

Skeletal muscle alterations in long COVID and ME/CFS

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Post-exertional malaise (PEM)

- worsening of general symptoms, or the development of new symptoms,
- typically within 48 hr after
- physical, cognitive or mental exertion,
- above a patient- and time-specific threshold,
- that can last for days to weeks or even months.

Similar in patients with long COVID and ME/CFS and other post-acute infectious diseases

Patients tell that PEM comes in many different flavours

“Exercise above the PEM threshold is NOT medicine” for some patients with Long COVID and ME/CFS

Dimensions of post-exertional malaise



Source: DSQ-PEM, 2018

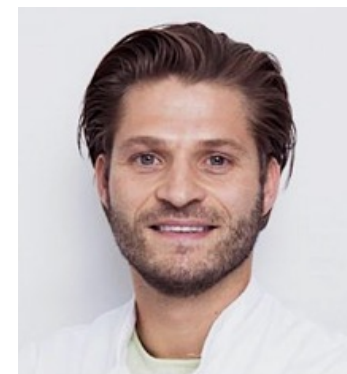
ME-pedia.org

Current diagnosis:

1. an *unethical* two-day exercise test
2. DSQ-PEM questionnaire

Protocol – “two-day biopsy test”

- 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

nature > nature communications > articles > article

Article | [Open access](#) | Published: 04 January 2024

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 Vugt](#) & [Rob C. I. Wüst](#)

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[Matters Arising](#) to this article was published on 11 February 2025

Abstract

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Reply: Muscle abnormalities in Long COVID

B. Appelman, B. T. Charlton ... R. C. I. Wüst
Nature Communications | **Matters Arising**
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Reply to: Should we be careful with exercise in post-exertional malaise after Long COVID?

Brent Appelman, Braeden T. Charlton ... Rob C. I. Wüst
Nature Communications | **Matters Arising**
[Open Access](#) | 18 Feb 2025

Lower exercise capacity & post-exertional malaise in patients with Long COVID

Contributions to the reduced exercise capacity:

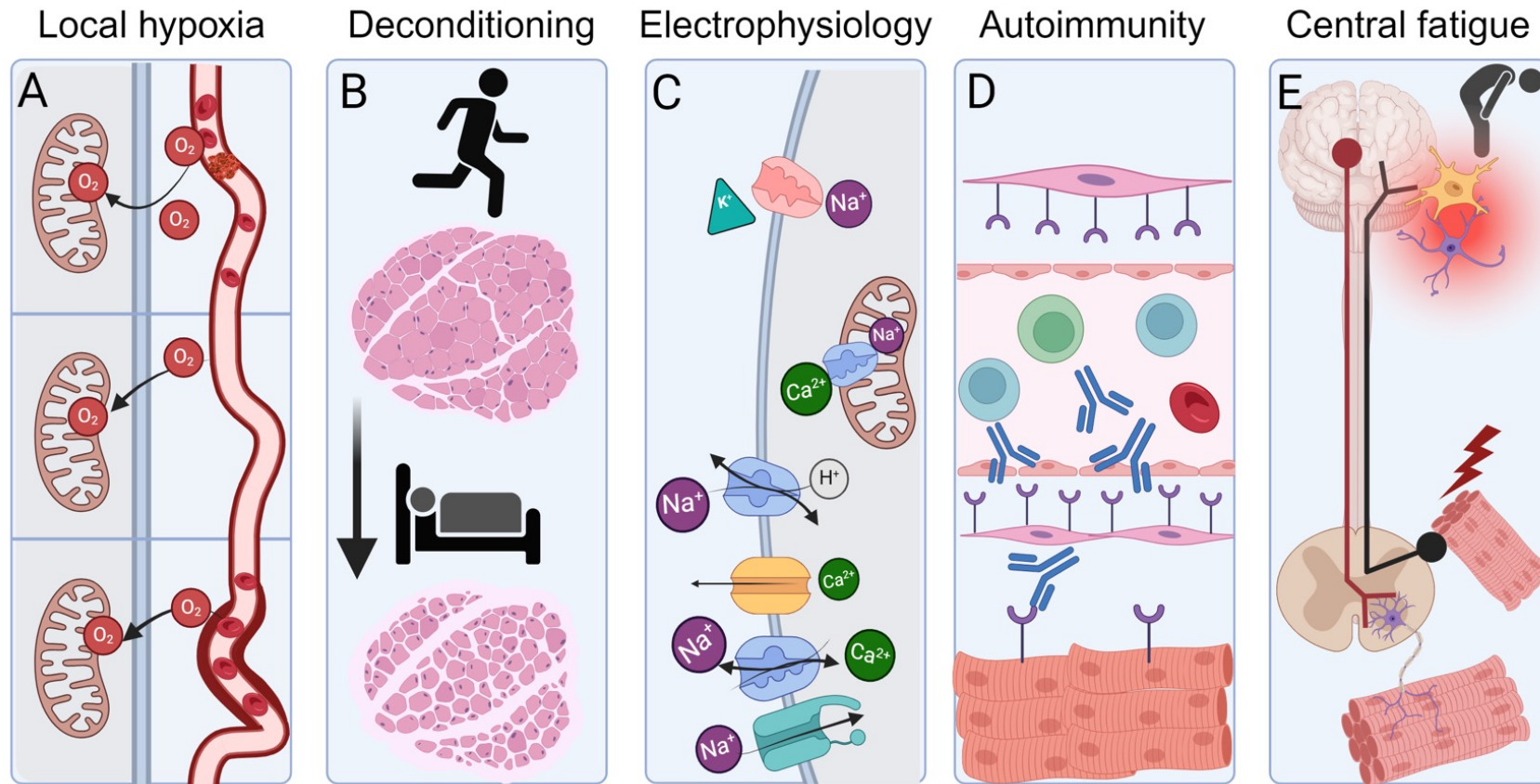
- Lower mitochondrial respiration
- More metabolites related to fatigue
- More glycolytic fibers
- Lower power output per muscle cross-sectional area

