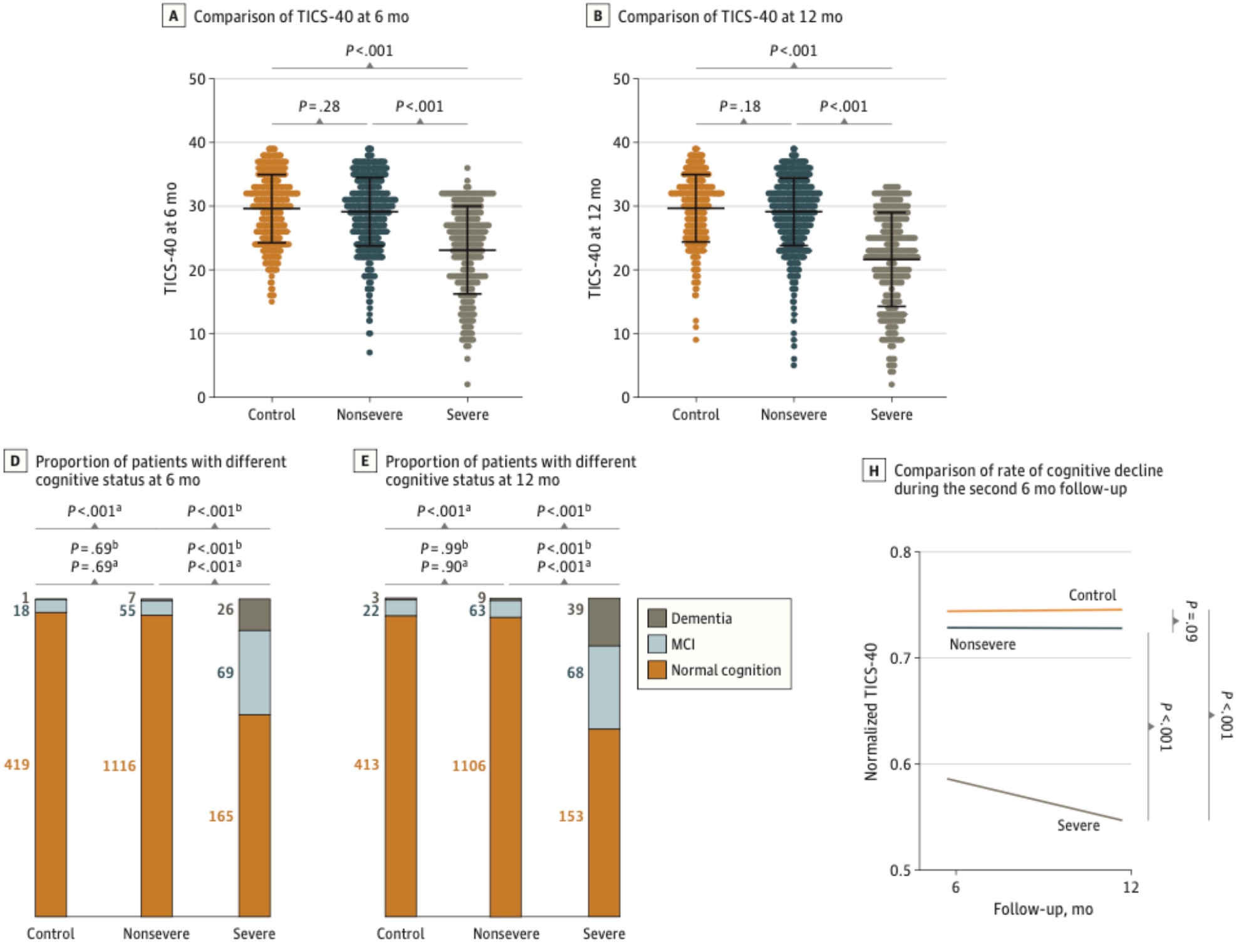


Longitudinal cognitive decline was assessed using the Chinese version of the short form of the Informant Questionnaire on Cognitive Decline in the Elderly, current cognitive impairment using the Informant Questionnaire on Cognitive Decline in the Elderly and the Telephone Interview of Cognitive Status-40.

