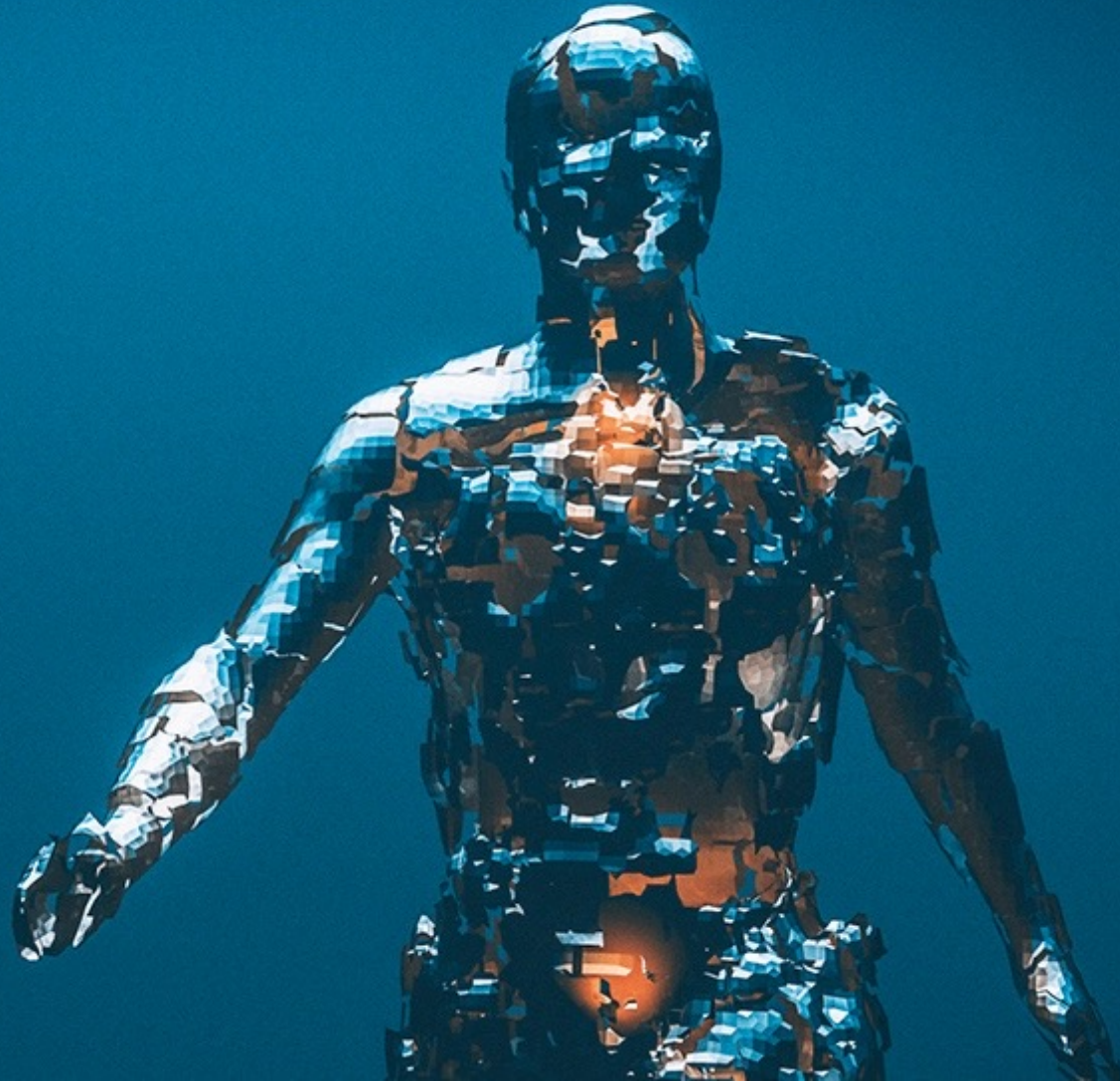


Skeletal muscle adaptations worsen after post-exertional malaise in patients with long COVID

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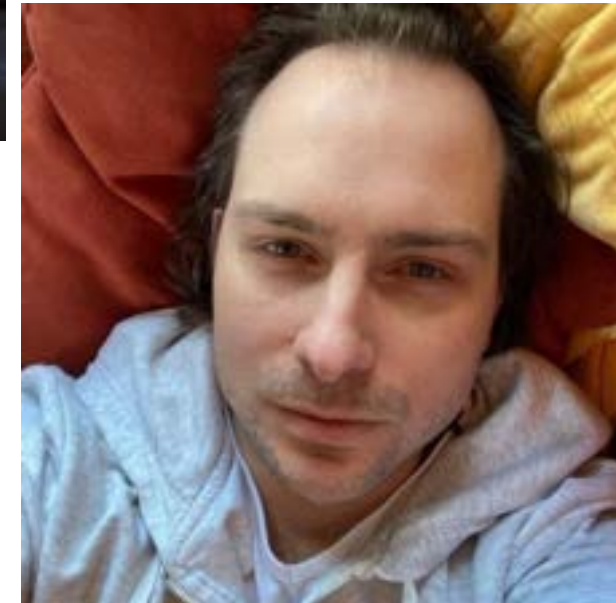


