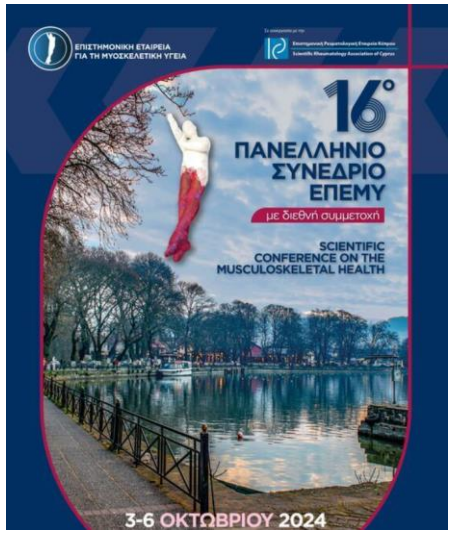


Long Covid or Fibromyalgia ?

Στυλιανός Πανόπουλος

Εντεταλμένος Διδάσκων

1η Προπαιδευτική και Παθολογική Κλινική

Γενικό Νοσοκομείο Αθηνών ΄΄ΛΑΙΚΟ΄΄

No conflict of interest

Post-Acute sequelae of COVID-19 / Long COVID Definition (WHO)

A condition 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. Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time.

**definition of NIH: 4 weeks*

Soriano et al. Lancet Infect Dis. 2022 Apr; 22(4): e102–e107

Epidemiology

- 650-700 million documented COVID-19 cases worldwide

- estimated prevalence of long COVID: 10%-15% of infected individuals

10–30% of non-hospitalized cases, 50–70% of hospitalized cases

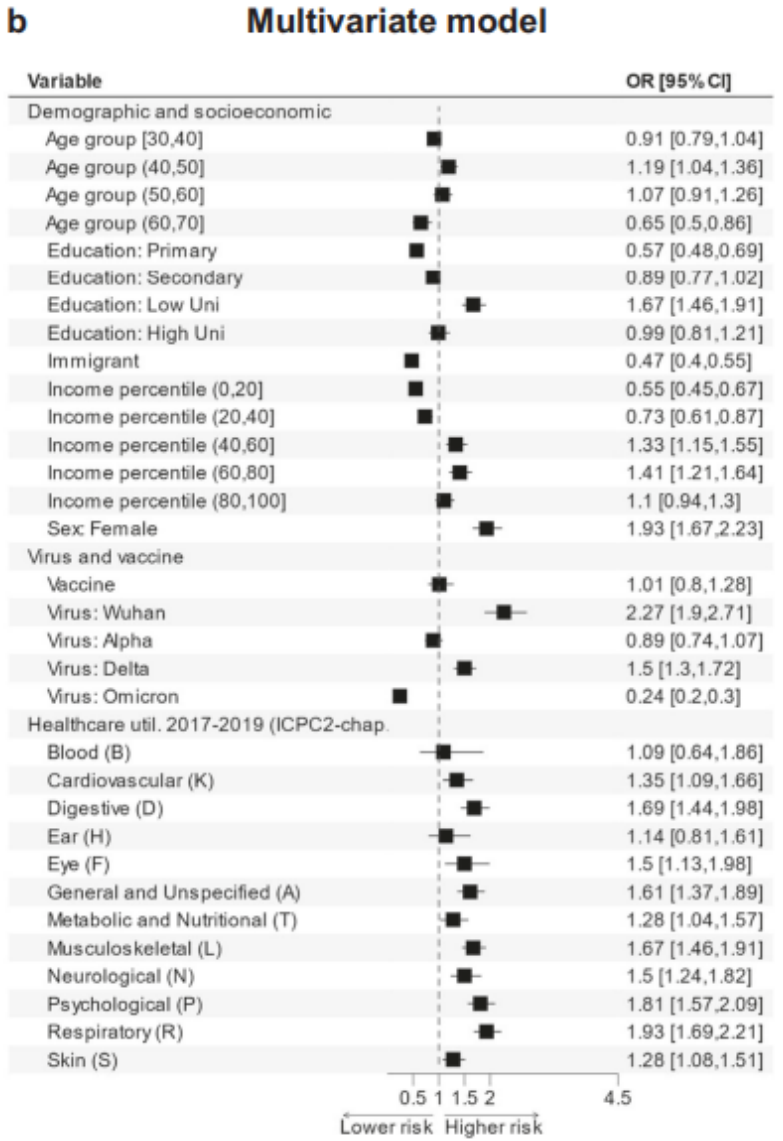
- more prevalent between the ages of 36 and 50 years

- one-fifth of cases remain symptomatic beyond 2 years

Bull-Otterson et al. *MMWR Morb. Mortal. Wkly Rep.2022;*71:713
Ceban, F. *Brain Behav. Immun.2022;*101:93–135
Al-Aly, Z., et al. *Nat. Med.2022*

Predictors for long Covid

- Female gender
- hispanic and Latino origin
- attention deficit hyperactivity disorder, diabetes type 2, chronic urticaria, mood disorders, respiratory diseases
- more severe COVID-19 illness, (hospitalization or ICU)
- variants (omicron 40%-70% less probability) / vaccination



Su, Y. et al.2022. *Cell* 185, 881–895.e20
Merzon, E. et al. *Int. J. Environ. Res. Public Health2021;* 19:5993
Papagoras et al. Clin Rheumatol. 2023 Dec;42:3375-3385.

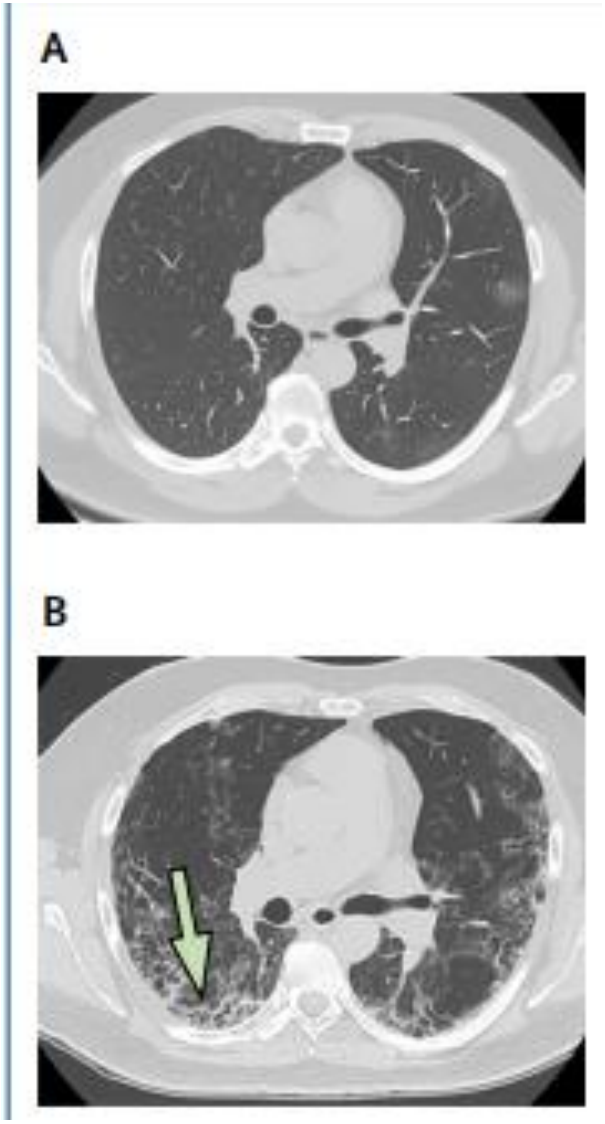
Post-Acute sequelae of COVID-19

clear evidence of underlying tissue damage

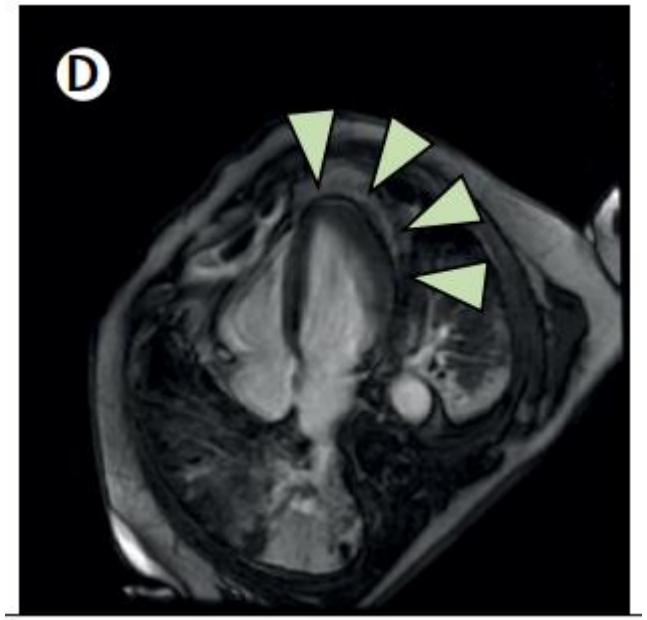
- pulmonary scarring/pulmonary fibrosis

(objective pulmonary abnormalities in 20%)

- cardiomyopathy
- vascular thrombosis
- anosmia/ageusia



fibrotic changes after 3 weeks post COVID19(arrows)



subepicardial late gadolinium enhancement of the apex and inferior wall (arrowheads)

Doyen et al.Lancet 2020; 395: 1516
Spagnolo et al. Lancet.2020;8:750-752

Long COVID

- fatigue
- post exertional malaise
- neurocognitive dysfunction (‘brain fog’)
- sleep disturbances
- varying forms of pain including myalgia, arthralgia, headache, chest pain, abdominal pain

Long Covid; A distinct entity or another facet of Fibromyalgia?

2016 American College of Rheumatology Fibromyalgia Diagnostic Criteria

Generalized pain, defined as pain in at least four of five regions, is present.

Symptoms have been present at a similar level for at least three months.

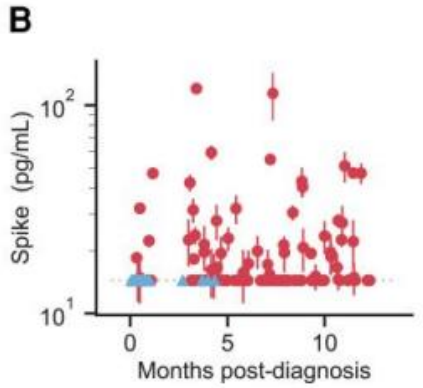
Widespread pain index score is ≥ 7 and symptom severity scale score is ≥ 5, or widespread pain index score is 4 to 6 and symptom severity score is ≥ 9.