Contributions to post-exertional malaise:

- Rapid local and systemic metabolic changes
- Exercise-induced markers for muscle damage (& recovery)
- Infiltration of immune cells (T-cells and macrophages) and amyloid-like structures into skeletal muscle

(Not specifically more N-protein accumulation in muscle)

Current Hypotheses



Charlton BT, et al.
Trends Endocrinol Metab. 2025
PMID: 39694730

Are skeletal muscle abnormalities distinct from those after strict bedrest?



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Skeletal muscle properties in long COVID and ME/CFS differ from those induced by bed rest

Posted May 06, 2025.

[Braeden T Charlton](#), [Anouk Slaghekke](#), [Brent Appelman](#), [Moritz Eggelbusch](#), [Jelle Y Huijts](#), [Wendy Noort](#), [Paul W Hendrickse](#), [Frank W Bloemers](#), [Jelle J Posthuma](#), [Paul van Amstel](#), [Richie P Goulding](#), [Hans Degens](#), [Richard T Jaspers](#), [Michele van Vugt](#), [Rob Wüst](#)

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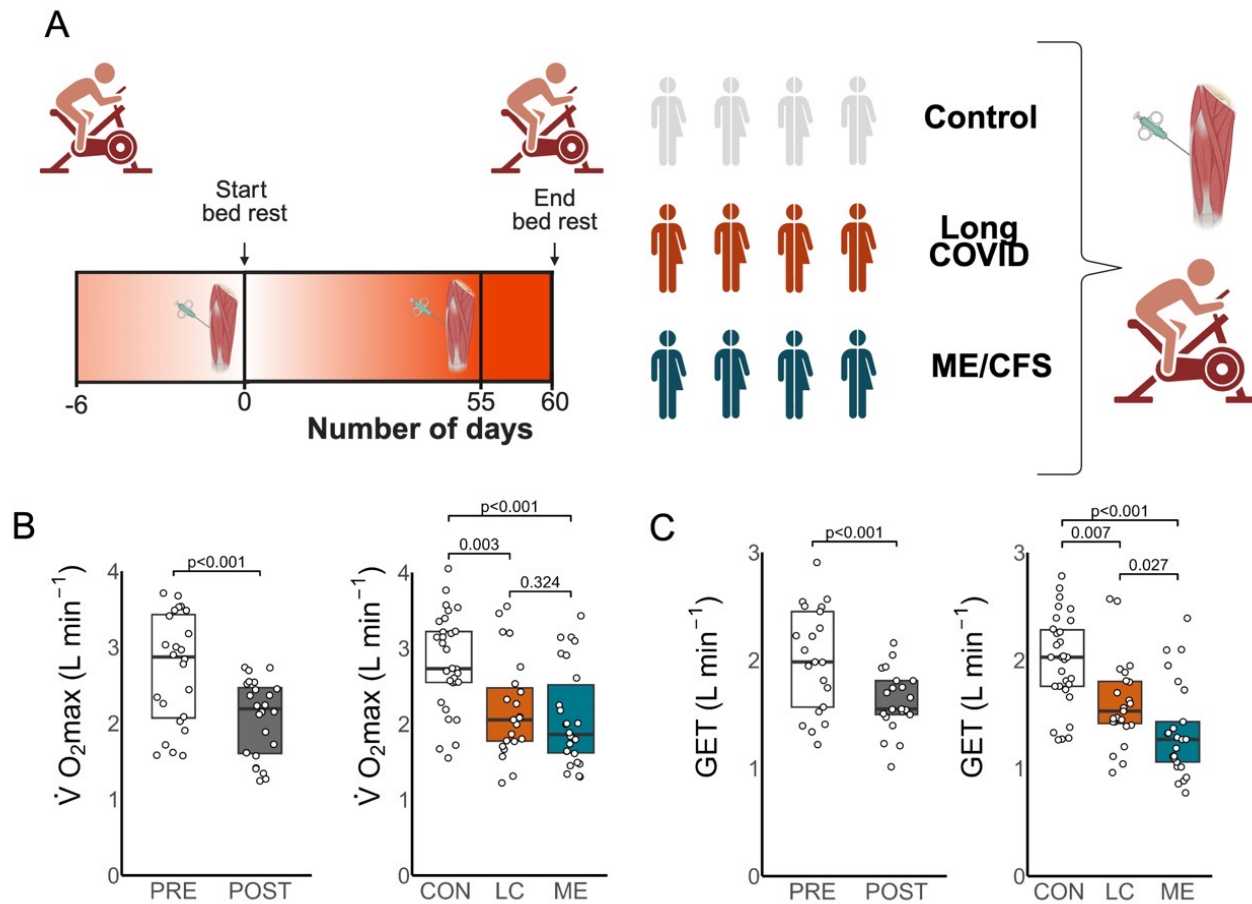
Patients with long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) suffer from a reduced exercise capacity, skeletal muscle abnormalities and post-exertional malaise (PEM), where symptoms worsen with cognitive or physical exertion. PEM often results in avoidance of physical activity, resulting in a lower aerobic fitness, which may contribute to skeletal muscle abnormalities. Here, we compared whole-body exercise responses and skeletal muscle adaptations after strict 60-day bed rest in healthy people with those in patients with long COVID and ME/CFS, and healthy age- and sex-matched controls. Bed rest altered