Braeden Charlton ME Star of Tomorrow

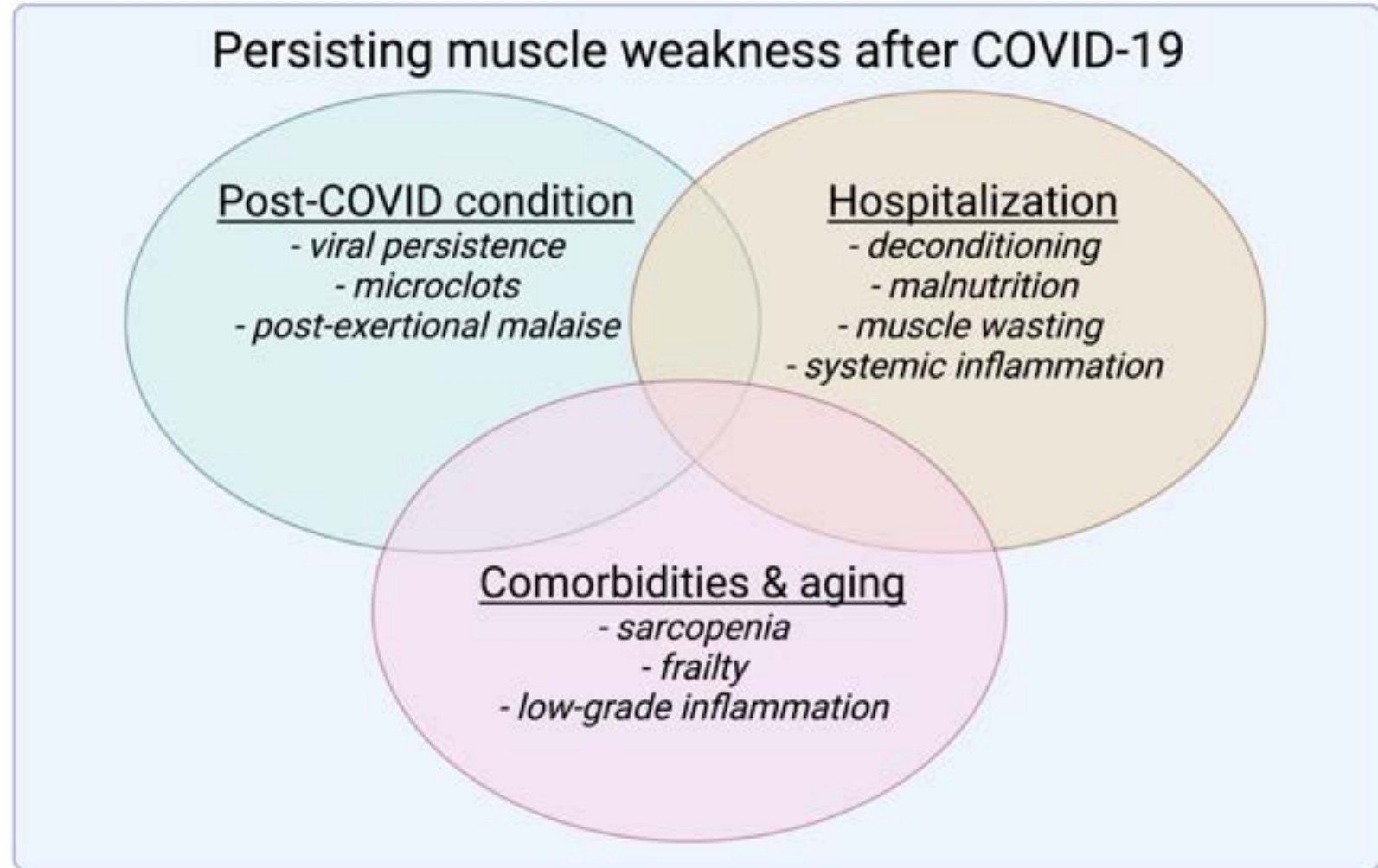


ICanCME

Mildly infected patients do not recover and develop extreme fatigue



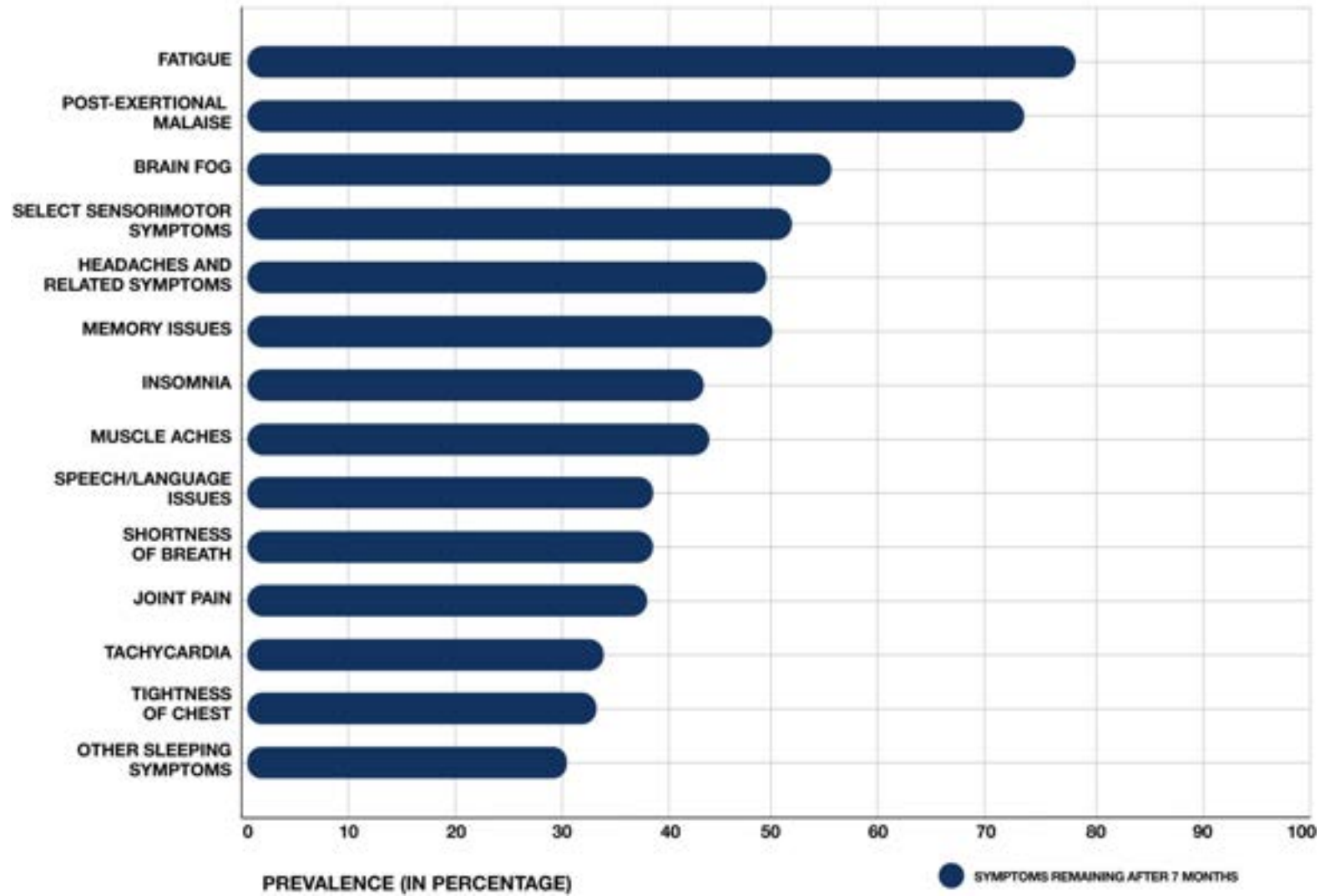
Long COVID / post-acute sequelae of Covid-19 (PASC) or Post-COVID-19 condition



Kerkhoff TJ, Charlton BT, Appelman B, van Vugt M, Wüst RCI. J Cachexia Sarcopenia Muscle. 2022

Post-exertional malaise

REMAINING SYMPTOMS AFTER MONTH 7 (PREVALENCE >30%)



(Intense) exercise is NOT medicine for some patients!