Liu, Y.-H., Chen, Y., Wang, Q.-H., Wang, L.-R., Jiang, L., Yang, Y., Chen, X., Li, Y., Cen, Y., Xu, C., Zhu, J., Li, W., Wang, Y.-R., Zhang, L.-L., Liu, J., Xu, Z.-Q., & Wang, Y.-J. (2022). One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. *JAMA Neurology*. https://doi.org/10.1001/jamaneurol.2022.0461

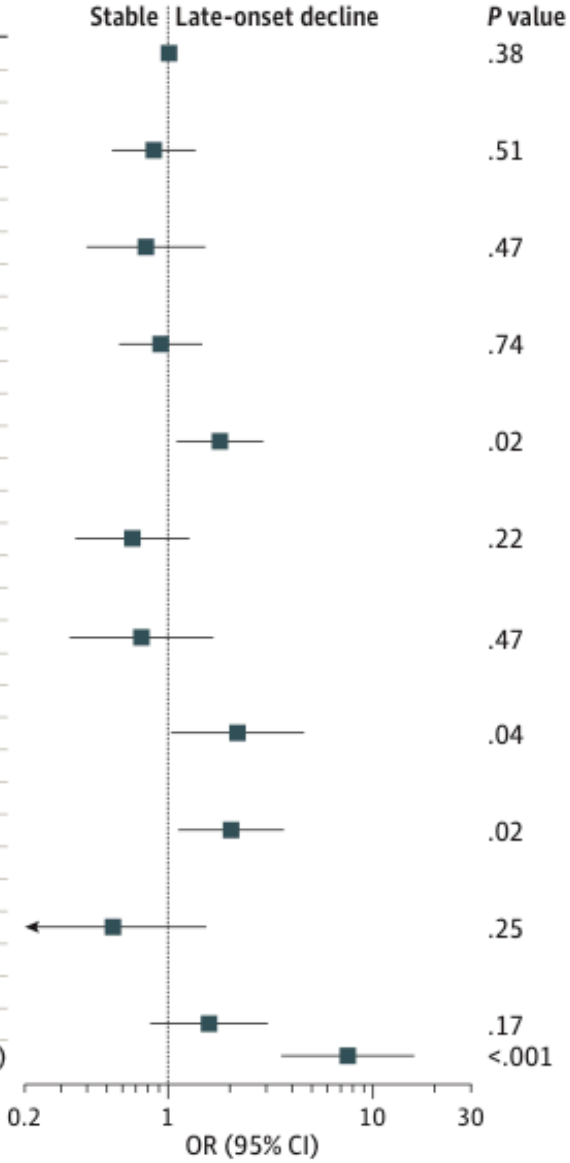
Definitions of Severity of SARS-CoV-2 infection

- Individuals with severe COVID-19 were defined as confirmed SARS-CoV-2 infection plus 1 of the following conditions:
  - respiratory rate higher than 30 breaths per minute
  - severe respiratory distress, or oxygen saturation less than 90% on room air.
- SARS-CoV-2 infection and noninfection were confirmed by high-throughput sequencing or real-time reverse transcriptase–polymerase chain reaction assays of nasal and pharyngeal swab specimens.


A Comparison of TICS-40 at 6 mo
P<.001
P=.28
P<.001
TICS-40 at 6 mo
50
40
30
20
10
0
Control
Nonsevere
Severe
B Comparison of TICS-40 at 12 mo
P<.001
P=.18
P<.001
TICS-40 at 12 mo
50
40
30
20
10
0
Control
Nonsevere
Severe
D Proportion of patients with different cognitive status at 6 mo
P<.001a
P<.001b
P=.69b
P=.69a
P<.001b
P<.001a
1
18
419
7
55
1116
26
69
165
Control
Nonsevere
Severe
E Proportion of patients with different cognitive status at 12 mo
P<.001a
P<.001b
P=.99b
P=.90a
P<.001b
P<.001a
3
22
413
9
63
1106
39
68
153
Control
Nonsevere
Severe
Dementia
MCI
Normal cognition
H Comparison of rate of cognitive decline during the second 6 mo follow-up
Normalized TICS-40
0.8
0.7
0.6
0.5
Control
Nonsevere
Severe
P=.09
P<.001
P<.001
6
12
Follow-up, mo

C Risk factors for late-onset cognitive decline

	OR (95% CI)	P value
Age	1.01 (0.98-1.05)	.38
Sex		
Female	1 [Reference]	
Male	0.86 (0.53-1.37)	.51
Education		
≤ Middle school	1 [Reference]	
≥ College	0.78 (0.40-1.53)	.47
BMI		
18.5-23.9	1 [Reference]	
≥24.0	0.92 (0.58-1.48)	.74
Hypertension		
No	1 [Reference]	
Yes	1.80 (1.10-2.93)	.02
Diabetes		
No	1 [Reference]	
Yes	0.67 (0.35-1.28)	.22
Hyperlipidemia		
No	1 [Reference]	
Yes	0.74 (0.33-1.67)	.47
Stroke		
No	1 [Reference]	
Yes	2.19 (1.04-4.64)	.04
Coronary heart disease		
No	1 [Reference]	
Yes	2.04 (1.13-3.70)	.02
COPD		
No	1 [Reference]	
Yes	0.54 (0.19-1.54)	.25
Group		
Control	1 [Reference]	
Nonsevere COVID-19	1.59 (0.82-3.09)	.17
Severe COVID-19	7.58 (3.58-16.03)	<.001