Reviews and Context

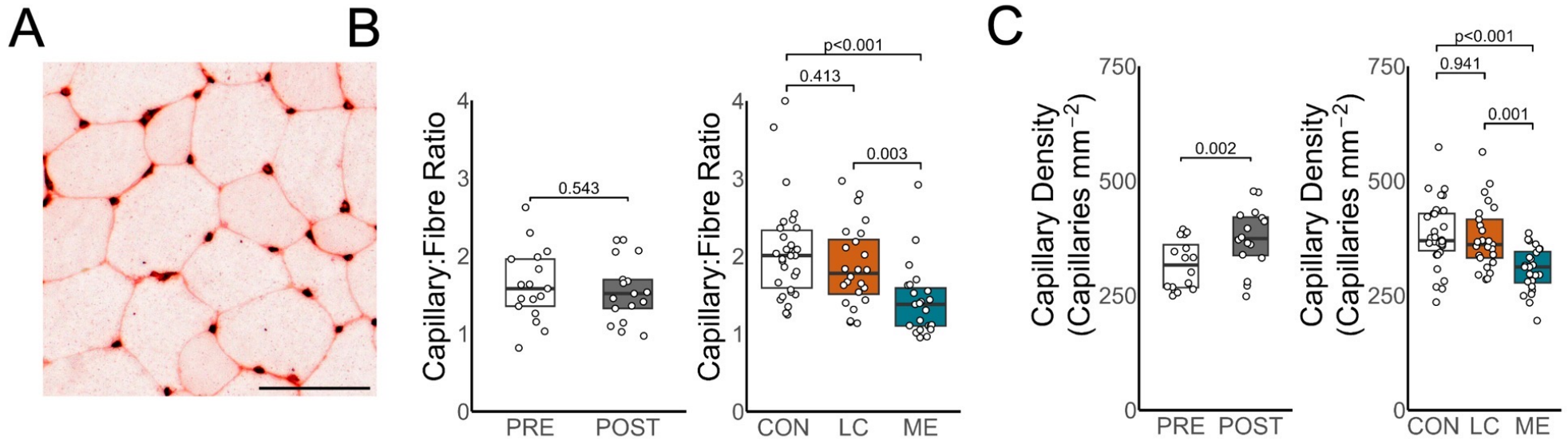
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- 0 Author Videos