Dimensions of post-exertional malaise



Source: DSQ-PEM, 2018

ME-pedia.org

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Muscle abnormalities worsen after post-exertional malaise in long COVID

[Brent Appelman](#), [Braeden T. Charlton](#), [Richie P. Goulding](#), [Tom J. Kerkhoff](#), [Ellen A. Breedveld](#), [Wendy Noort](#), [Carla Offringa](#), [Frank W. Bloemers](#), [Michel van Weeghel](#), [Bauke V. Schomakers](#), [Pedro Coelho](#), [Jelle J. Posthuma](#), [Eleonora Aronica](#), [W. Joost Wiersinga](#), [Michèle van Vuot](#) & [Rob C. I. Wüst](#)

[Nature Communications](#) **15**, Article number: 17 (2024) | [Cite this article](#)

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Abstract

A subgroup of patients infected with SARS-CoV-2 remain symptomatic over three months after infection. A distinctive symptom of patients with long COVID is post-exertional malaise, which is associated with a worsening of fatigue- and pain-related symptoms after acute mental or physical exercise, but its underlying pathophysiology is unclear. With this longitudinal case-control study (NCT05225688), we provide new insights into the pathophysiology of post-exertional malaise in patients with long COVID. We show that skeletal muscle structure is associated with a lower exercise capacity in patients, and local and systemic metabolic disturbances, severe exercise-induced myopathy and tissue infiltration of amyloid-containing deposits in skeletal muscles of patients with long COVID worsen after induction of post-exertional malaise. This study highlights novel pathways that help to understand the pathophysiology of post-exertional malaise in patients suffering from long COVID and other post-infectious diseases.

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Protocol

- Day -7:
 - Blood, vastus lateralis muscle biopsy, questionnaires
- Day 0:
 - Cardio-Pulmonary Exercise Test to study whole body exercise tolerance and to induce post-exertional malaise
- Day 1:
 - Blood, vastus lateralis muscle biopsy, questionnaires
- Day 2:
 - Questionnaires
- Day 7:
 - Blood, questionnaires



Jelle Posthuma



Frank Bloemers

Participant characteristics

Patients were diagnosed based on interviews and medical history

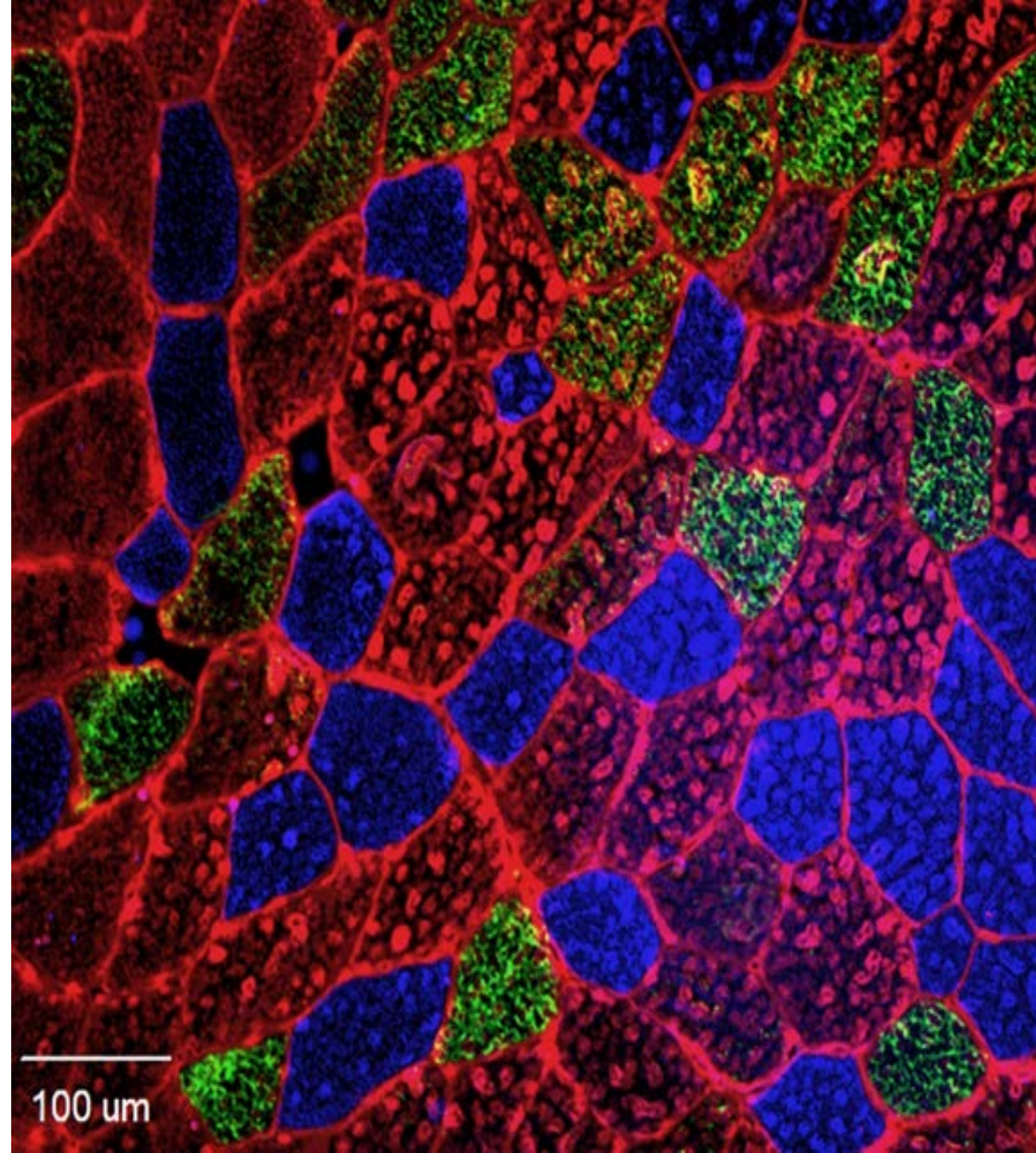
Inclusion criteria: Post-exertional malaise and minimum of 3 months persisting symptoms, controls recovered from acute COVID

Exclusion criteria: Hospitalisation after COVID infection and other comorbidities