Some preliminary conclusions

- Anatomically consistent patterns of brain volume and diffusivity changes comparing post-COVID patients to controls
- Clear involvement of the olfactory cortex and functionally-connected regions
    - Includes left parahippocampal gyrus which plays an integrative role in temporal order of episodic memory events
- Hyposmia and hypogeusia symptoms might be explained by anatomical changes
- More than 95% of COVID patients were either asymptomatic or mild suggesting that the effects seen were from the virus rather than the stress of severe infection and associated anxiety
- Post-COVID cognitive decline (by various measures) is documented in two large studies over the course of ~1 year.
- Post-hoc analysis of cases of non-COVID pneumonia cases in the dataset do not demonstrate the same COVID-related changes
- Mechanism of effect of the SARS-CoV2 virus may be:
    - Anterograde degeneration of nerves
    - Neuro-inflammatory process
    - Effect of direct spread of virus

Cardiovascular outcomes of COVID-19

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-022-01689-3

OPEN

Long-term cardiovascular outcomes of COVID-19

Yan Xie[1,2,3], Evan Xu[1,4], Benjamin Bowe[1,2] and Ziyad Al-Aly[1,2,5,6,7] ✉

Xie, Y., Xu, E., Bowe, B., & Al-Aly, Z. (2022). Long-term cardiovascular outcomes of COVID-19. *Nature Medicine*. https://doi.org/10.1038/s41591-022-01689-3