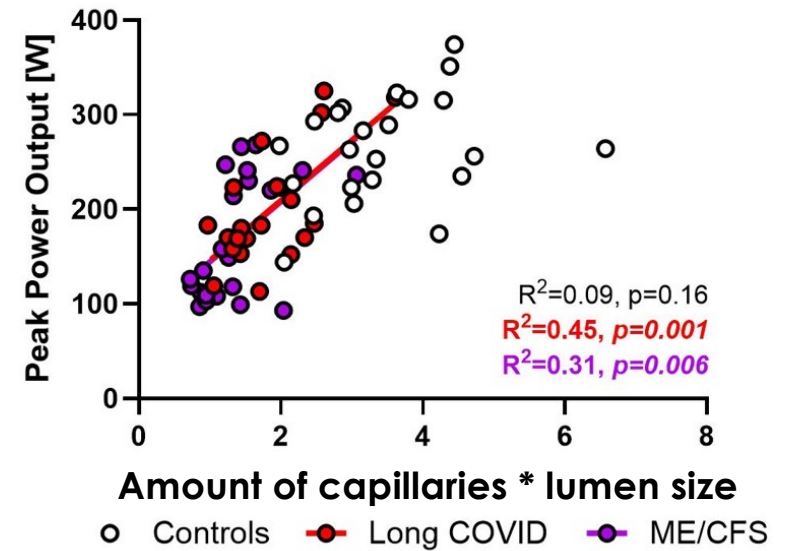
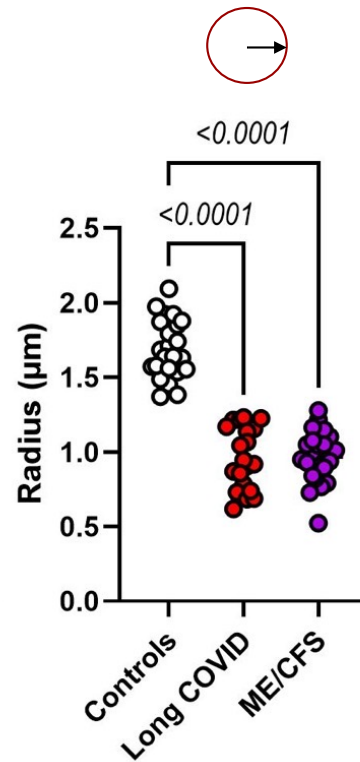
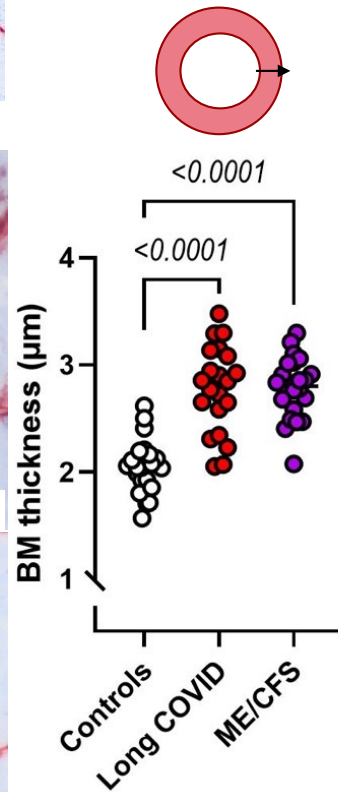
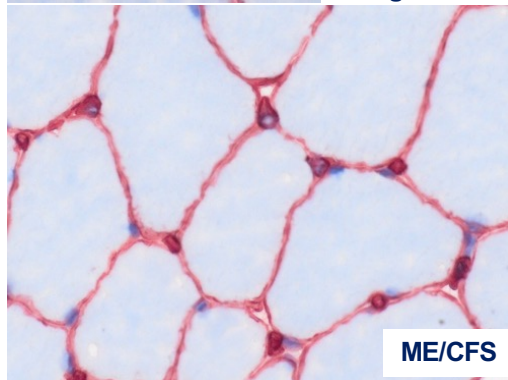
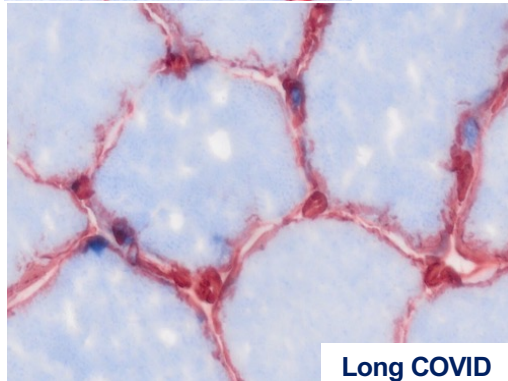
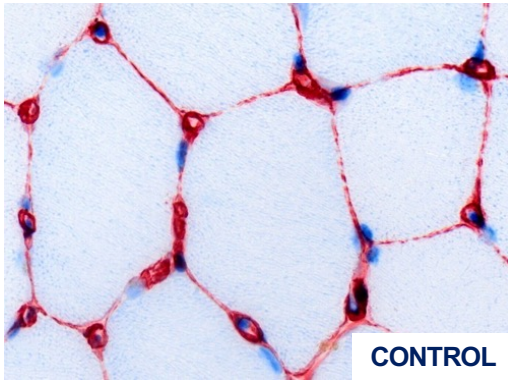
While exercise capacity is similarly reduced, skeletal muscle structure and function differ