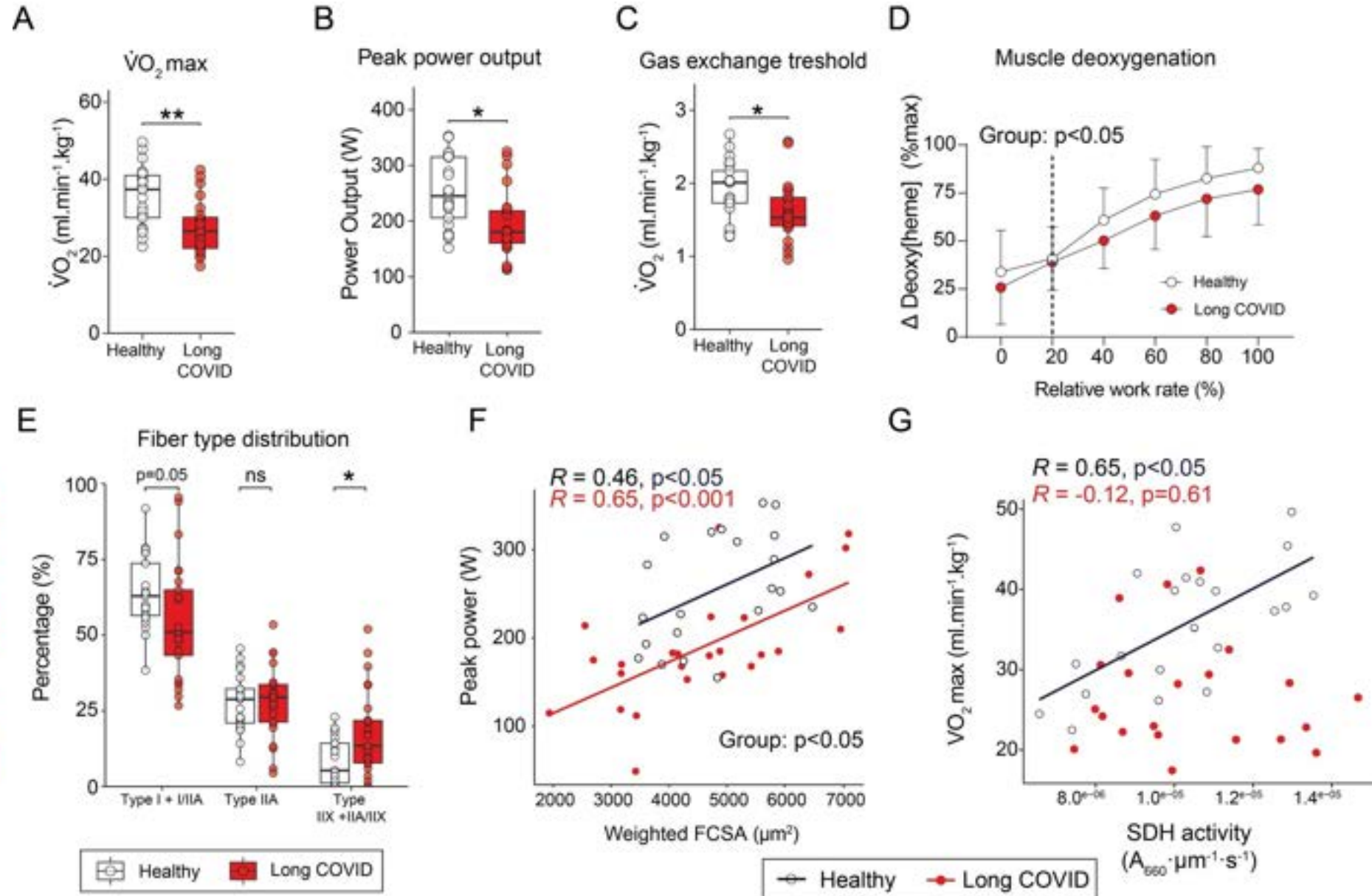
	Control n=21	Patients n=25
Sex (M/F)	10/11	13/12
Age (years)	43 ± 13	42 ± 11
Weight (kg)	77 ± 11	83 ± 21
Height (cm)	178 ± 7	178 ± 10

Output variables

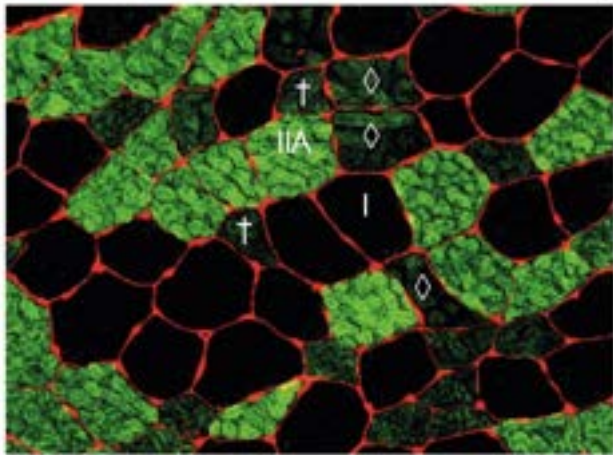
- Exercise capacity
- Skeletal muscle mitochondrial function
- Microclots
- Pathological characteristics of exercise-induced myopathy
- Viral persistence