Until today there is no clinical trial comparing directly patients with Long Covid versus patients with Fibromyalgia

Non fibromyalgia-associated pathogenic processes described in patients with long COVID

- **immune deficiency** → **prolonged SARS-CoV-2 positive PCR**

- **persisting reservoirs of SARS-CoV-2 in tissues**

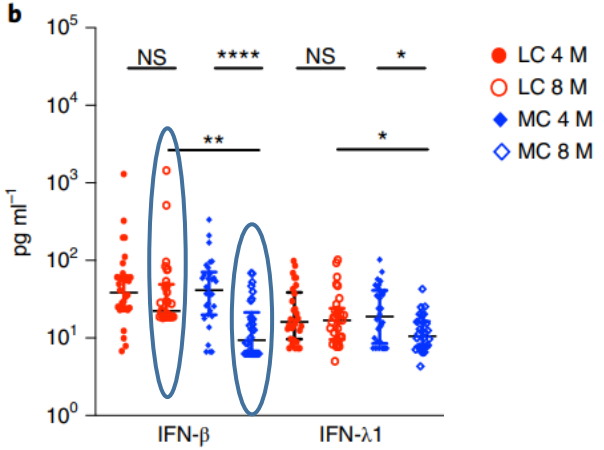


- **immune dysregulation**

T cell alterations

highly activated innate immune cells

elevated levels of cytokines, elevated expression of type I and III IFN



- **reactivation of underlying pathogens (i.e EBV, HHV-6)**

- **autoimmunity**

autoantibodies to ACE2 , β2-adrenoceptor, muscarinic M2 receptor, angiotensin II AT1 receptor and others

Davis et al.Nature Reviews Microbiology.2023;21:133–146

- **impact of SARSCoV-2 on the microbiota**

- **mitochondrial fragmentation** → impact on energy metabolism

- **microvascular blood clotting with endothelial dysfunction** → impaired oxygen delivery

A long-lasting reduction in vascular density, specifically affecting small capillaries, was found in patients with long COVID compared with controls, 18 months after infection

- **neuroinflammation and vasculopathy damage** → injury to neurons, myelin loss

dysfunctional signalling in the CNS

neuroinflammation in long COVID

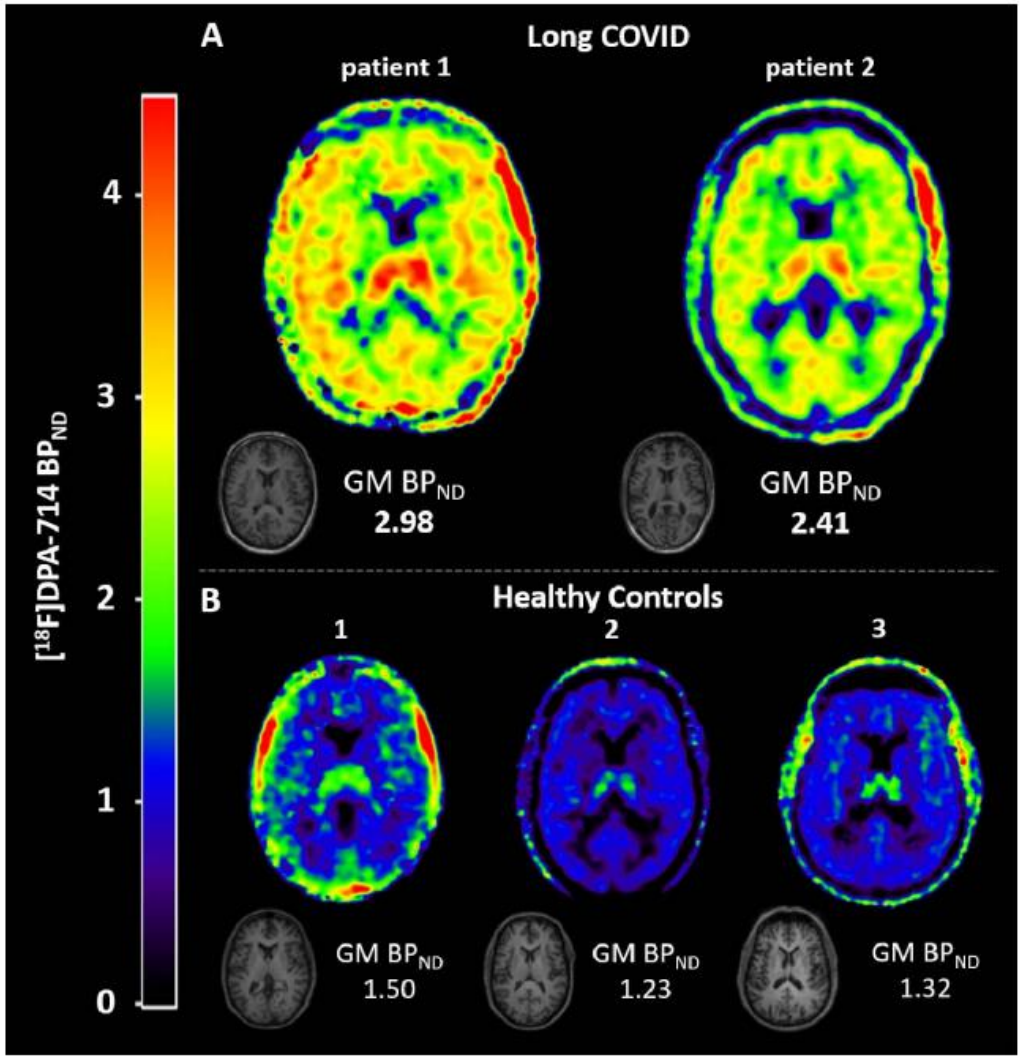
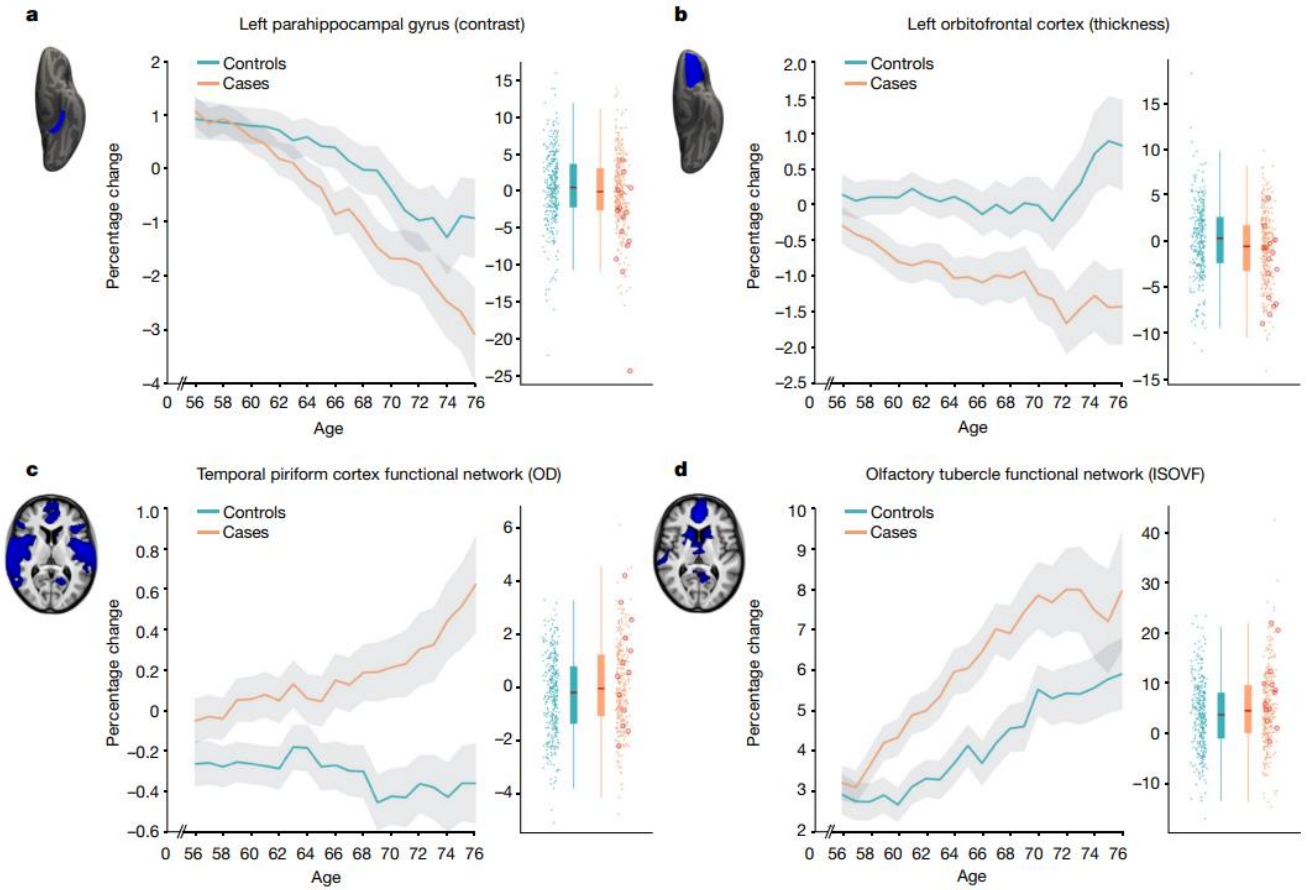


Figure 2. Neuroinflammation in two long COVID patients. To quantify [^{18}F]DPA-714 binding in whole brain

- greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex, parahippocampal gyrus and primary olfactory cortex in SARS-COV2 infected vs. controls
- greater reduction in global brain size in the SARS-CoV-2 cases.
- participants infected with SARS-CoV-2 showed on average a greater cognitive decline