Altered capillary supply



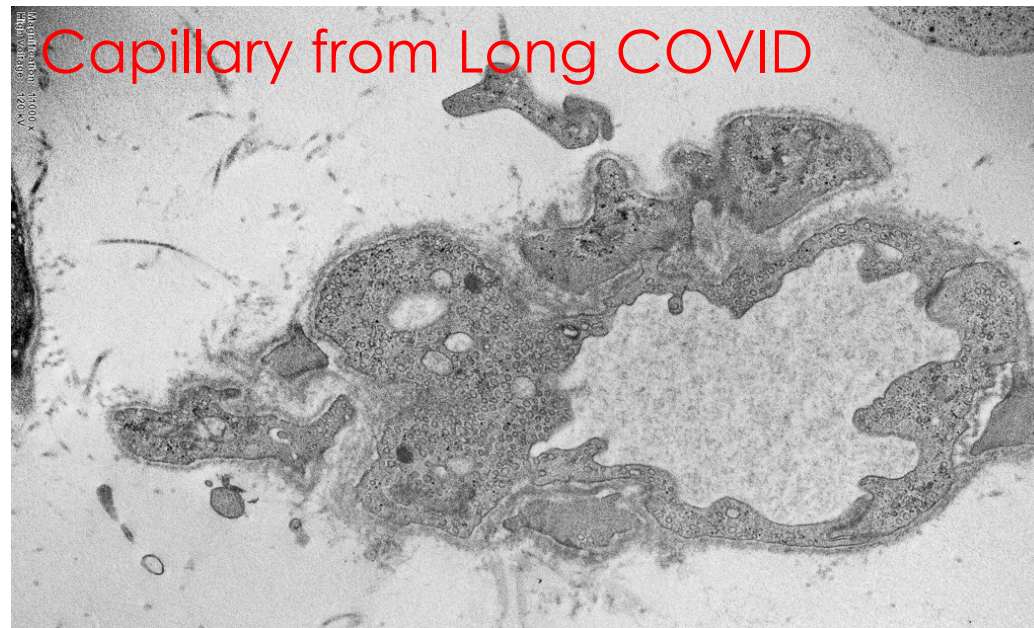
Microvascular dysfunction – novel diagnostic marker?