Exercise intolerance has a peripheral contribution

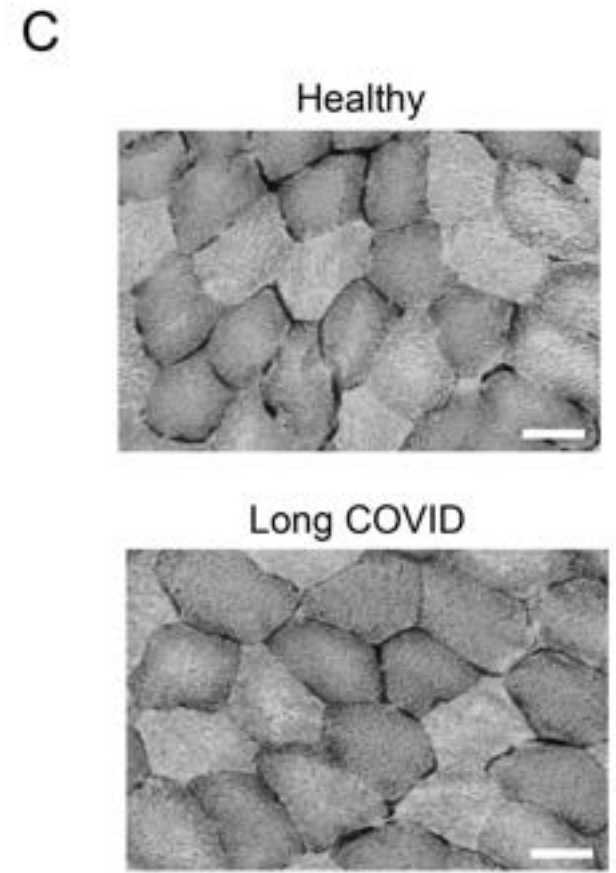
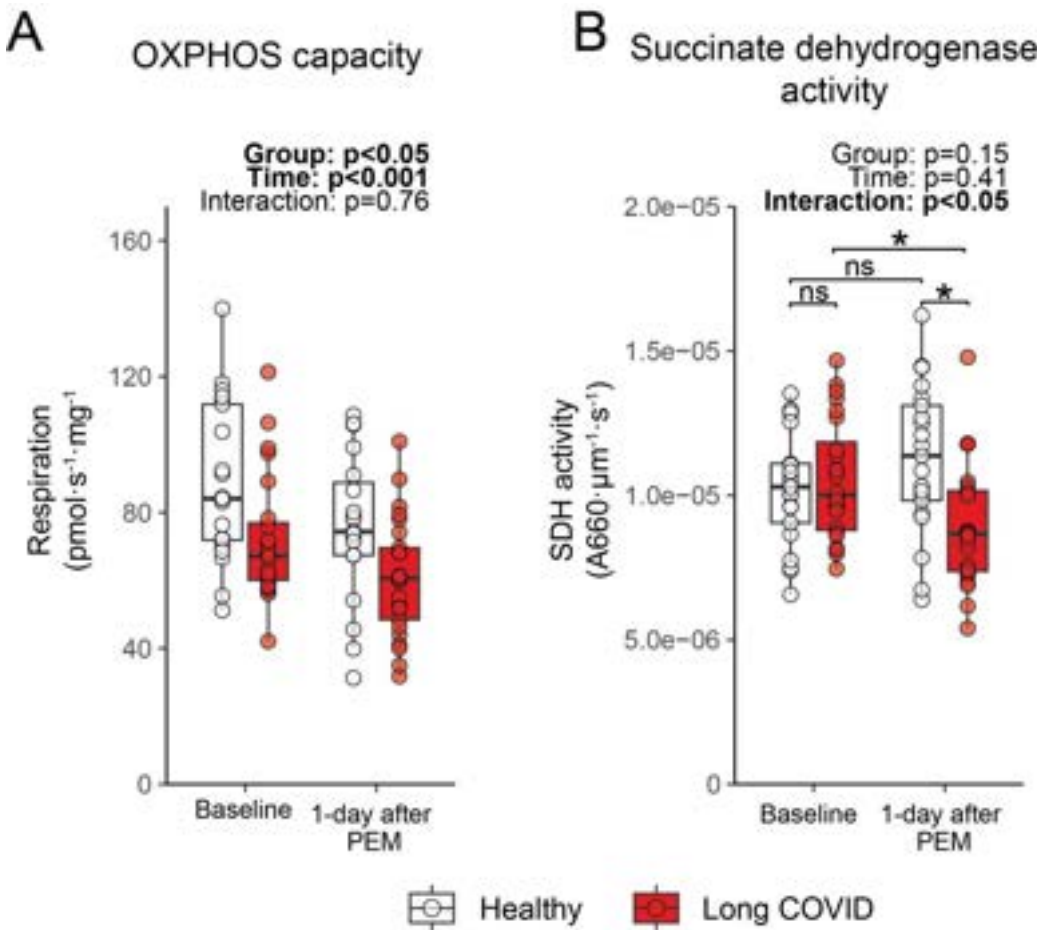
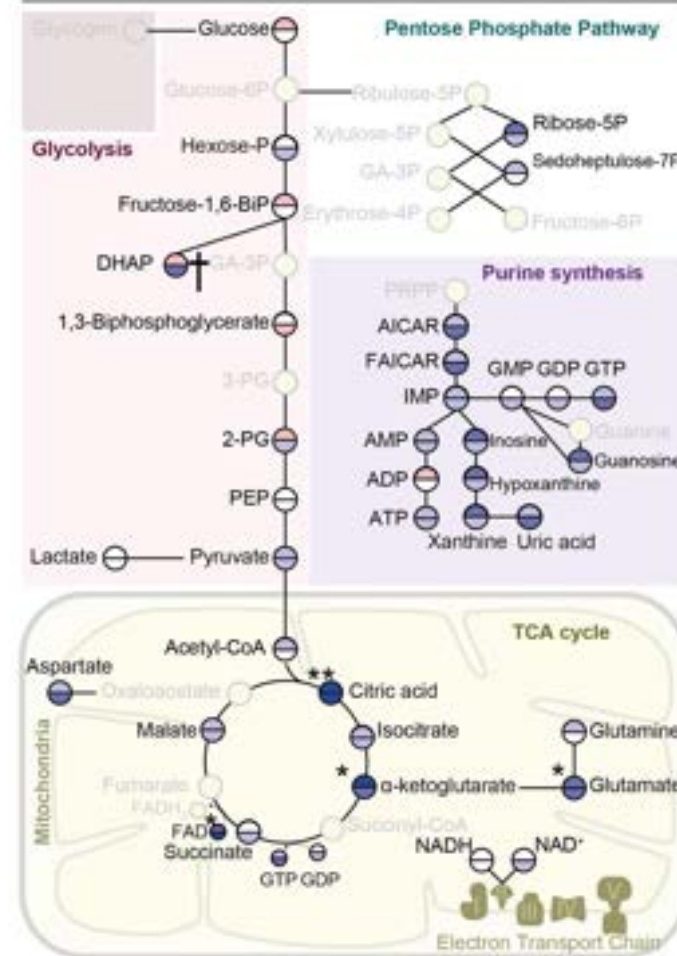


Type II (SC-71) - Cell membrane (WGA)

