nature communications

Matters arising

https://doi.org/10.1038/s41467-025-56431-7

Reply: Muscle abnormalities in Long COVID

Received: 27 April 2024

Accepted: 18 January 2025

Published online: 11 February 2025

Check for updates

B. Appelman[1,2,15], B. T. Charlton[3,4,15], R. P. Goulding[3,4], T. J. Kerkhoff[3,4,5,6], E. A. Breedveld[3,4], W. Noort[3,4], C. Offringa[3,4], F. W. Bloemers[4,7], M. van Weeghel[8], B. V. Schomakers[8], P. Coelho[9,10,11], J. J. Posthuma[7,12], E. Aronica[11], W. J. Wiersinga[1,2,13], M. van Vugt[2,14,15] ✉ & R. C. I. Wüst[3,4,15] ✉

REPLYING TO B. Ranque et al. *Nature Communications* https://doi.org/10.1038/s41467-025-56430-8 (2025)

We thank Ranque et al. for their interest in our recent work and alternative interpretation of our data. We refute that our findings are due to deconditioning, as Long COVID-related skeletal muscle differ fundamentally from those caused by deconditioning. We demonstrated significant physiological differences in Long COVID patients with post-exertional malaise (PEM) compared to healthy controls, even at matched physical activity levels. PEM encompasses a variety of symptoms and not only muscle soreness. Our study did not address the efficacy of exercise training, and we reject misinterpretations that all forms of exercise cause PEM. We advocate further research to define safe exercise thresholds and improve the understanding of PEM.

Ranque et al. state that "everyone can experience severe muscle pain when returning to intense exercise after periods of a few weeks of rest". Every participant experienced maximal exercise, healthy participants with low fitness also participated, and a proportion of Long COVID patients still possessed fitness levels >50th percentile for their respective sex and age, despite all patients experiencing PEM. Despite several controls having a $\dot{V}O_{2\,max}$ similar to patients, none reported PEM symptoms.

We acknowledge the general population experiences muscle soreness, particularly after eccentric contractions, but cycle exercise involves little or no eccentric work. PEM encompasses more than muscle pain, and as can be appreciated from our clinical evaluation in Table 2, we do not reduce PEM to muscle pain or fatigue alone. We also do not link PEM symptoms and duration described in Long COVID with post-exercise symptoms of known inflammatory myopathies, metabolic, or mitochondrial disorders, as PEM is a symptom specific to post-infectious diseases[1]. We utilized the DSQ-PEM questionnaire for the clinical definition of PEM, as is common practice[2]. Contrary to the assertion of Ranque et al., Long COVID patients reported more muscle or joint pain (64% before and 80% 1-day after PEM induction) and significantly greater fatigue intensity (self-reported and with the Multidimensional Fatigue Inventory; Table 2 and Fig. S2A). Ranque et al. refer to pivotal work by Walitt and colleagues[3] to substantiate a psychological explanation of PEM, while the study rather provides multiple physiological explanations for ME/CFS pathophysiology, including autonomic dysfunction, differential cerebrospinal fluid catecholamines and metabolite profiles, and lower post-exercise cortisol responses. Ranque et al. claim that "post-exercise symptoms could result from the interaction between altered [..] unconscious self-awareness of internal bodily state [... and] failure of stress adaptation with perceived burden that influences how current and future energy needs are maintained", however Wallit et al. state that "peak measures did not correlate with effort preference in ME/CFS", refuting the claim that effort preference dictates $\dot{V}O_{2\,max}$. Importantly, this paper also confirms our findings of lower $\dot{V}O_{2\,max}$ and impairments in skeletal muscle mitochondrial metabolism, albeit in ME/CFS patients[3]. That our Long COVID patients also exhibited significantly lower gas exchange thresholds and respiratory compensation points, which are effort-independent, indicates a reduction in aerobic function that is not effort-independent.