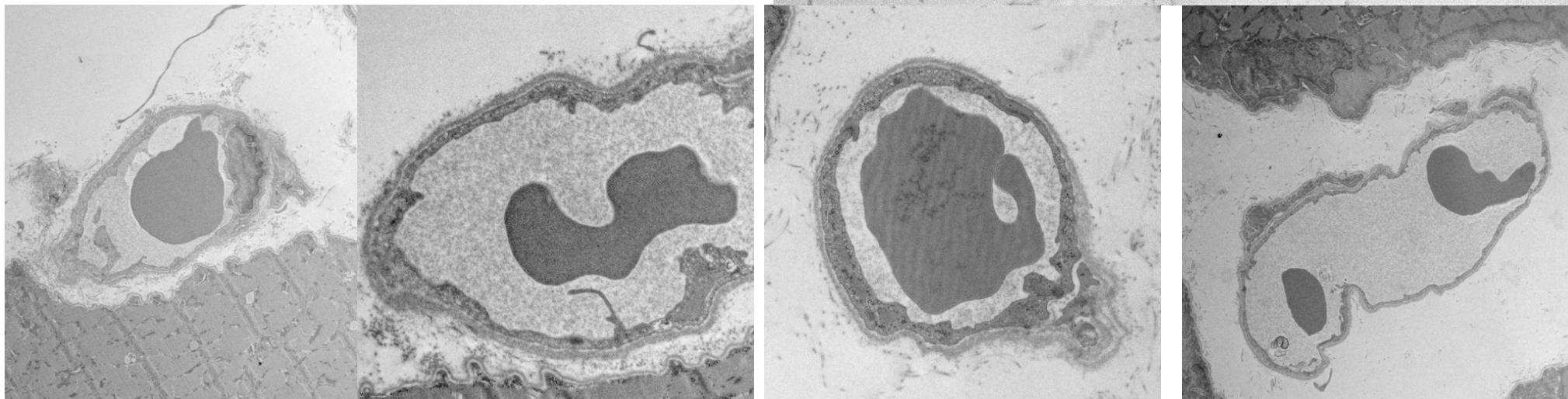
A Slaghekke et al. Poster



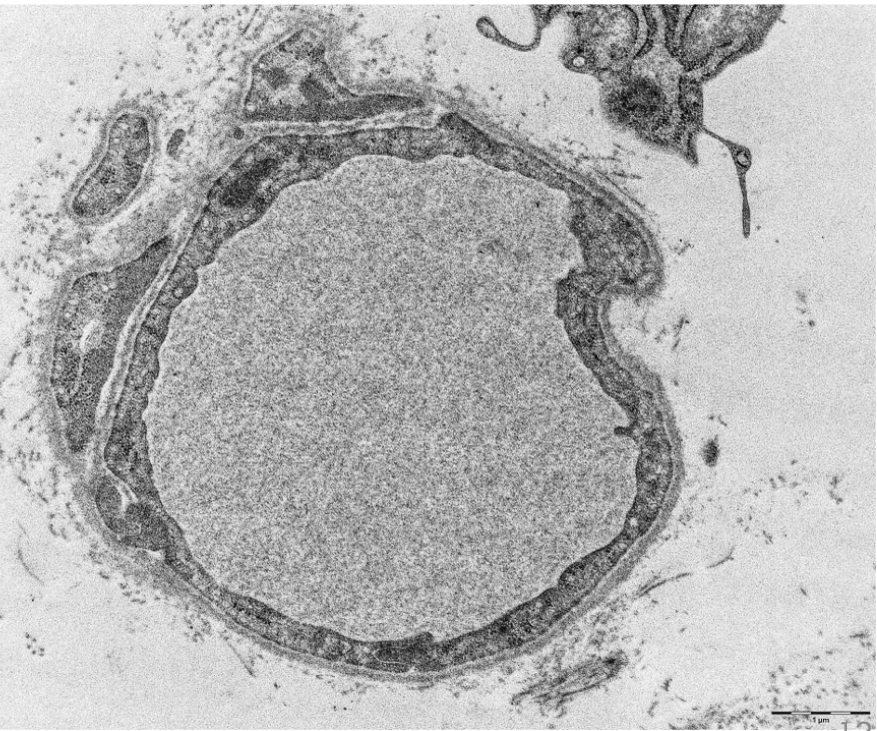
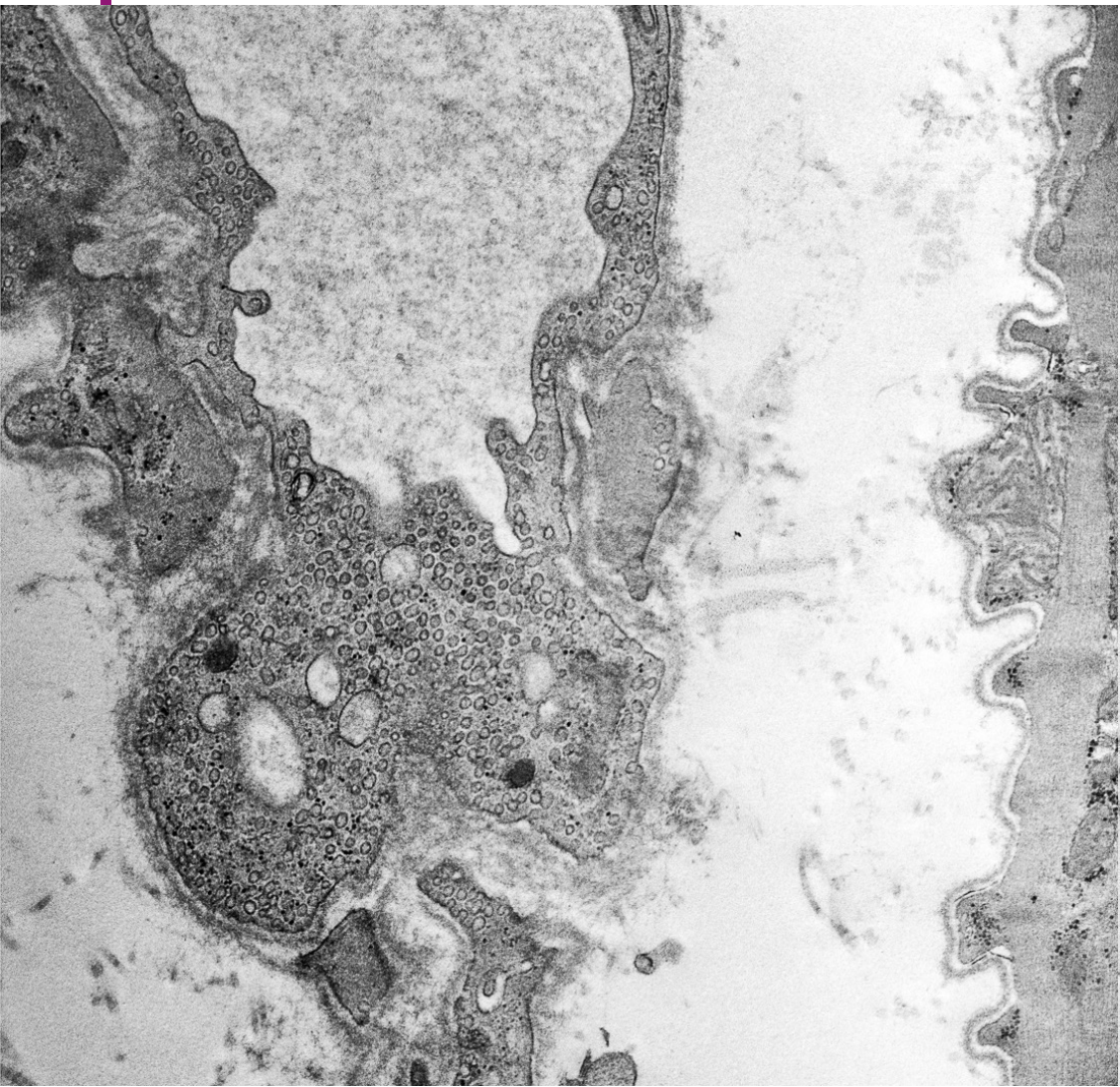
Endothelial cell abnormalities