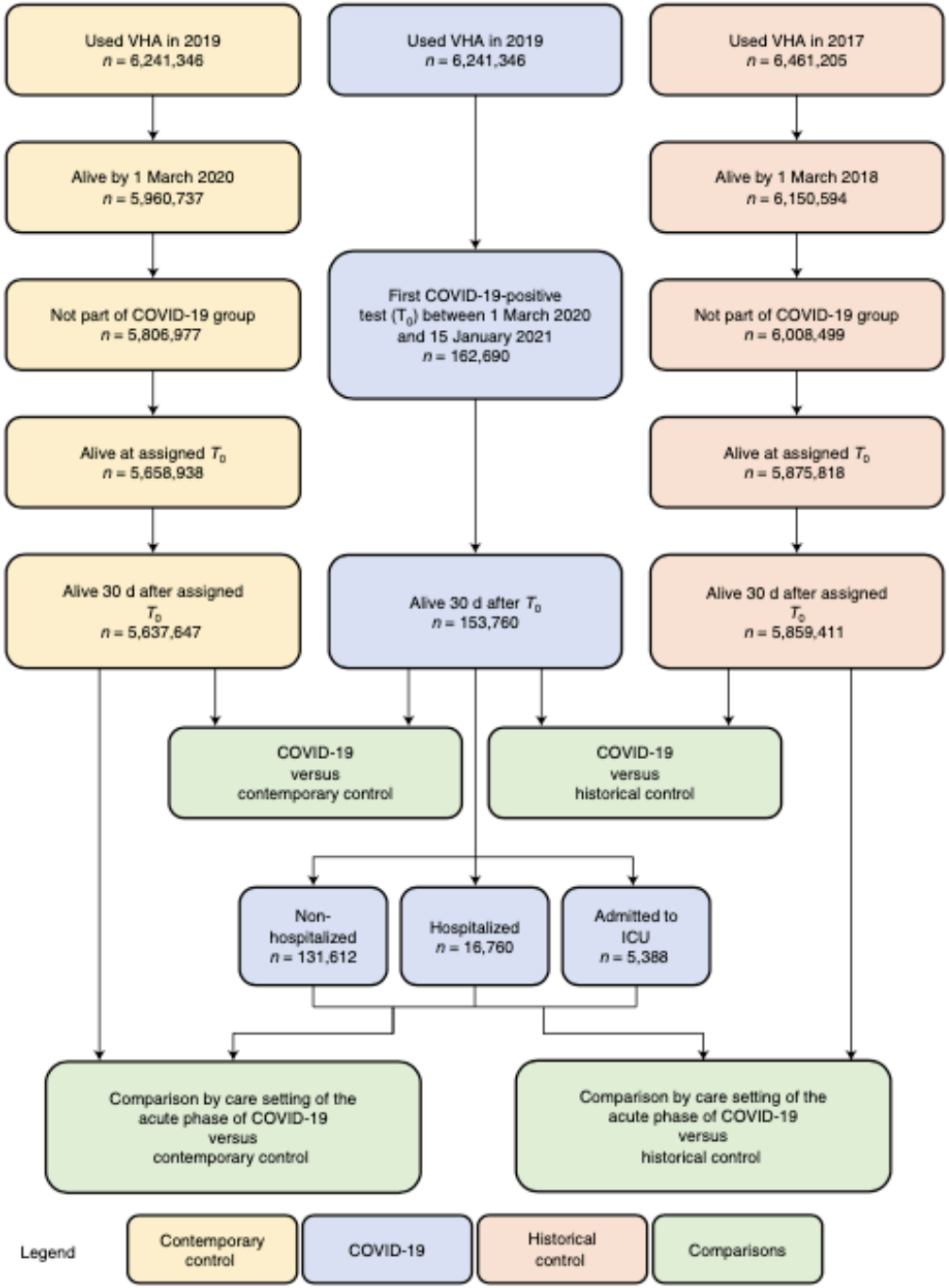
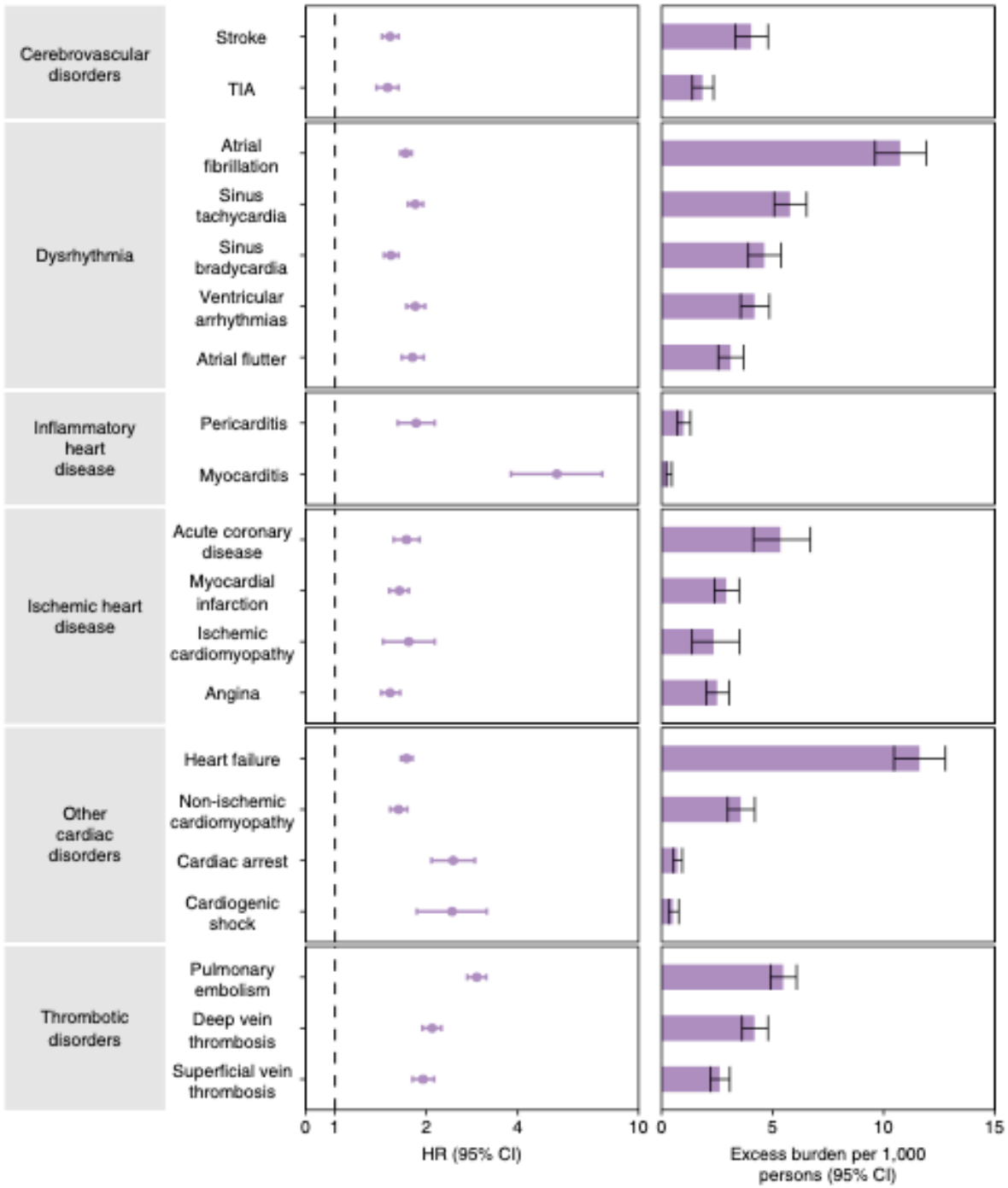
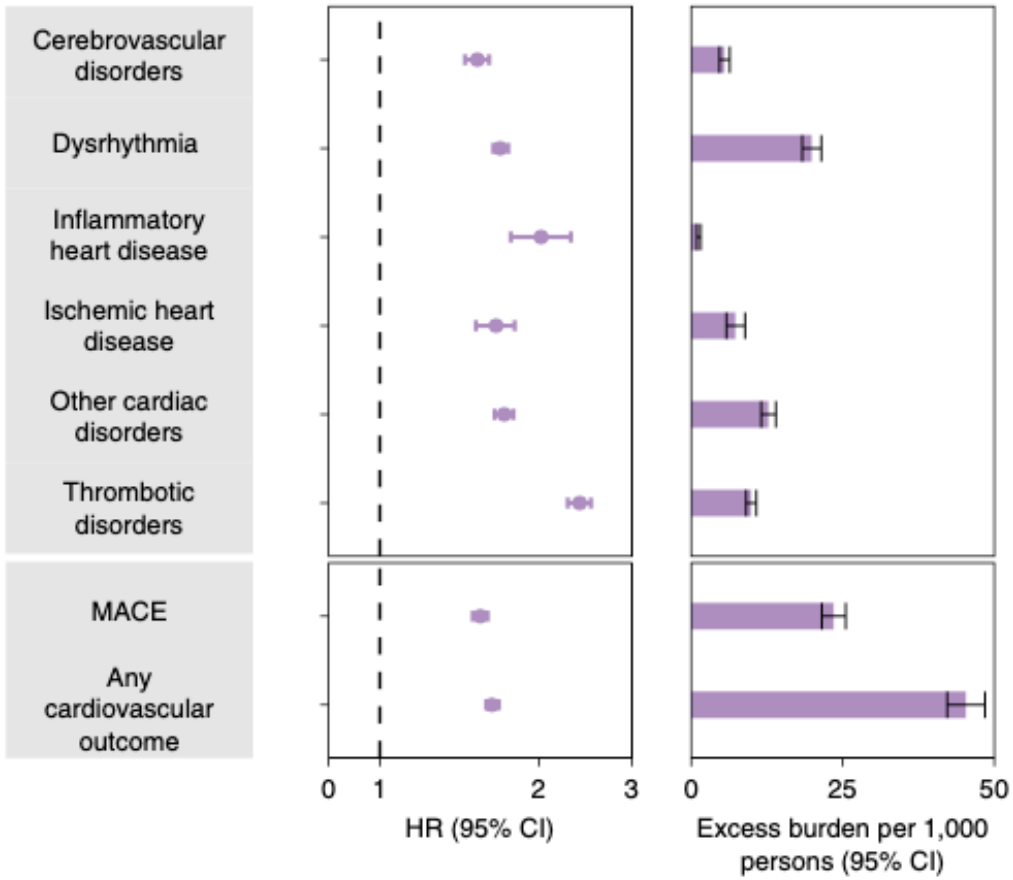