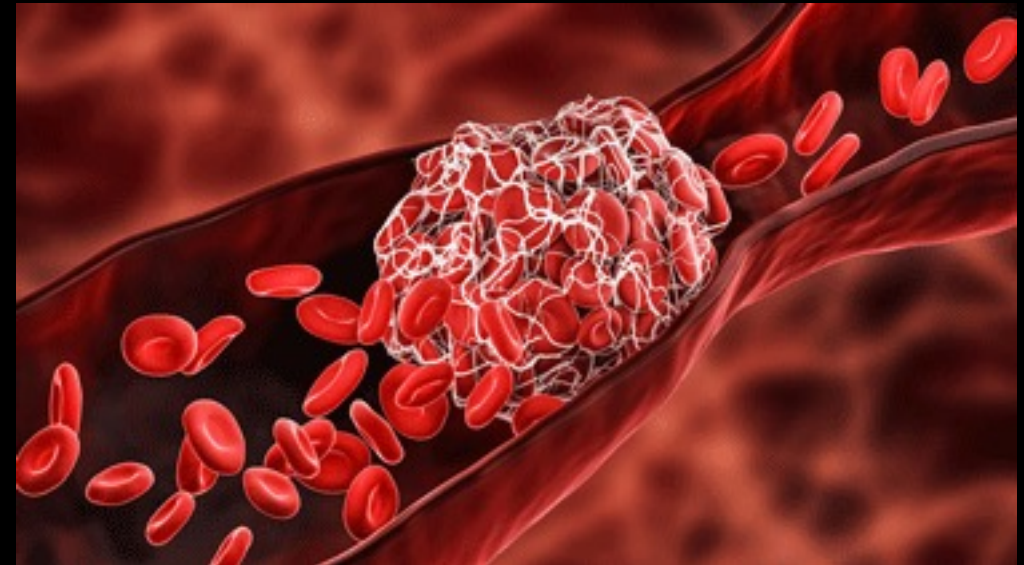
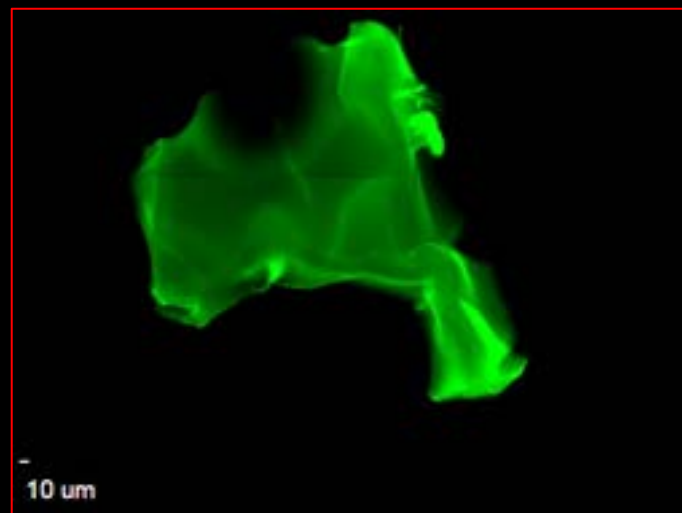
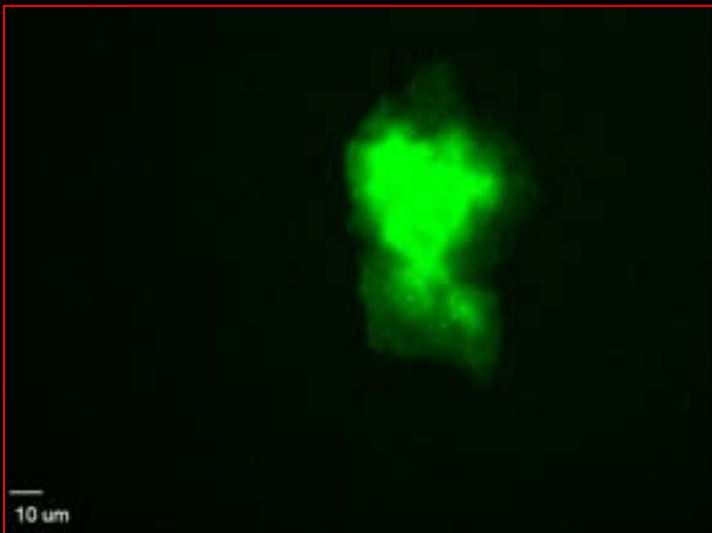
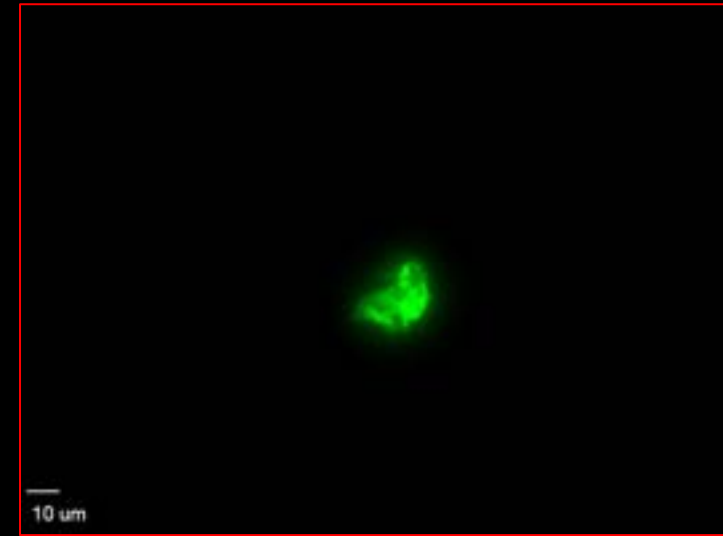
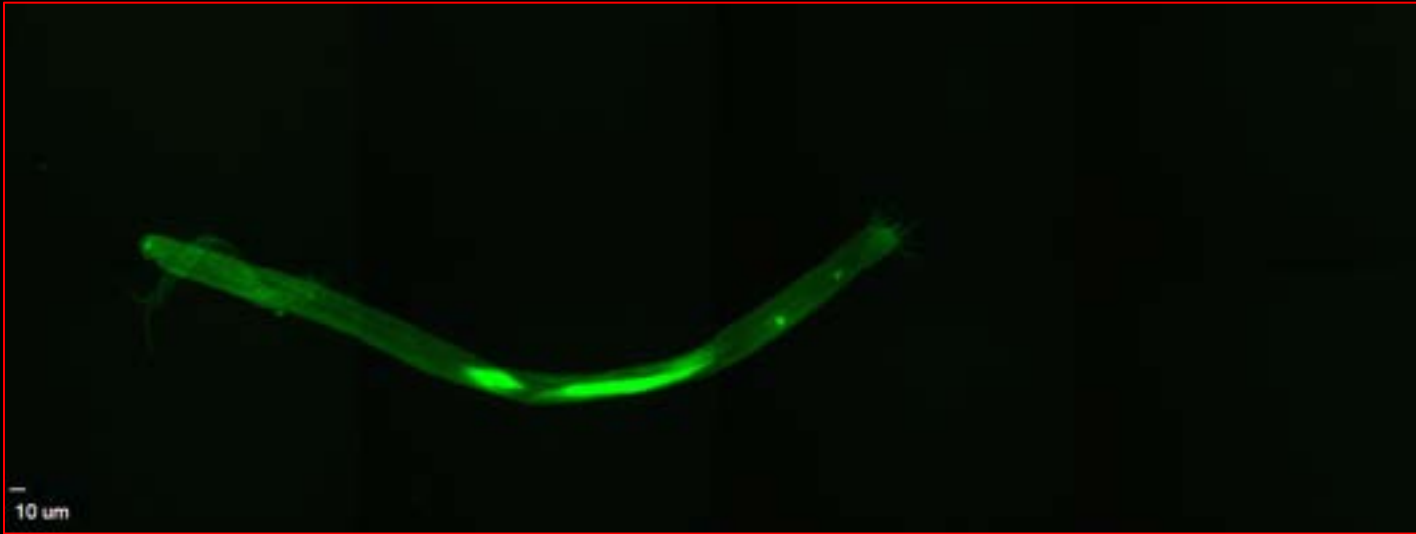


Metabolic and mitochondrial dysfunction in long COVID patients worsens with post-exertional malaise