Capillaries from healthy controls



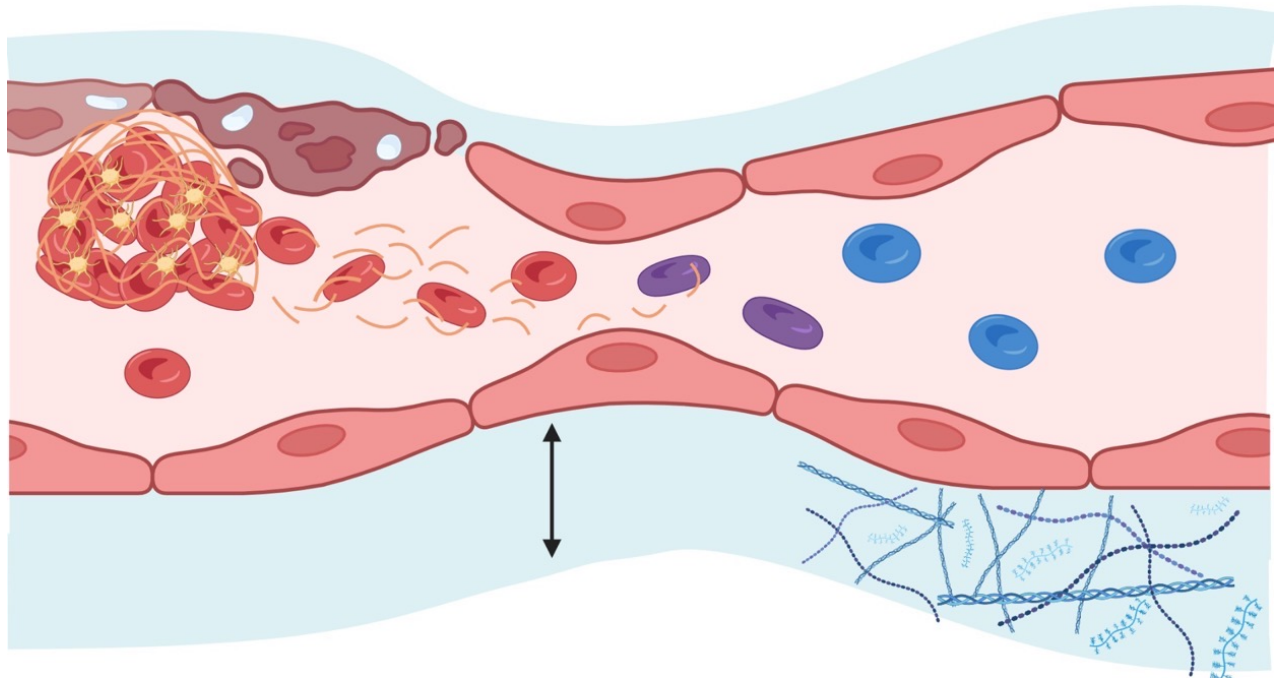
Endothelial cell abnormalities



Microvascular dysfunction in long COVID & ME/CFS

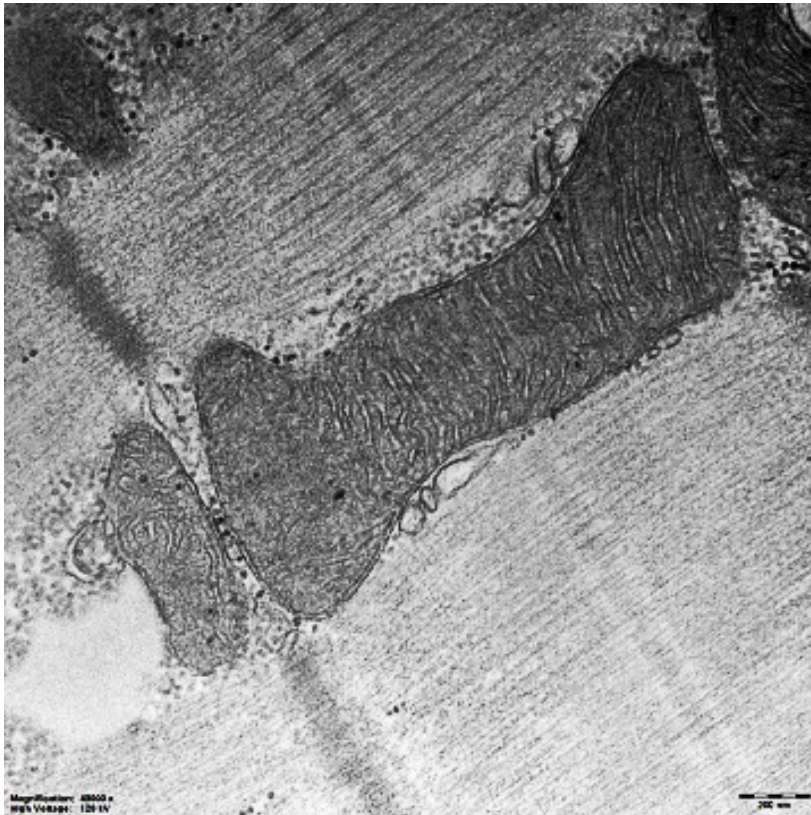
- Reduced lumen space
- Endothelial activation & dysfunction
- Basement membrane thickening