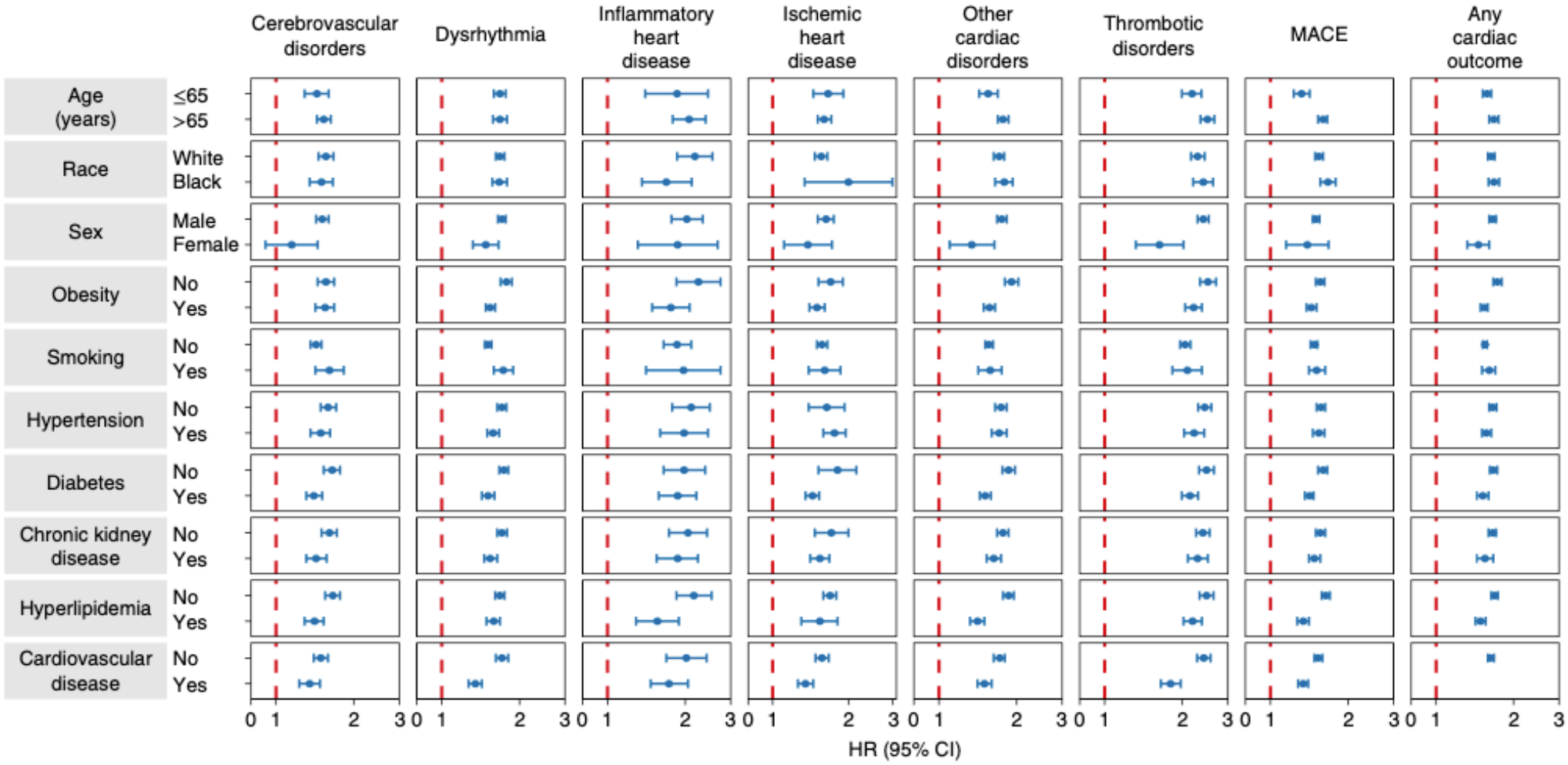
Fig. 1 | Flowchart of cohort construction. Cohort construction for COVID-19 group (blue), contemporary control group (yellow) and historical control group (orange). Comparisons between groups are presented in green.