Ranque et al. state that we did not provide an adequate control group and that the observed changes could be due to deconditioning. While we recognize that a full age-, sex- and activity-matched control group would have improved the quality of the study, we disagree that

[1]Center for Infection and Molecular Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [2]Amsterdam Institute for Infection and Immunity, Amsterdam, The Netherlands. [3]Department of Human Movement Sciences, Faculty of Behavioral and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. [4]Amsterdam Movement Sciences, Amsterdam, The Netherlands. [5]Department of Physiology, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. [6]Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands. [7]Department of Trauma Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [8]Core Facility Metabolomics, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [9]Departamento de Neurociências e Saúde Mental, Hospital de Santa Maria, CHULN, Lisbon, Portugal. [10]Centro de Estudos Egas Moniz, Faculdade de Medicina, University of Lisbon, Lisbon, Portugal. [11]Department of (Neuro)pathology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [12]Division of Surgery, Flevoziekenhuis, Almere, The Netherlands. [13]Department of Internal Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [14]Division of Infectious Diseases, Tropical Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands. [15]These authors contributed equally: B. Appelman, B. T. Charlton, M. van Vugt, R. C. I. Wüst. ✉e-mail: m.vanvugt@amsterdamumc.nl; r.wust@vu.nl

deconditioning alone explains these results. The skeletal muscle alterations observed in our Long COVID group display marked differences compared to healthy humans undergoing strict bed rest[4–6]. We found no differences in either capillarization or fibre cross-sectional area between Long COVID patients and healthy controls. Conversely, bed rest rapidly induces muscle atrophy, reduces capillary density, and alters mitochondrial structure and function within days[4,7,8]. Further, skeletal muscle intrinsic mitochondrial function was reduced in Long COVID patients compared to healthy controls (Fig. S5), indicative of qualitative alterations in mitochondrial respiration, rather than loss of mitochondrial content typically observed with bed rest[4]. While step reduction alters muscle substantially[9,10], this is typically associated with reductions in fibre cross-sectional area and reduced mitochondrial markers, which (at baseline) was not observed in Long COVID patients. We performed additional analyses on our publicly available data file and matched participants by step count (5181 *vs.* 4727 steps/day for patients and controls, respectively). In this small, but matched cohort, we still observed a significant group difference for $\dot{V}O_{2\,max}$ (−24%, $p = 0.004$) and peak power output (−31%, $p = 0.043$). Althoff et al. indicated that the daily steps in the United States were 4774 steps/day[11]; therefore, our cohort, while likely less active than prior to infection, were not less active than expected in the general USA population. Yet, Long COVID patients presented with abnormal histopathology even prior to the exercise bout - also confirmed by others[12,13] - while our less aerobically fit, healthy controls exhibited little to no abnormal histopathology (see source data). These differences in skeletal muscle characteristics between Long COVID and human bed rest studies imply that the effect of Long COVID on skeletal muscle structure and function fundamentally differs from that of deconditioning alone. While we cannot neglect that deconditioning may impact Long COVID progression, the evidence provided suggests deconditioning itself does not fully explain symptoms experienced by Long COVID patients with PEM.

Long COVID is reported to be a heterogeneous disease, which is why we chose to focus on PEM, as ~90% of patients present with this symptom[14]. We recognize our results only pertain to those experiencing PEM. While we acknowledge that Long COVID patients without PEM were not included as a control group, the study was designed to use acute exercise to induce PEM and measure systemic changes before and after PEM induction. We therefore disagree that we cannot link the acute exercise mediated alterations of Long COVID patients to PEM[14]. Our findings demonstrated physiological alterations in Long COVID patients with PEM after maximal exercise that did not occur in healthy controls, whom do not experience PEM. PEM research is still in its infancy, and we will applaud studies with well-defined cohorts and experimental designs that can provide additional insights into PEM pathophysiology.

Ranque et al. suggest that many patients have reported full recovery in ME/CFS, despite experiencing PEM; however, the meta-analysis cited[15] concludes that while exercise provided a small positive effect, quality of life did not improve. Further, multiple studies included in the meta-analysis include participants with other comorbidities that would benefit from exercise (i.e., asthma, diabetes, chronic heart disease). Ranque et al. also refer to several other studies that have shown successful rehabilitation of patients, however, these studies also include up to ~30% of patients exhibiting other comorbidities[16–18]. One strength of our current study is that patients did not exhibit other comorbidities that may conflate with Long COVID.

Ranque et al. state that our "findings have been widely interpreted in the media as indicating that exercise in people with Long COVID causes muscle damage and implying that people with Long COVID should not exercise", but simultaneously agree "that intense exercise, such as the one tested in the study, is not recommended", albeit without providing argumentation. While we speculate that PEM could result in fear of exercising at intensities above the PEM threshold, this was not the focus of our research, and feel this critique does not pertain to our publication. We appreciate that frequency, intensity, and duration are vital in improving aerobic fitness in healthy individuals[19], and positively modulate many chronic diseases. However, Long COVID and PEM are poorly understood, and our study did not address the efficacy or advisability of exercise training in Long COVID treatment. Further, we find there is a dearth of high-quality scientific information surrounding dedicated exercise training in Long COVID patients, and disagree with the standard of evidence surrounding graded exercise therapy. In the training studies cited, none involved interventions that systematically induced, monitored, or avoided PEM. Additionally, adherence and other comorbidities are often ill-described. While exercise below the PEM-inducing threshold may benefit Long COVID patients, this was not the topic of our current publication, and therefore we refrained from conclusive scientific or clinical statements. Given our clinical experience and scientific evidence, we advocate caution regarding intense exercise in Long COVID patients with PEM. While pacing and moderate exercise below he PEM-inducing threshold may be performed, these thresholds are ill-defined and more research is needed to elucidate the physiological onset of PEM.