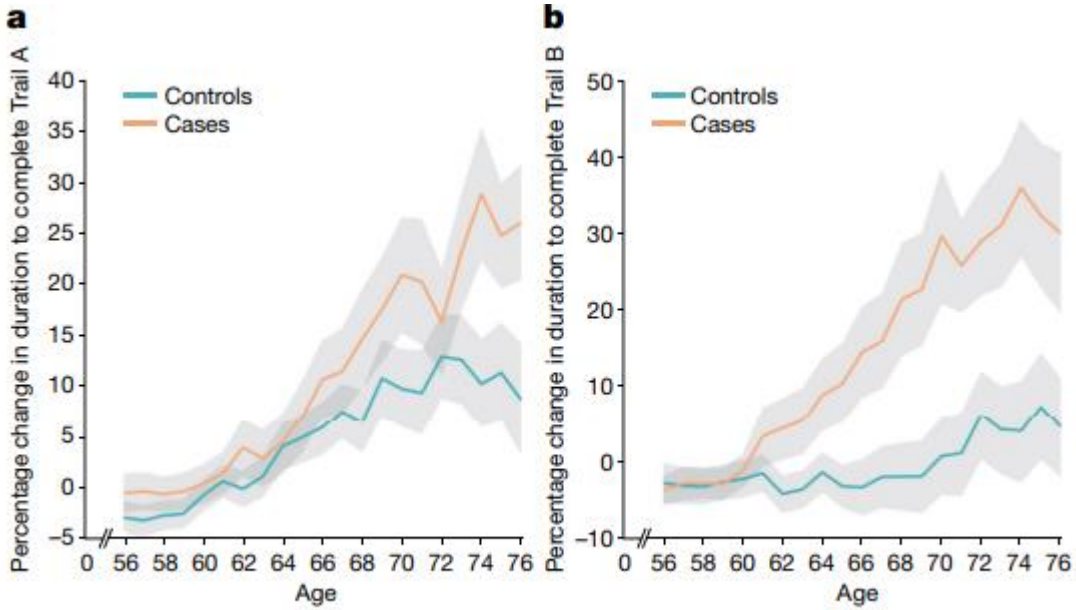


Fig. 3 | Significant longitudinal differences in cognition. a, b, The

Douaud et al.Nature.2022;604: 697-707

nature communications

Article

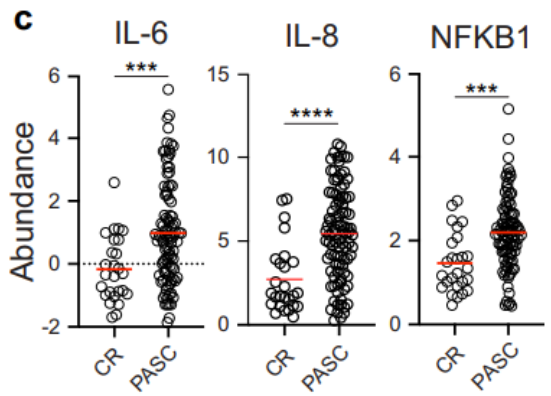
https://doi.org/10.1038/s41467-023-40012-7

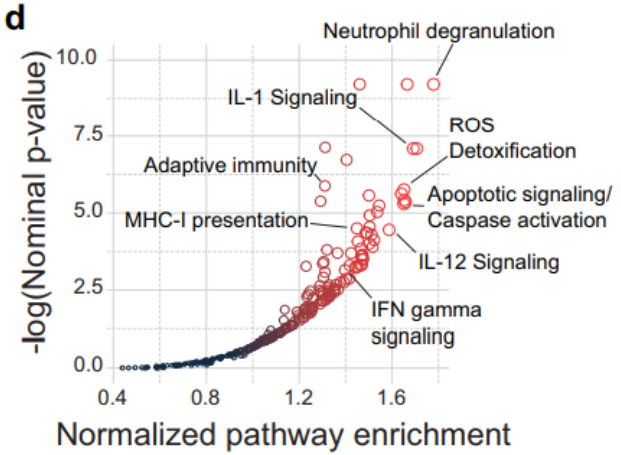
Chronic inflammation, neutrophil activity, and autoreactivity splits long COVID

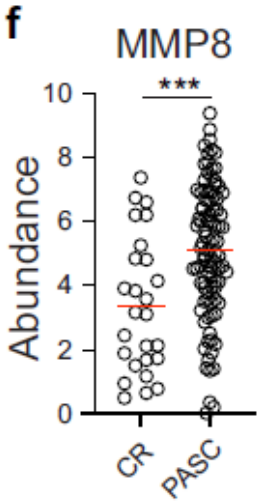
- broad serological screening and B-cell response characterization with novel machine-learning methods
- comparison of 97 patients with long COVID vs. 26 no long COVID convalescents (controls)
- clustering of patients with long COVID

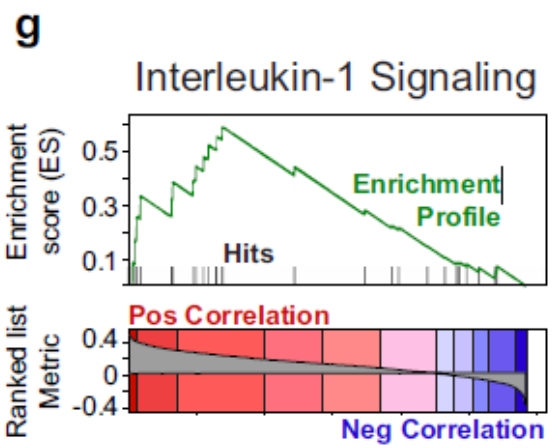
long COVID cohort (vs. controls) had

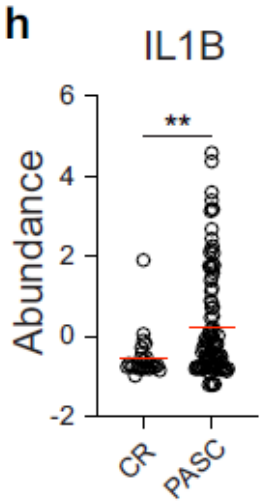
- ➢ abundance of several inflammatory proteins
- ➢ Increased neutrophil activity
- ➢ Increased IL-1B signaling pathway











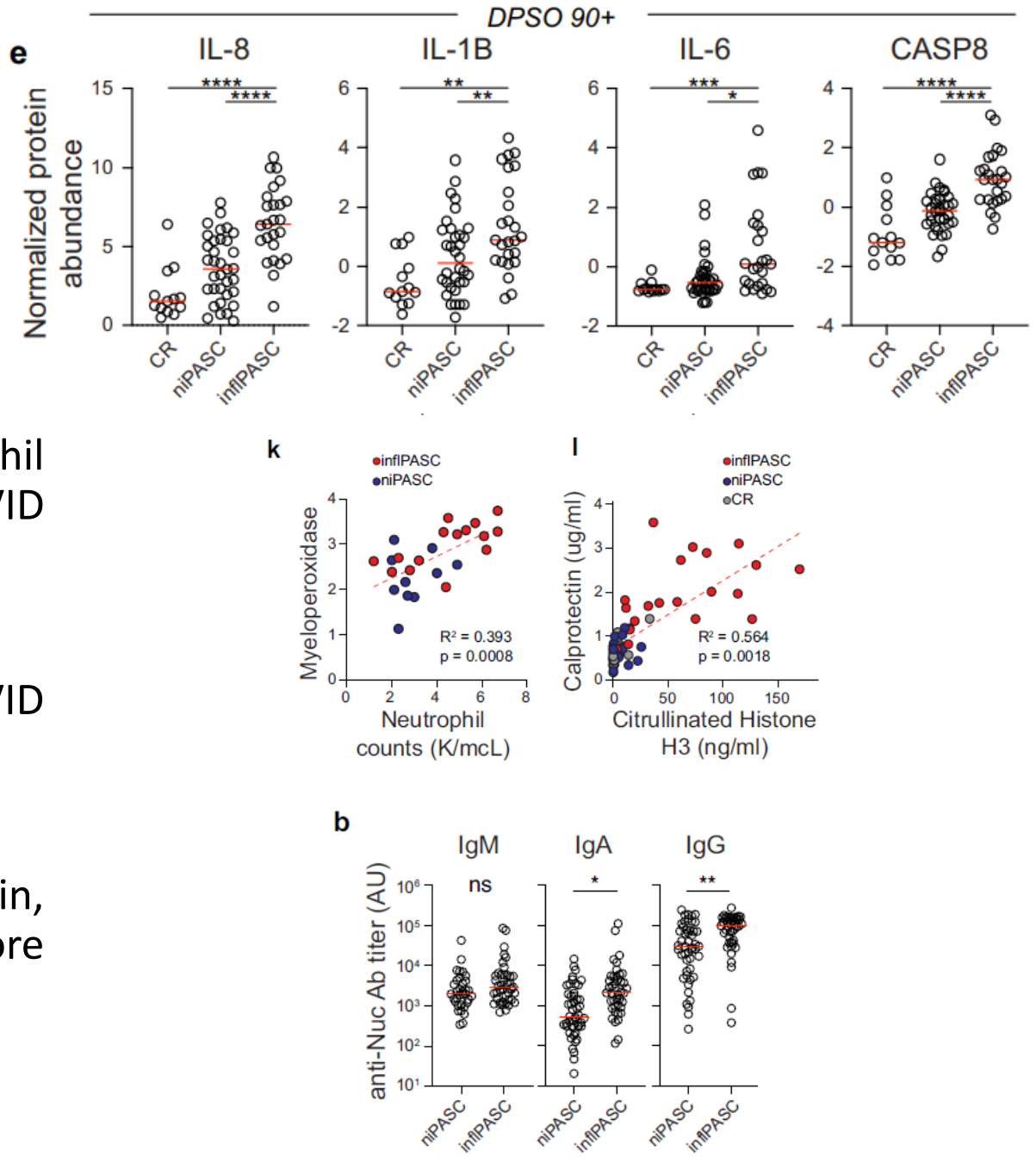
Woodruff et al. Nature Communications.2023;4:4201

- division of the long COVID cohort into two subsets.

pro-inflammatory cytokines, neutrophil counts and neutrophil activity significantly increased in one of the two long COVID subsets (inflammatory long COVID)

- Increased humoral (auto)immunity in the inf-long COVID cohort

- non-inflammatory long COVID reported more joint pain, brain fog and anxiety while inf-long COVID reported more muscle weakness, numbness and general weekness.