↓ metabolite removal & O₂ and nutrient delivery, predisposing to fatigue

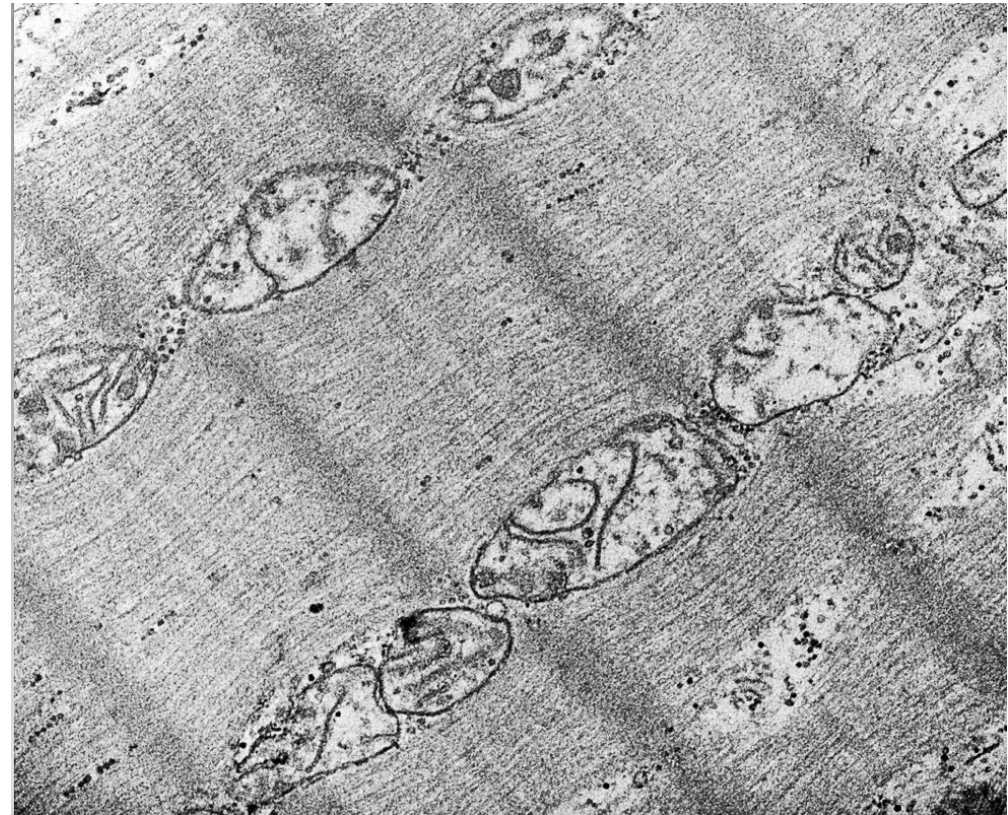


We are currently looking for collaborators with skeletal muscle biopsies for validation

Electron microscopy: Abnormal mitochondrial cristae structures in Long COVID



Healthy mitochondria



Long COVID

Take home messages

- Many patients with Long COVID (& ME/CFS) suffer from post-exertional malaise, where symptoms worsen with exercise
- Do not use terms like “exertional dyspnea” or “fatigue” when meaning PEM
- **Exercise above PEM threshold is counter-productive for recovery. This threshold is patient- and time-dependent**
- Distinct factors contributing to reduced exercise capacity (“fatigue”) and others to PEM -> Underlying X-factor unknown
- Skeletal muscle alterations after strict bed rest are different from post-viral diseases
- Microvascular adaptations might be valuable for diagnostics

Acknowledgements



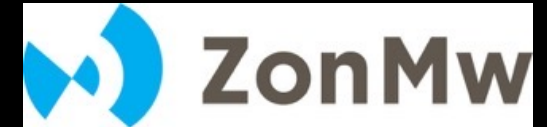
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David Systrom



Jaarcampagne VUfonds

And all patients and participants