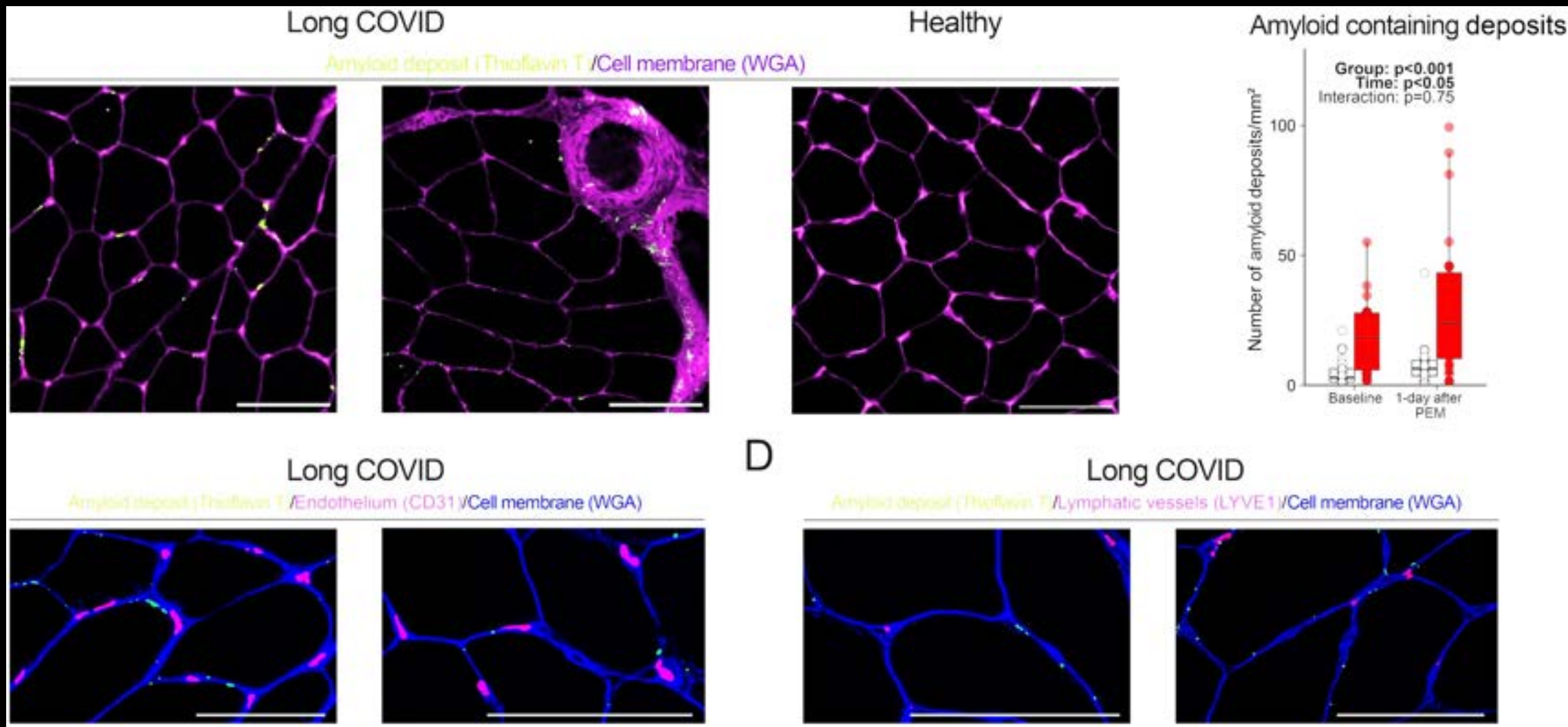
Muscle metabolomics long COVID compared to healthy



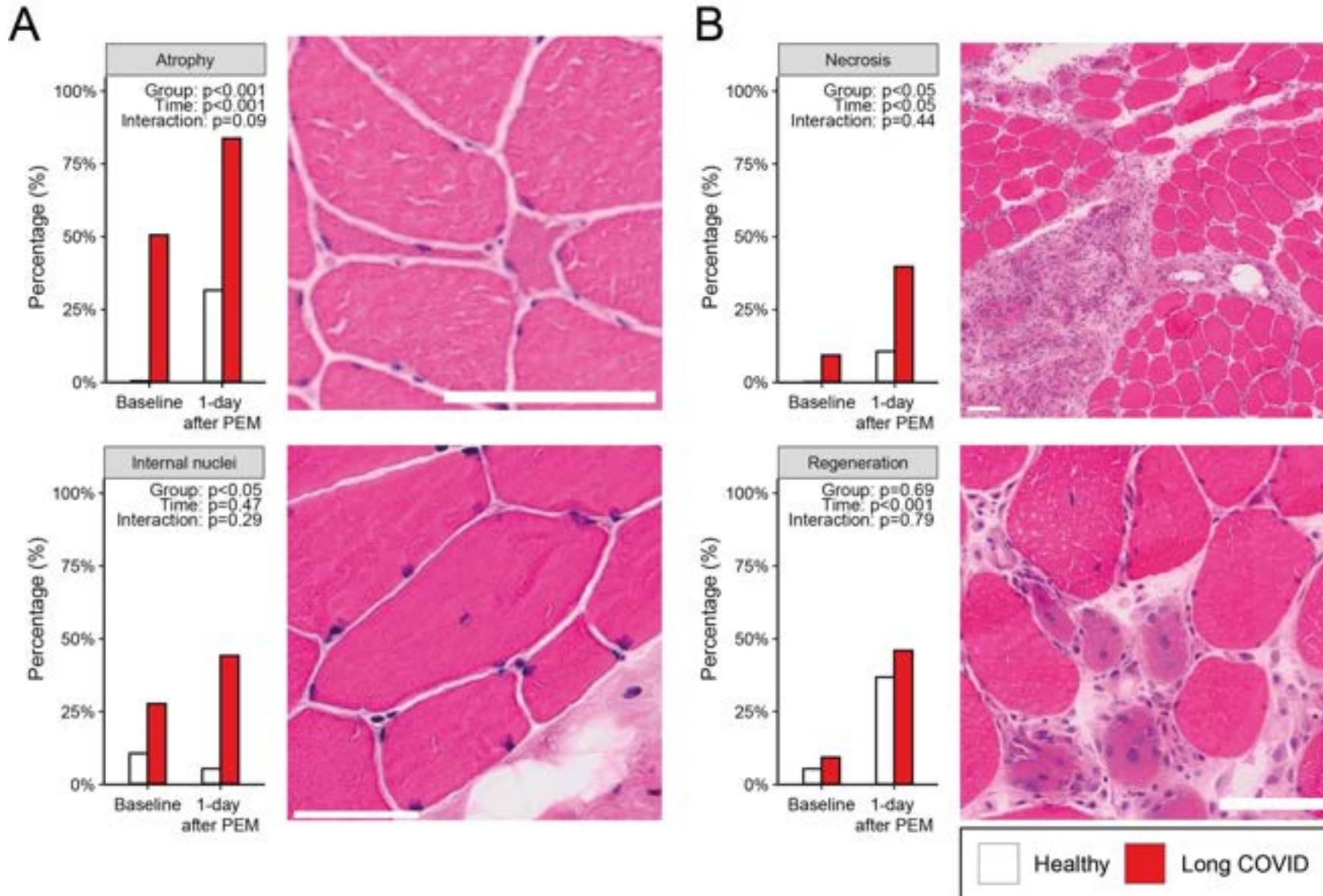
Microclot theory in Long COVID



Amyloid-containing deposits in skeletal muscle, but not in capillaries!