Woodruff et al. Nature Communications.2023;4:4201

Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial

Carolyn T Bramante, John B Buse, David M Liebovitz, Jacinda M Nicklas, Michael A Puskarich, Ken Cohen, Hrishikesh K Belani,

metformin vs. ivermectin vs. fluvoxamine vs. placebo after SARS-CoV-2 positive PCR or antigen test (within 3 days after positive PCR)

metformin

- suppresses protein translation via mTOR inhibition

- restores autophagic flux
- Inhibites release of interleukin-1β and interleukin-18
- prevents a senescent phenotype induced by COVID-19 in dopaminergic neurons in vitro

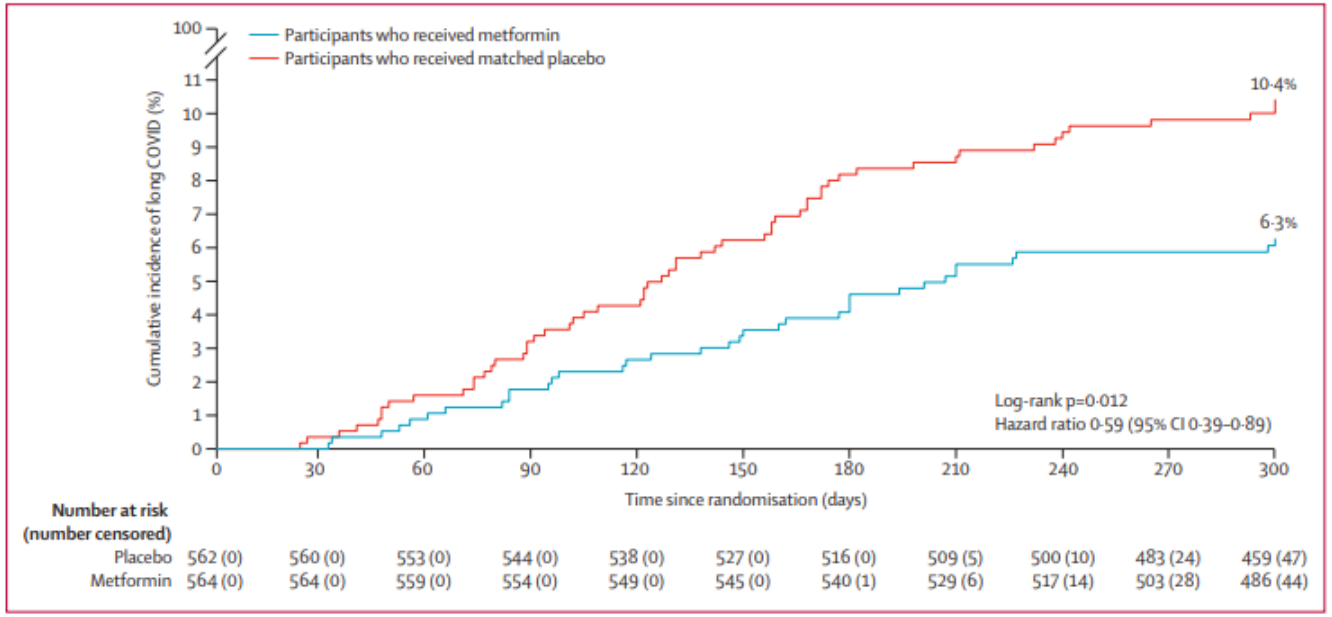


Figure 2: **Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomisation**
The absolute risk reduction for metformin compared with matched placebo was 4·1% (95% CI 0·9–7·4).

Bramante et al. Lnacet. 2023; 23:1119-1129

Effectiveness of COVID-19 vaccines to prevent long COVID: data from Norway

the entire Norwegian population of approximately 5·4 million inhabitants. Data from six registries covering primary and secondary care, hospitalisations, vaccinations, communicable disease notifications, of that symptom 180 days before SARS-Cov-2 infection, and were therefore identified as long COVID cases, compared with 2922 (0·17%) of the unvaccinated individuals (table). Background characteristics

Published Online
April 10, 2024
https://doi.org/10.1016/
S2213-2600(24)00082-1

See Articles page 225

RESEARCH

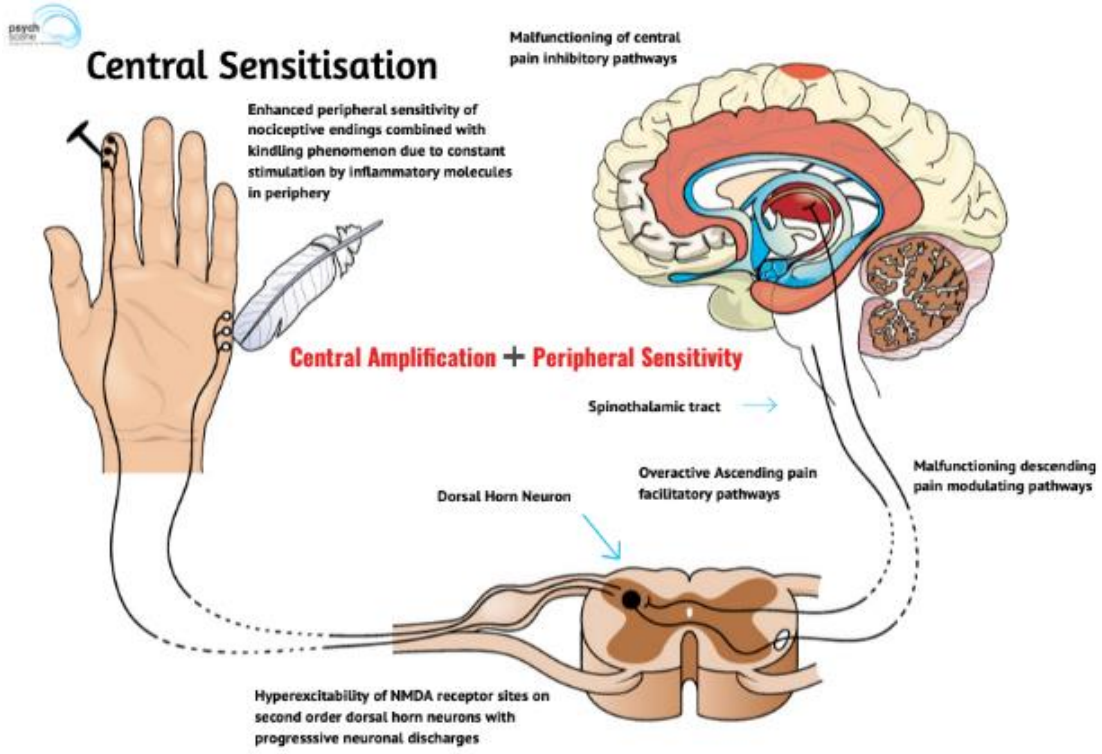
Covid-19 vaccine effectiveness against post-covid-19 condition among 589 722 individuals in Sweden: population based cohort study

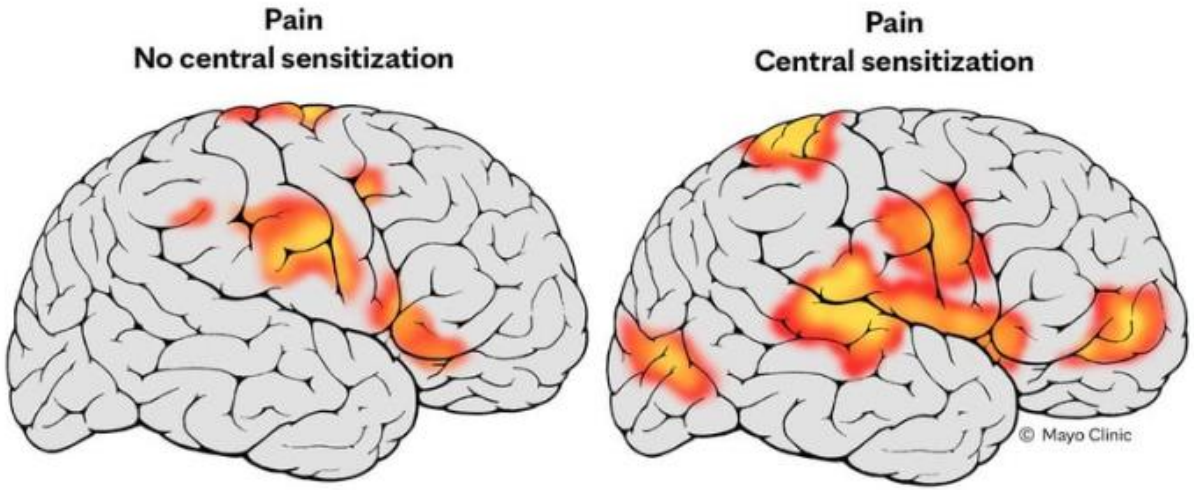
Lisa Lundberg-Morris,[1,2] Susannah Leach,[1,3] Yiyi Xu,[4] Jari Martikainen,[5] Ailiana Santosa,[4] Magnus Gisslén,[6,7] Huiqi Li,[4] Fredrik Nyberg,[4] Maria Bygdell[4,8]

BMJ: first published as 1

Fibromyalgia-like post-COVID-19 syndrome

- psychosomatic syndrome close to post-traumatic stress
- Stress may induce central nervous consequences leading to central sensitization of pain





Similarities of long COVID to fibromyalgia or ME/CSF

similar symptomatic and cognitive abnormalities of Long COVID to Myalgic encephalitis/Chronic fatigue syndrome (ME/CSF) or fibromyalgia

Approximately 40-50% of long-Covid patients fulfill ME/CSF or fibromyalgia criteria

- **features of dysautonomia**

severe forms of disabling postural tachycardia syndrome (POTS) more common in long COVID or ME/CSF

- **neuroinflammation**

- **common biochemical disorders**

ie. low cortisol levels

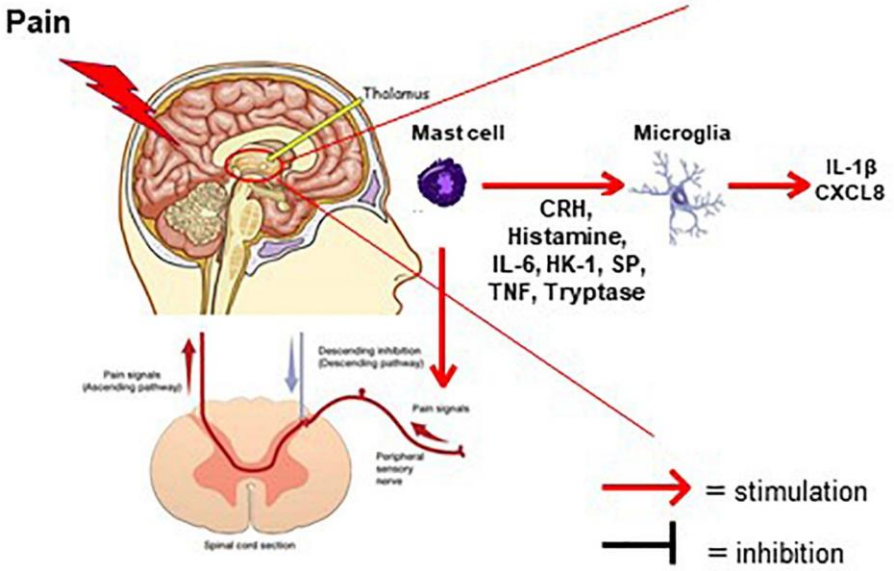
Proposed Diagnostic Criteria for ME/CFS

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance



neuroinflammation in fibromyalgia

Goldenberg et al.Semin Arthritis Rheum. 2024;67:152455
Yavropoulou et al. Clin Immunol.2022:245:109133