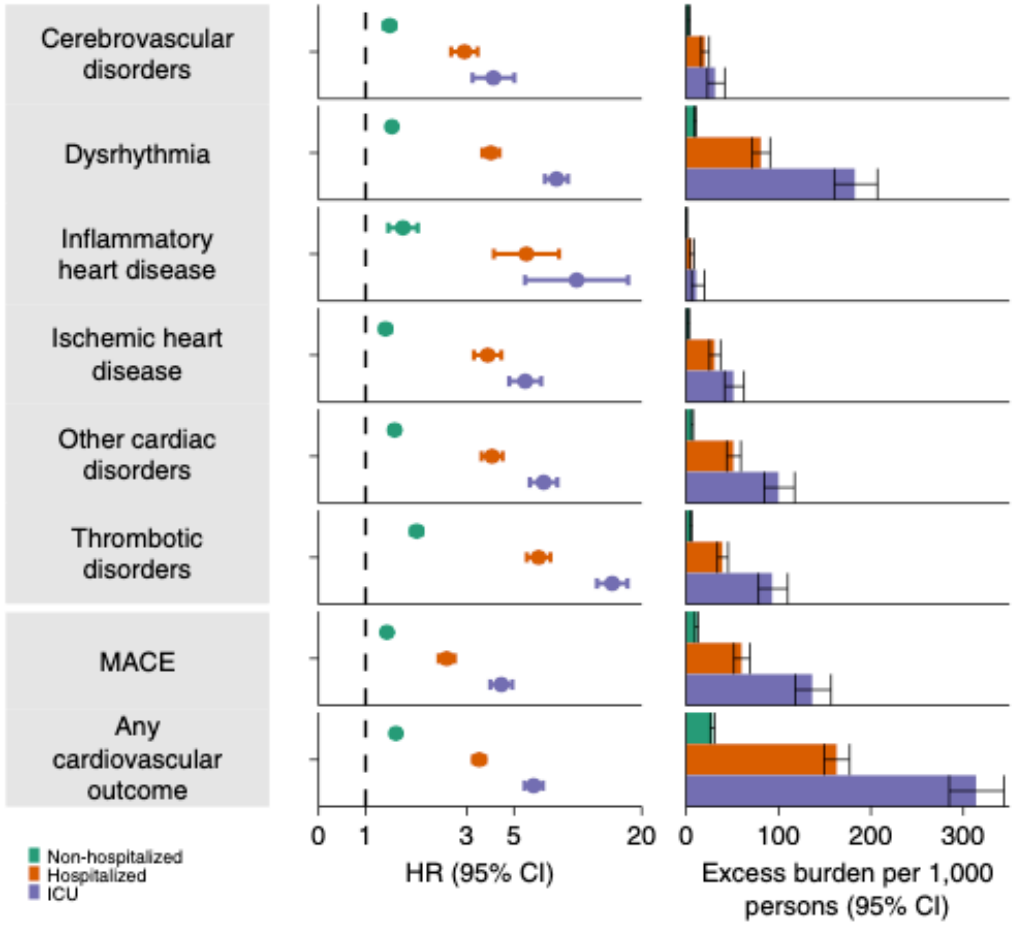
Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort. Outcomes were ascertained 30 d after the COVID-19-positive test until the end of follow-up. COVID-19 cohort (n = 153,760) and contemporary control cohort (n = 5,637,647). Adjusted HRs and 95% CIs are presented. The length of the bar represents the excess burden per 1,000 persons at 12 months, and associated 95% CIs are also shown.



Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary control cohort.

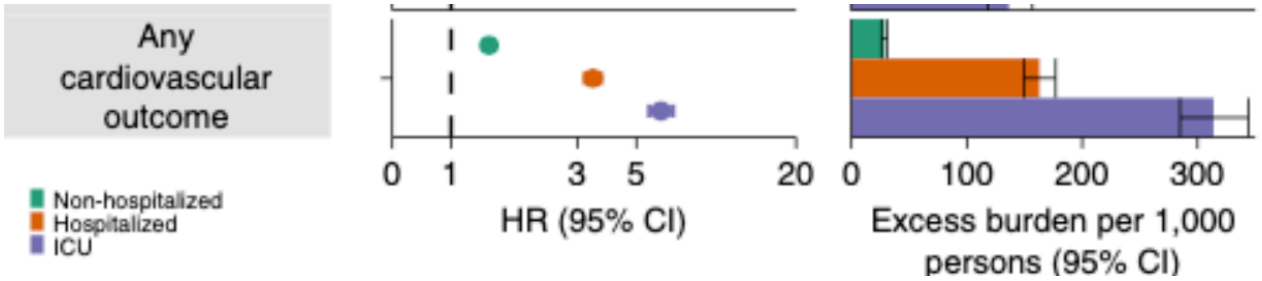


Subgroup analyses of the risks of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary control cohort.



Risks and 12-month burdens of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary control cohort by care setting of the acute infection.

Some approximate extrapolations for the US



- ~ 80,000,000 reported infections
- 4,500,000 hospitalizations to date
  - ~ 20% ICU admissions = 900,000 ICU admissions
  - ~ 3,600,000 non-ICU admissions
- Among all infect-ees not hospitalized
  - ~ 2% * 76,000,000 = 1,500,000 cases of some cardiovascular outcome
- Among non-ICU hospitalized patient
  - = ~15% * 3.6 million = 540,000 cardiovascular outcomes
- Among ICU hospitalized admissions
  - ~ 30% * 900,000 = 270,000 cardiovascular outcomes
- Total CV burden of COVID-19 to date = ~ 2.3 million patients

Long-term infections in COVID-19

Long-Term Persisting SARS-CoV-2 RNA and Pathological Findings: Lessons Learnt From a Series of 35 COVID-19 Autopsies

Maccio, U., Zinkernagel, A. S., Schuepbach, R., Probst-Mueller, E., Frontzek, K., Brugger, S. D., Hofmaenner, D. A., Moch, H., & Varga, Z. (2022). Long-Term Persisting SARS-CoV-2 RNA and Pathological Findings: Lessons Learnt From a Series of 35 COVID-19 Autopsies. *Frontiers in Medicine*, *9*, 778489. https://doi.org/10.3389/fmed.2022.778489

Altogether, postmortem swabs were positive for SARS-CoV- 2 RNA in the following organs/tissues with the following frequencies:

- trachea (18/26, 69%),
- lung (19/27, 70%),
- heart (8/27, 30%),
- liver (13/27, 48%),
- spleen (10/26, 38%),
- gut (9/26, 35%),
- kidney (13/26, 50%),
- testicles (9/19, 47%),
- ovary (1/7, 14%),
- brain (2/6, 33%),
- lamina cribrosa (3/4, 75%).