References

1. Poenaru, S., Abdallah, S. J., Corrales-Medina, V. & Cowan, J. COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. *Ther. Adv. Infect. Dis.* **8**, 20499361211009384 (2021).
2. Cotler, J., Holtzman, C., Dudun, C. & Jason, L. A. A brief questionnaire to assess post-exertional malaise. *Diagnostics* **8**, 66 (2018).
3. Walitt, B. et al. Deep phenotyping of post-infectious myalgic encephalomyelitis/chronic fatigue syndrome. *Nat. Commun.* **15**, 907 (2024).
4. Eggelbusch, M. et al. The impact of bed rest on human skeletal muscle metabolism. *Cell Rep. Med.* **5**, 101372 (2024).
5. Soares, M. N. et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J. Cachexia Sarcopenia Muscle* **13**, 11–22 (2022).
6. Charlton, B. T. et al. Skeletal muscle adaptations and post-exertional malaise in long COVID. Trends Endocrinol Metab. https://doi.org/10.1016/j.tem.2024.11.008 (2024). Epub ahead of print
7. Hendrickse, P. W. et al. Capillary rarefaction during bed rest is proportionally less than fibre atrophy and loss of oxidative capacity. *J. Cachexia Sarcopenia Muscle* **13**, 2712–2723 (2022).
8. Hyatt, H. W. & Powers, S. K. Mitochondrial dysfunction is a common denominator linking skeletal muscle wasting due to disease, aging, and prolonged inactivity. *Antioxidants* **10**, 588 (2021).
9. Narici, M. et al. Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. *Eur. J. Sport Sci.* **21**, 614–635 (2021).
10. Edwards, S. J. et al. Short-term step reduction reduces citrate synthase activity without altering skeletal muscle markers of oxidative metabolism or insulin-mediated signaling in young males. *J. Appl Physiol.* **131**, 1653–1662 (2021).
11. Althoff, T. et al. Large-scale physical activity data reveal worldwide activity inequality. *Nature* **547**, 336 (2017).
12. Hejbøl, E. K. et al. Myopathy as a cause of fatigue in long-term post-COVID-19 symptoms: evidence of skeletal muscle histopathology. *Eur. J. Neurol.* **29**, 2832–2841 (2022).
13. Colosio, M. et al. Structural and functional impairments of skeletal muscle in patients with postacute sequelae of SARS-CoV-2 infection. *J. Appl. Physiol.* **135**, 902–917 (2023).

14. Thaweethai, T. et al. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA* **329**, 1934–1946 (2023).
15. Larun, L., Brurberg, K. G., Odgaard-Jensen, J. & Price, J. R. Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Syst. Rev.* https://doi.org/10.1002/14651858.CD003200.pub7 (2017).
16. McGregor, G. et al. Clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-covid-19 condition (REGAIN study): multicentre randomised controlled trial. *BMJ* e076506 https://doi.org/10.1136/bmj-2023-076506 (2024).
17. Espinoza-Bravo, C. et al. Effectiveness of functional or aerobic exercise combined with breathing techniques in telerehabilitation for patients with Long COVID: a randomized controlled trial. *Phys. Ther.* **103**, pzad118 (2023).
18. Jimeno-Almazán, A. et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. *Scand. J. Med Sci. Sports* **32**, 1791–1801 (2022).
19. Holloszy, J. O. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J. Biol. Chem.* **242**, 2278–2282 (1967).

Author contributions

B.A., B.T.C., R.P.G., and R.C.I.W. drafted the response. B.A., B.T.C., R.P.G., T.J.K., E.A.B., W.N., C.O., F.W.B., M.v.W., B.S., P.C., J.J.P., E.A., W.J.W., M.v.V. and R.C.I.W. critically reviewed and accepted the final version.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M. van Vugt or R. C. I. Wüst.

Peer review information *Nature Communications* thanks David Poole and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.