Infect Dis Ther (2022) 11:2279–2285
https://doi.org/10.1007/s40121-022-00698-6

BRIEF REPORT

Excess of Post-Acute Sequelae of COVID-19 After the First Wave of the Pandemic

Marc Scherlinger · Cédric Lemogne · Renaud Felten ·

- Relative risk for long COVID was 82% higher during the first pandemic wave than afterward [OR 1.82,[1.55–2.15)]
- aggregation of long COVID cases around lock down announcement

same variant of SARS-COV2 in different periods
no vaccination

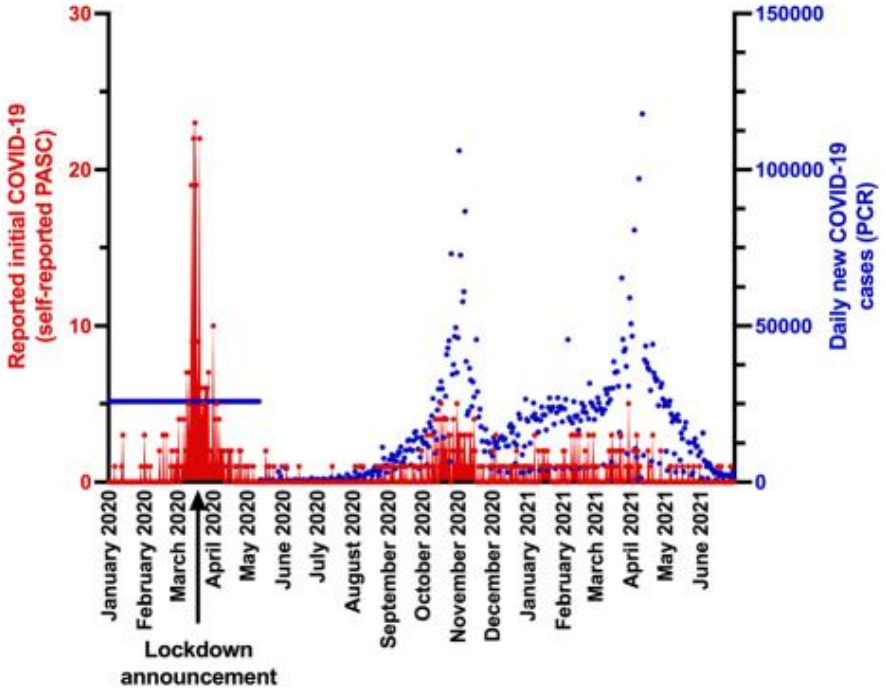


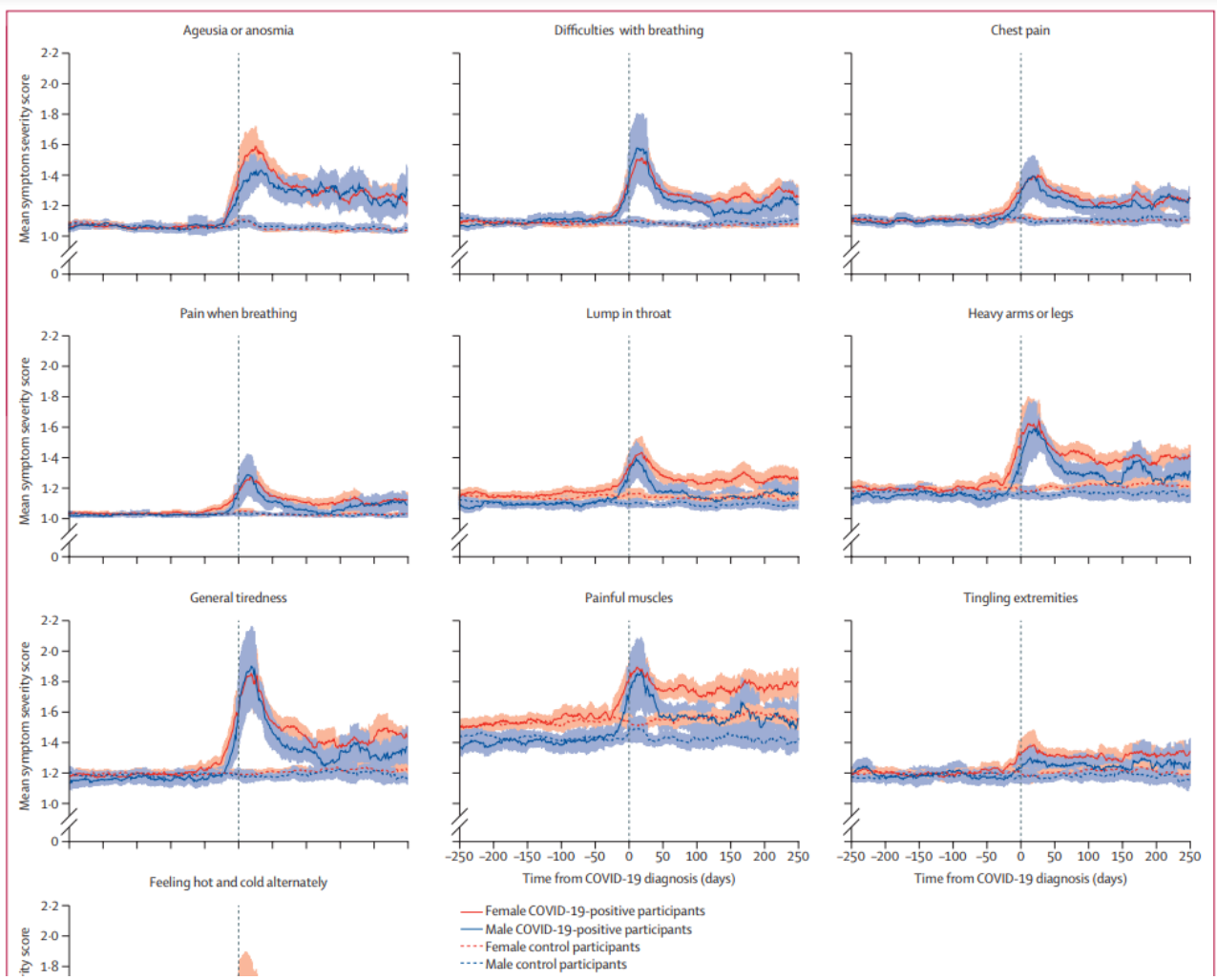
Fig. 1 Distribution of initial COVID-19 in patients with self-reported PASC compared to the incidence of new COVID-19 cases in France. Concerning the incidence of COVID-19 during the first wave, only the mean number of cases is shown since their distribution was not modeled (straight blue line instead of a Gaussian curve). The lockdown was announced by an unprecedented presidential address on March 16, 2020

Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study

*Aranka V Ballering, Sander K R van Zon, Tim C olde Hartman, Judith G M Rosmalen, for the Lifelines Corona Research Initiative**

Dutch cohort study (n=76422), March 2020-August 2021

- around 12% more patients complaining of one of the long COVID symptoms at 90–150 days after COVID-19 compared with matched not infected controls



Ballering AV, et al.Lancet 2022;400:452–61.

prevalence of persistent symptoms in Covid-19 comparable to other viral and acute respiratory infections