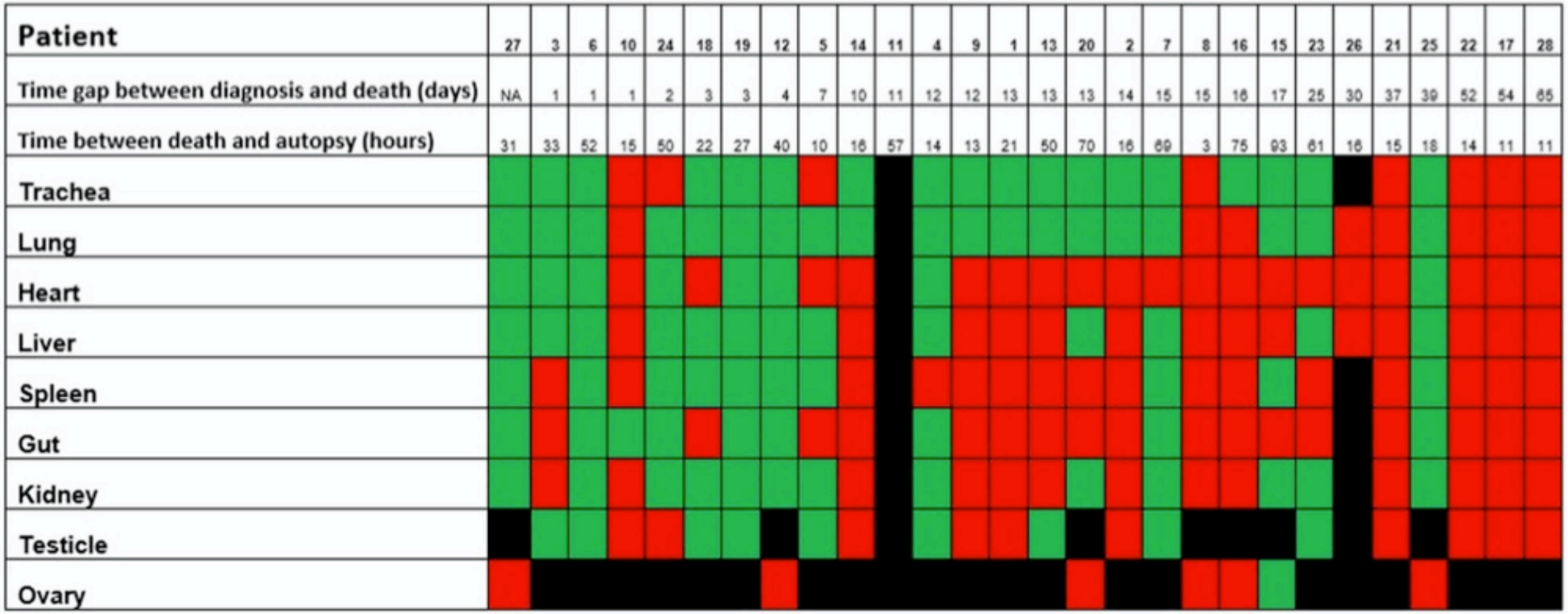


FIGURE 7 | Positivity of the postmortem swabs in the different organs (green: positive, red: negative, black: not available). The patients are ordered from left to right in a crescent pattern based on the number of days between diagnosis of COVID-19 through nasopharyngeal swab and death. Abbreviations: NA, not available.

Final thoughts

Concept of Long COVID is evolving and far from complete

- COVID is clearly a multi-organ disease
- Virus may persist for many weeks post-infection
- Long-term objective consequences of COVID now demonstrated for:
  - Brain
    - Imaging and “clinical” —> cognitive decline, even among mild or asymptomatic COVID
  - Heart
    - Clinical —> multiple cardiovascular effects
  - Lung
    - Severity of diffuse alveolar damage correlates with persistence of virus
- The impacts of the various forms of “Long COVID” will be huge

Questions?

Alan Zelicoff
e-mail: zalan8587@q.com