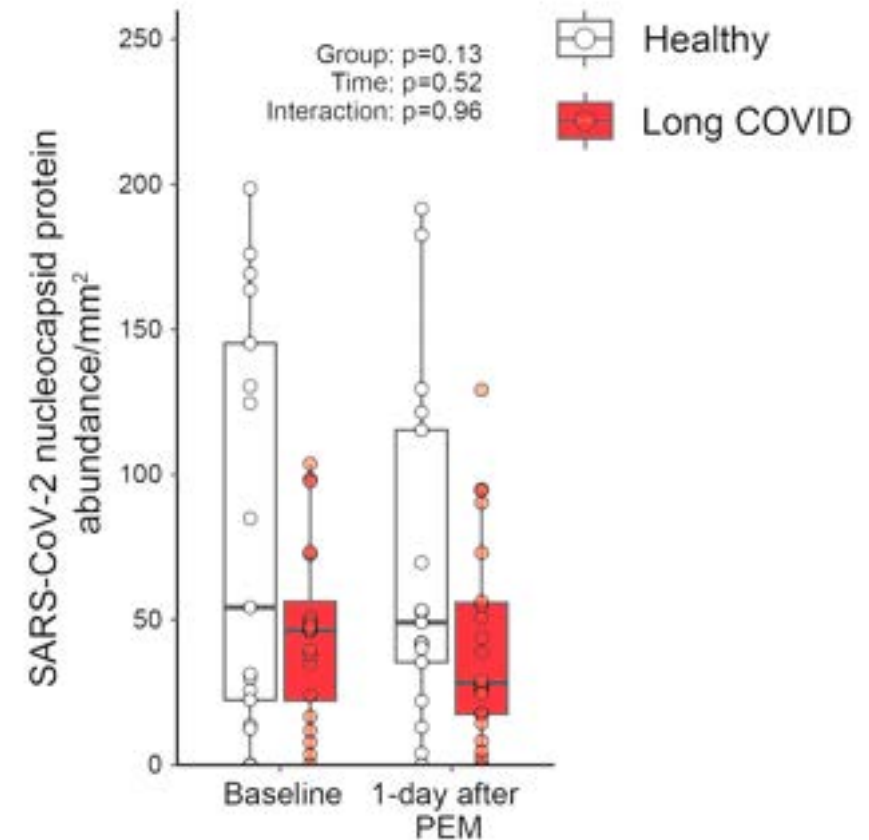
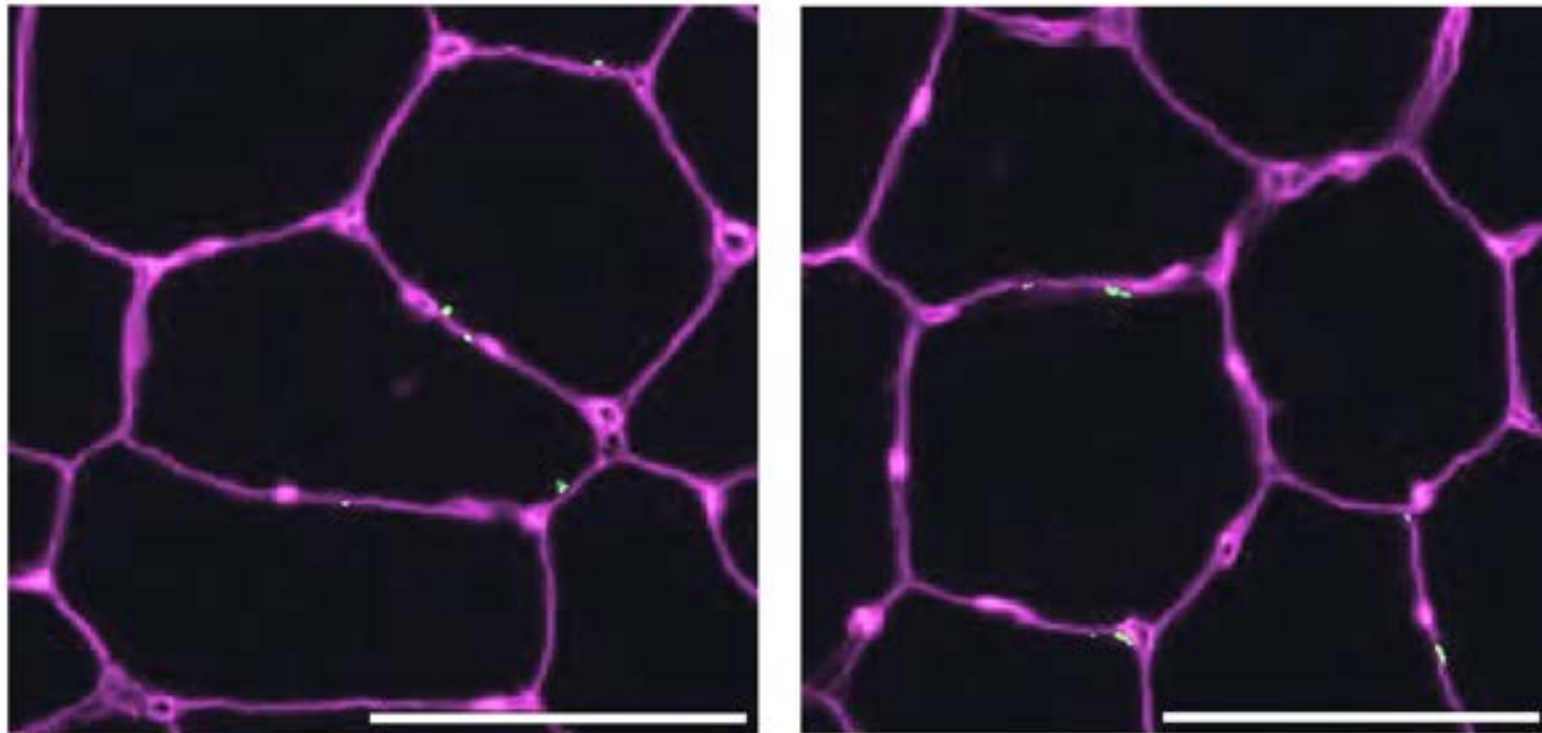


Pathological features in skeletal muscle in patients with long COVID



Nucleocapsid protein present in almost all participants, but not more abundant in long COVID

Polyclonal IgG anti-nucleocapsid protein



Reduced exercise capacity and post-exertional malaise in patients with long COVID

Contributions to reduced exercise capacity:

- Lower mitochondrial respiration
- More glycolytic fibers
- Smaller fibers

Contributions to post-exertional malaise:

- Local and systemic metabolic disturbances
- Severe exercise-induced myopathy, including necrosis
- Tissue infiltration with amyloid-containing deposits

Take home messages

- Post-exertional malaise is a critical and serious symptom limiting daily functioning and work
- Patients with long COVID have peripheral alterations that help to explain their fatigue and muscle pain

We don't have the X-factor yet that causes these alterations

Neurological and immunological alterations in LC patients have been described in the literature

- Exercise is counter-productive when above the PEM-induction threshold. We encourage exercise below this threshold
- Our results are in accordance with work in ME/CFS

Future work

- What are the similarities/differences between PEM in Long COVID and Me/CFS?
 - We just finished testing 25 additional patients with ME/CFS
 - Are there subgroups of patients with post-viral conditions?
- What is the contribution of physical inactivity in the skeletal muscle abnormalities?
 - We compare our data with a set of biopsies obtained before and after 60 days of strict bed rest (Eggelbusch et al., 2024 Cell Report Medicine)
- Can heart rate variability be used as a marker for detecting PEM and its related crash/recovery?
 - A MSc student is currently studying this in collaboration with Dr Janssen (sports physician)
- Treatments....
 - We have some ideas...

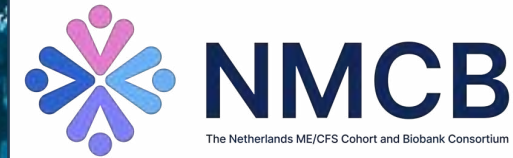
Translational research in Amsterdam



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Jelle Posthuma
Bauke Schomakers
Michèle van Vugt
Michel van Weeghel
Joost Wiersinga



Jaarcampagne VUfonds

And all participating patients and healthy controls