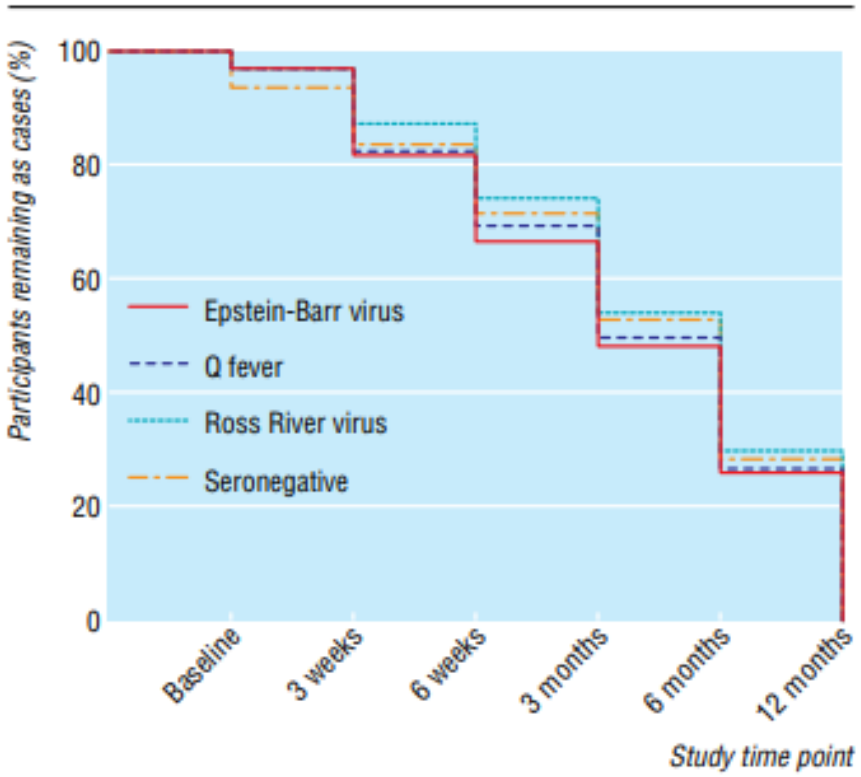
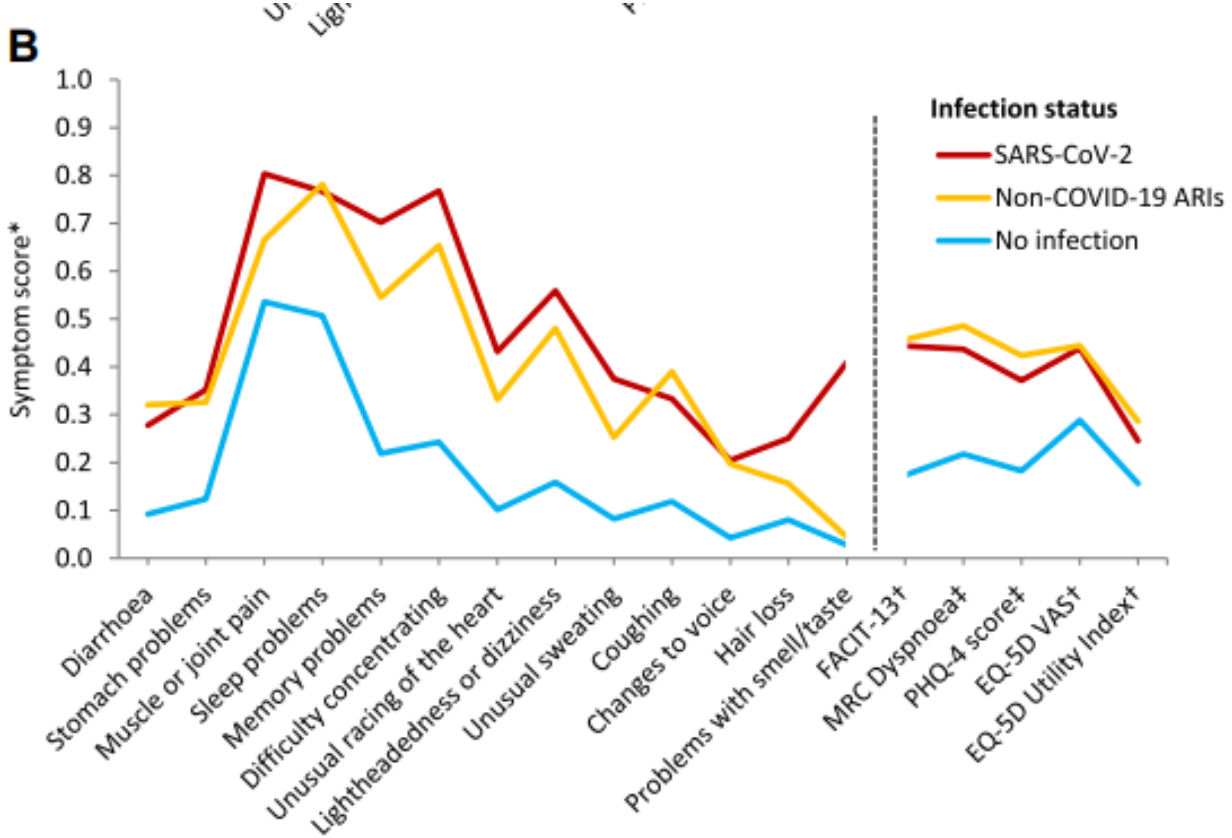


Fig 1 Survival curves of post-infective fatigue syndrome by infective agent after onset of acute infection. Kaplan-Meier analyses of proportion of participants within each infective subcohort who remained as cases. Test of equality across groups: χ^2=3.45, df=3, P>0.05



Hickie I, et al. BMJ 2006;333:575.
Vivaldi et al. eClinicalMedicine 2023;65: 102251

Long Covid in Rheumatic diseases

More patients in a Dutch ARD cohort than controls reported long COVID condition : 77 (21%) of 365 versus 23 (13%) of 172
OR: 1·73; p=0·033

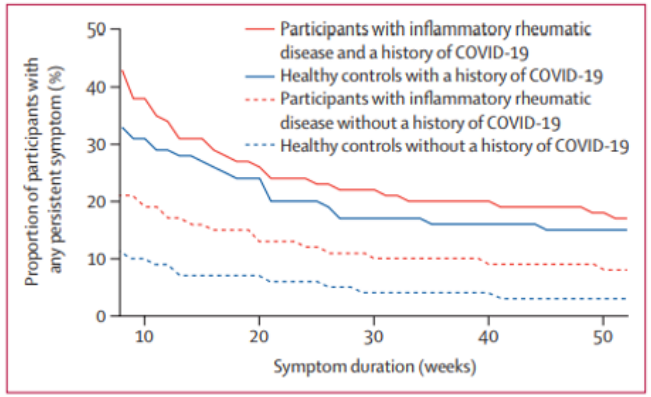
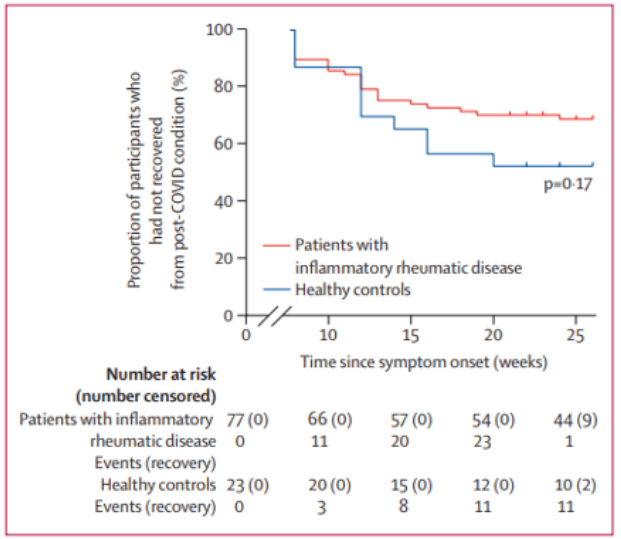


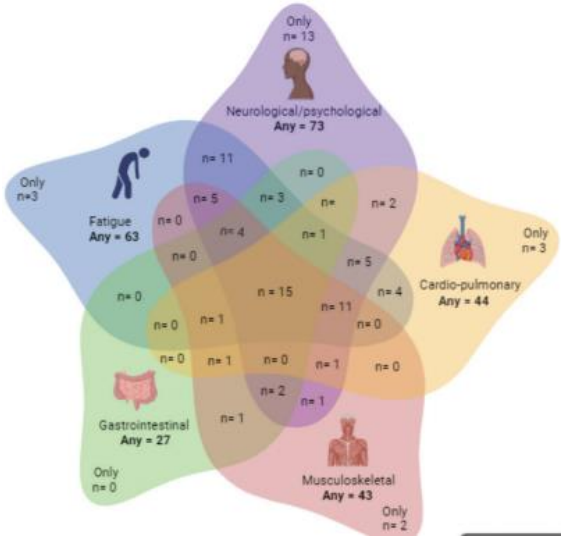
Figure 3: **Prevalence of persistent symptoms during the first 2 years of the COVID-19 pandemic**



Number at risk (number censored)					
Patients with inflammatory rheumatic disease	77 (0)	66 (0)	57 (0)	54 (0)	44 (9)
Events (recovery)	0	11	20	23	1
Healthy controls	23 (0)	20 (0)	15 (0)	12 (0)	10 (2)
Events (recovery)	0	3	8	11	11

Figure 2: **Kaplan-Meier curve of time until recovery from a post-COVID condition**
Only participants who met WHO criteria for post-COVID condition were included for analyses.

In a USA ARD cohort (n=299) with SARS-COV2 infection, 30% reported long COVID, 76% had ≥ 2 domains and 17% reported symptoms across all 5 domains



In an Italian cohort of the general population (n=616), (30.7%) satisfied the ACR survey criteria for FM, 6±3 months after the COVID-19 diagnosis.

Boekel et al.Lancet Rheumatol. 2023;7:e375–e385
Telles et Al. The Journal of Rheumatology 2024;51:928–33
Ursini et al. RMD Open 2021;7:e001735

JAMA Internal Medicine | Original Investigation

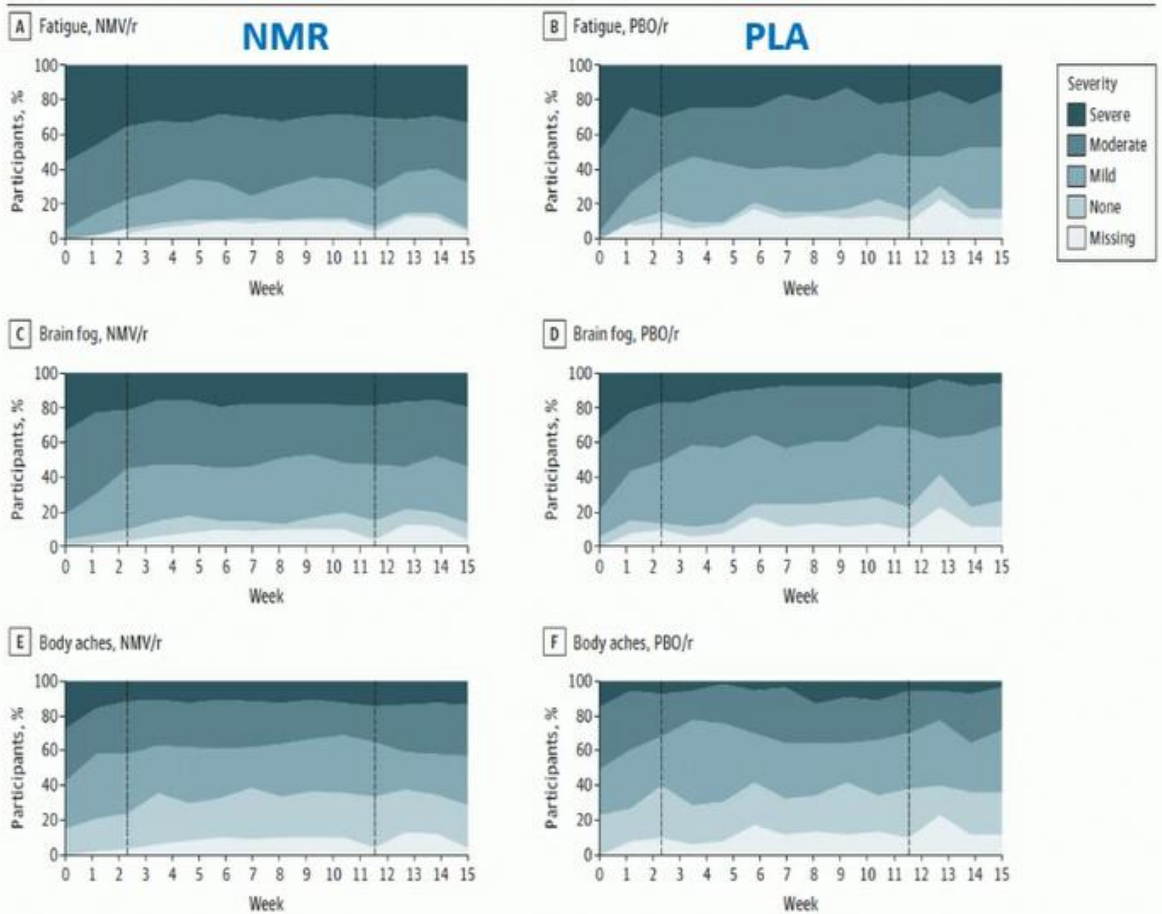
Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection

The STOP-PASC Randomized Clinical Trial

Linda N. Geng, MD, PhD; Hector Bonilla, MD; Haley Hedlin, PhD; Karen B. Jacobson, MD; Lu Tian, DSc; Prasanna Jagannathan, MD; Phillip C. Yang, MD; Aruna K. Subramanian, MD; Jane W. Liang, PhD; Sa Shen, PhD; Yaowei Deng, MA; Blake J. Shaw, MS; Bren Botzheim, MS; Manisha Desai, PhD; Divya Pathak, MS; Yasmin Jazayeri, MPH; Daniel Thai, BS; Andrew O'Donnell, MA; Sukanya Mohaptra, BS; Zenita Leang, BS; Gabriella Z. M. Reynolds, BS; Erin F. Brooks, MS; Ami S. Bhatt, MD, PhD; Robert W. Shafer, MD; Mitchell G. Miglis, MD; Tom Quach; Anushri Tiwari; Anindita Banerjee, PhD; Rene N. Lopez, MPH; Magdia De Jesus, PhD; Lawrence R. Charnas, MD, PhD; Paul J. Utz, MD; Upinder Singh, MD

- 155 patients with « long COVID »
- Randomisation between 15-day course of nirmatrelvir-ritonavir and placebo
- Time between index SARS-CoV-2 infection and randomization was 17.5 months

Figure 2. Distribution of Core Symptom Severity Scores Over Time in Adults With Postacute Sequelae of SARS-CoV-2 Infection



Geng L et al. JAMA Intern Med. June 7, 2024

Annals of Internal Medicine

ORIGINAL RESEARCH

A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings

Michael C. Sneller, MD; C. Jason Liang, PhD; Adriana R. Marques, MD; Joyce Y. Chung, MD; Sujata M. Shanbhag, MD; Joseph R. Fontana, MD; Haniya Raza, DO; Onyi Okeke, MD; Robin L. Dewar, PhD; Bryan P. Higgins, RN; Katie Tolstenko, FNP; Richard W. Kwan, MPAS; Kathleen R. Gittens, RN; Catherine A. Seamon, RN; Genevieve McCormack; Jacob S. Shaw; Grace M. Okpali; Melissa Law, RN; Krittin Trihemasava; Brooke D. Kennedy; Victoria Shi, MS; J. Shawn Justement; Clarisa M. Buckner, PhD; Jana Blazkova, PhD; Susan Moir, PhD; Tae-Wook Chun, PhD; and H. Clifford Lane, MD

Comparison between SARS-COV2 infected long COVID/no long COVID patients and uninfected controls.

no significant differences between groups
i) in inflammatory biomarkers
ii) plasma levels of CD4+ and CD8+ T-lymphocyte subsets
iii) no signs of persistent viral infection

Figure 5. CD4$^+$ and CD8$^+$ T cell populations in peripheral blood.

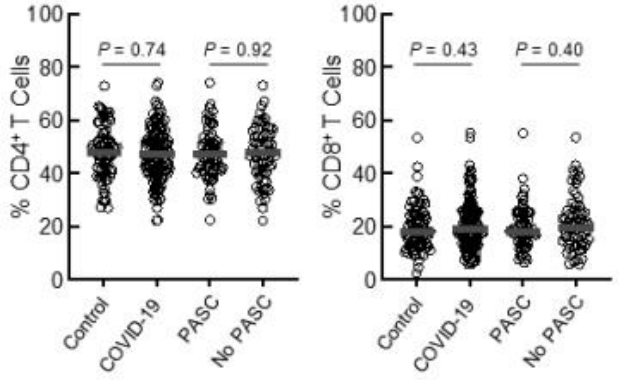
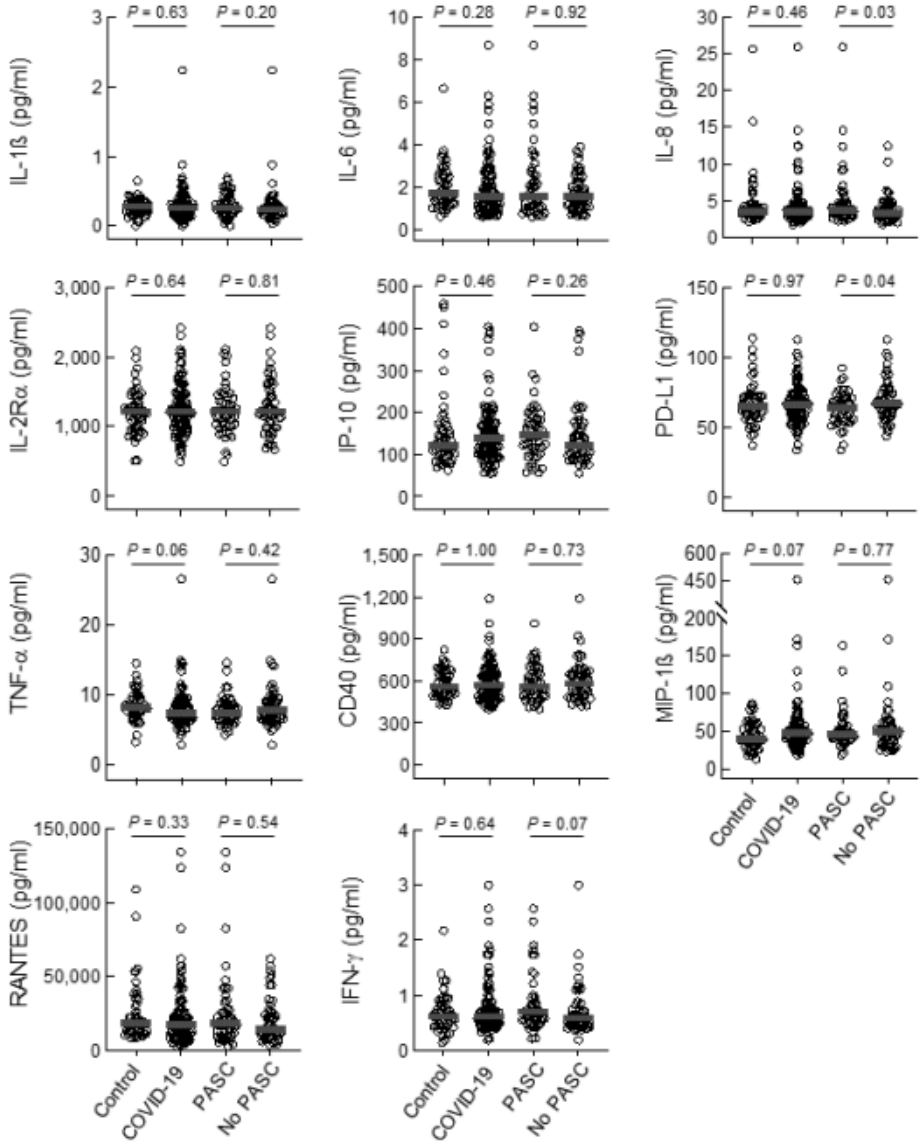


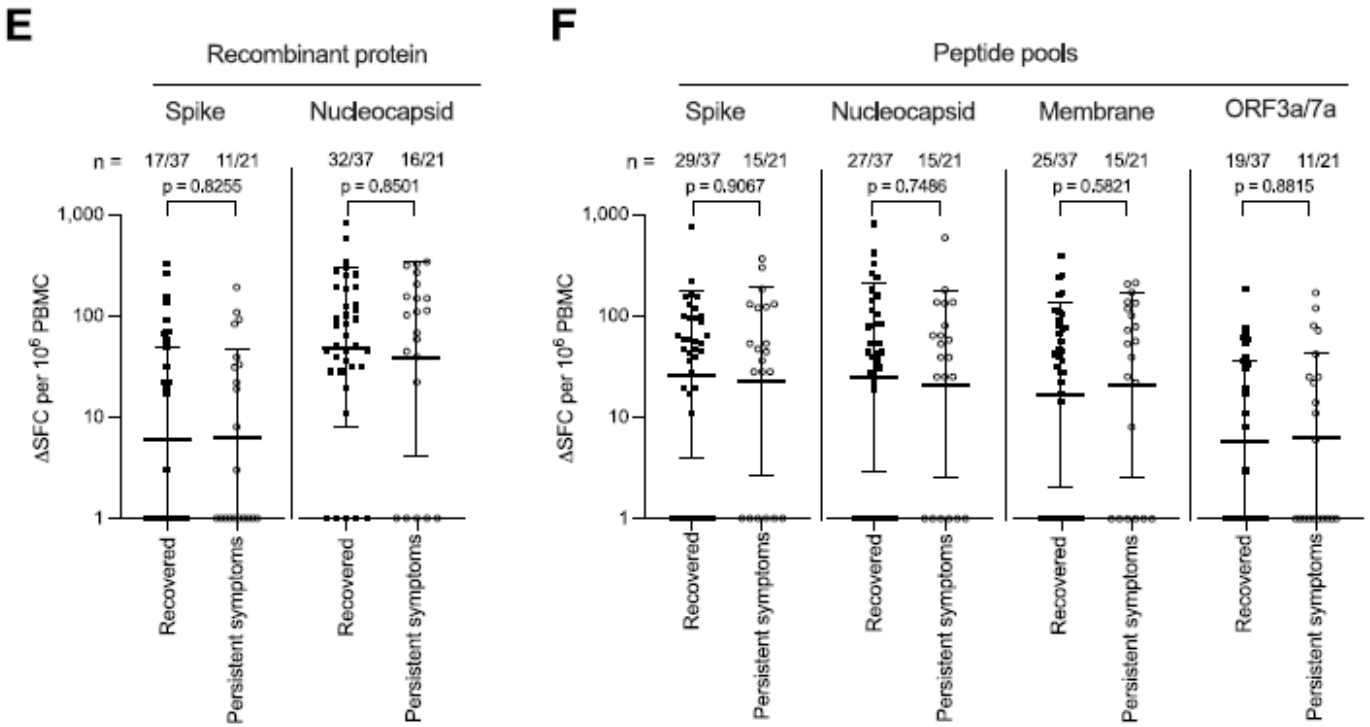
Figure 4. Levels of biomarkers in the plasma of study participants.

