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Graded exercise therapy should not be recommended for patients with post-exertional malaise

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We read with great interest the Review by Fedorowski et al. (A. Fedorowski et al. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-023-00962-3 (2024))[1]. The authors provide a timely overview of the aetiology and clinical management of cardiovascular autonomic dysfunction (CVAD) in patients with long COVID (also known as post-COVID-19 syndrome). As clinicians involved in the care of, and research into, patients with long COVID, we endorse the statement that the recognition of CVAD is essential to the adequate management of long COVID. However, we cannot agree with the recommendations for graded exercise therapy for people living with long COVID who have post-exertional malaise.

Post-exertional malaise is a constellation of disabling signs and symptoms, which mainly begin after physical and cognitive exertion[2]. Post-exertional malaise is characterized by a delayed onset after exertion, and the period of recovery from exacerbations of post-exertional malaise can be prolonged and can severely limit daily functioning[2]. Post-exertional malaise is considered a hallmark of other syndromes commonly associated with infection, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Up to 85% of chronically and severely ill people living with long COVID can have a combination of post-exertional malaise and CVAD[3].

In their Review[1], the authors suggest graded exercise therapy for patients with post-exertional malaise based on the PACE trial, which reported positive effects of a combined intervention with graded exercise therapy and cognitive behavioural therapy in patients with ME/CFS. However, the results of this trial have been called into question owing to substantial protocol deviations and retrospective adjustment of the criteria used to define recovery. A post hoc, per-protocol reanalysis of the trial data showed that the combination of cognitive behavioural therapy and graded exercise therapy was ineffective[4]. Contemporary clinical guidelines for ME/CFS now advise against graded exercise therapy as a treatment and suggest just a supportive role for cognitive behavioural therapy[2].

The only studies that describe positive responses of people living with long COVID to cognitive behavioural therapy and graded exercise therapy either did not include patients with post-exertional malaise or did not account for post-exertional malaise[5]. On the contrary, exercise-based therapies often lead to negative health effects in patients with ME/CFS, especially when modern, more-accurate diagnostic criteria for post-exertional malaise are applied[6]. This finding was also demonstrated in a cross-sectional study of 477 people living with long COVID, in which 75% of participants reported symptomatic and functional deterioration after following recommendations to exercise[7].

Knowledge about the underlying pathophysiological mechanisms of post-exertional malaise is rapidly evolving in people living with long COVID[3]. Landmark research showed that exercise in people living with long COVID is significantly associated with abnormal immune and metabolic responses to exercise in skeletal muscle compared with healthy control participants[8]. Therefore, graded exercise therapy should not be recommended for people living with long COVID and post-exertional malaise.

Some people living with long COVID and CVAD do not have post-exertional malaise, so the exercise recommendations in the Review[1] can safely be followed for these individuals[9]. However, people living with long COVID and post-exertional malaise must be supported in keeping daily activities within their available fund of energy or 'energy envelope'[10]. We advise a 'do no harm' approach. All people living with long COVID and CVAD should be assessed for post-exertional malaise. People living with long COVID without post-exertional malaise can be guided towards exercise approaches that might improve autonomic responses, while continuing to monitor them for a potential emergence of post-exertional malaise. Graded exercise therapy should be avoided in people living with long COVID and post-exertional malaise, and these individuals should be managed using the remaining non-pharmacological and pharmacological interventions outlined in the otherwise-helpful Review[1].

There is a reply to this letter by Fedorowski, A. et al. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-024-00994-3 (2024).

Femke Christina Ching-Chuan van Rhijn-Brouwer[1] ✉, Merel Hellemons[2], Michael Stingl[3], Kathryn Hoffmann[4], Joanne VanDerNagel[5], Todd E. Davenport[6], Eva Untersmayr[7], Carmen Scheibenbogen[8] & David Putrino[9]

[1]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, Netherlands. [2]Department of Pulmonary Medicine, Erasmus University Medical Center, Rotterdam, Netherlands. [3]Facharztzentrum Votivpark, Vienna, Austria. [4]Department of Primary Care Medicine, Medical University of Vienna, Vienna, Austria. [5]Department of Human Media Interaction, University of Twente, Enschede, Netherlands. [6]Department of Physical Therapy, School of Health Sciences, University of the Pacific, Stockton, CA, USA. [7]Institute of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria. [8]Institute of Medical Immunology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [9]Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
✉e-mail: fccbrouwer@gmail.com

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Competing interests
F.C.C.-C.v.R.-B. and J.V. have not been practising medicine since March 2022 owing to long COVID. The other authors declare no competing interests.