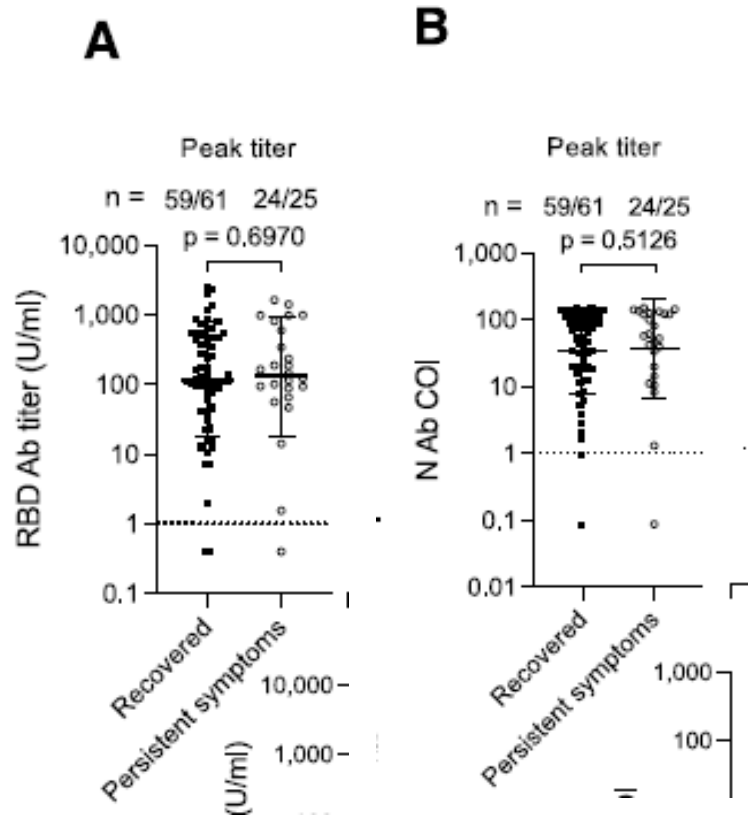


Comparison of infected SARS-COV2 (n=91), with or without long COVID

up to 18-weeks post-infection, no difference in

- i) antibody responses to spike RBD or nucleoprotein
- ii) T cell responses to various viral proteins





Altmann et al.Nature Communications. 2023;14:5139

distinct pattern of auto-reactivity between individuals with prior SARS-CoV-2 infection vs. uninfected controls

No difference in autoreactivity was observed for patients with long COVID versus post-COVID convalescents.

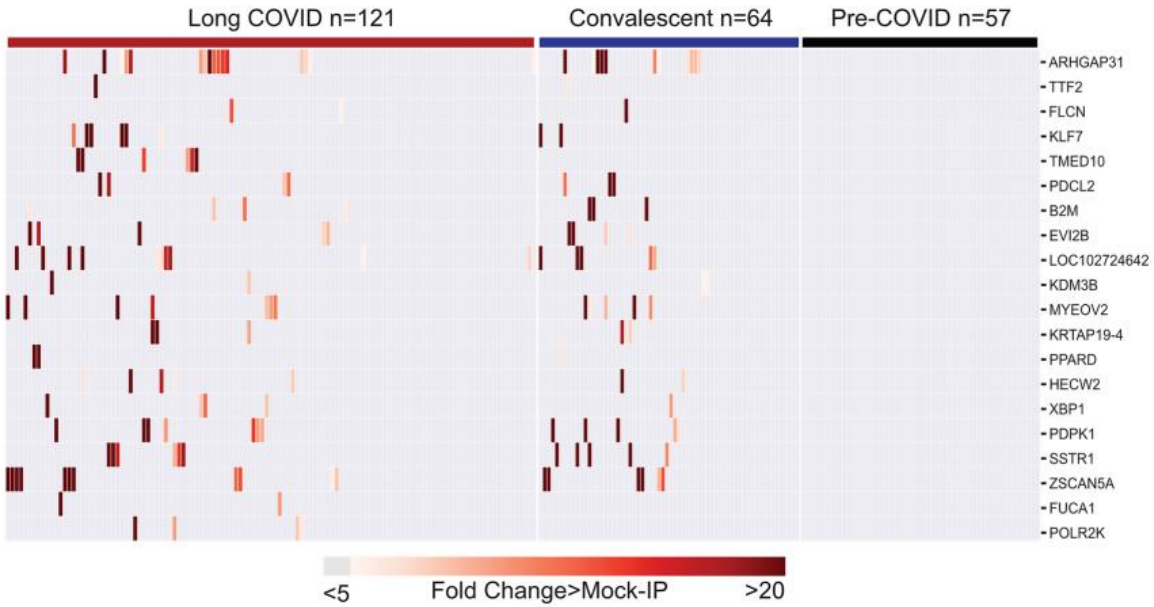
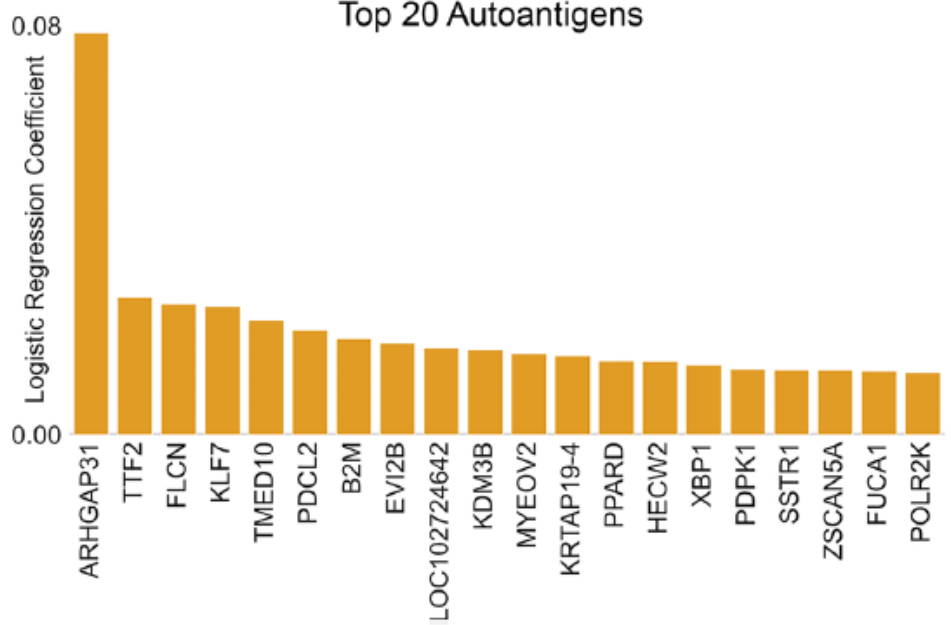
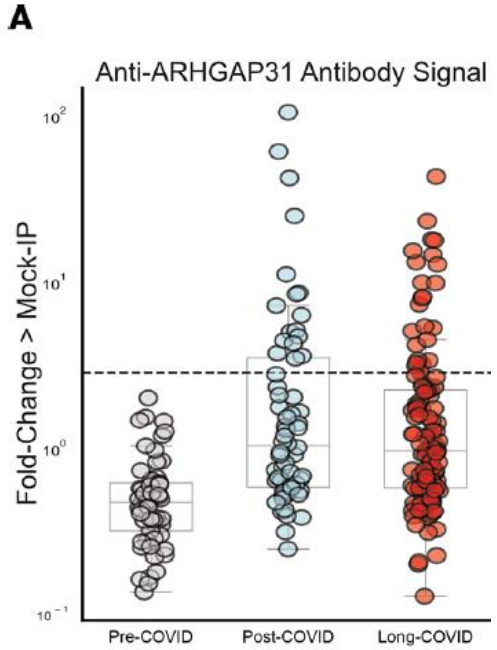


Figure 3. Post-COVID autoreactivities are similarly distributed among long COVID and controls. Hierarchically clustered (Pearson's) heatmaps showing the PhIP-Seq enrichment for the top 20 autoreactivities ranked by logistic regression coefficient in each patient with long COVID, each convalescent COVID patient, and each pre-COVID control.

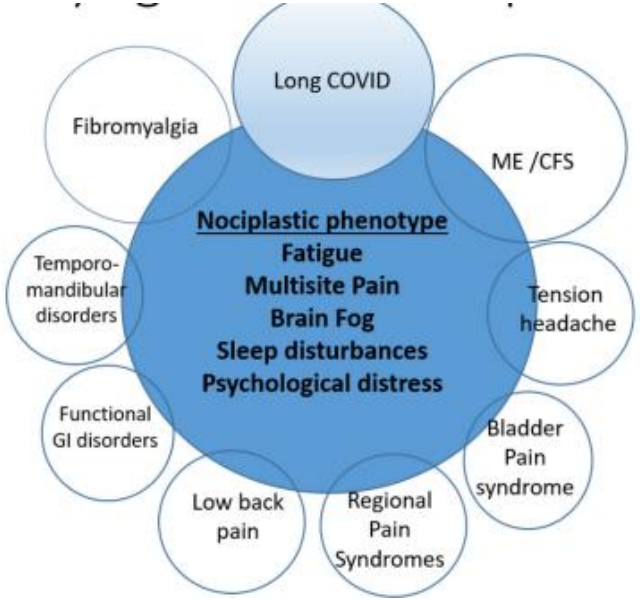




Bodansky et al.JCI Insight. 2023;8(11):e169515.

Take home messages

- SARS-COV2 infection presents distinct pathophysiologic` disorders from fibromyalgia, so far with unknown relevance to long COVID development
- Long COVID shares several pathophysiologic and phenotypic characteristics with ME/CSF or fibromyalgia
- Long Covid comprises a wide spectrum of clinical phenotypes. It is possible that subgroups of patients represent unique populations with inflammatory/autoimmune pathophysiology while other subsets have an overlap with fibromyalgia.



- Further basic and clinical research, including immunometabolism, neuroimaging and clinical psychology is needed to better understand long COVID syndrome and its differences or similarities with fibromyalgia.

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