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Altered effort and deconditioning are not valid explanations of myalgic encephalomyelitis/chronic fatigue syndrome

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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, systemic disease with significant pathophysiological uncertainties and variable presentations[1]. Here, we challenge Walitt et al.'s[2] conclusion that post-infectious (PI) ME/CFS is a disorder defined by altered effort preference, leading to activity avoidance and subsequent deconditioning. We believe this interpretation risks reinforcing skepticism about the serious biological nature of ME/CFS and its hallmark of post-exertional malaise (PEM), as well as its potential misclassification as a mental health condition.

Walitt et al.[2] utilized a single CPET to evaluate systems-level physiological responses to exercise. However, this methodology does not allow for measuring responses after an initial exertion, which is critically important for fully understanding PEM[3]. Over the past two decades, 2-day CPET has been used to characterize the systems-level metabolism of ME/CFS[3]. This paradigm uses an initial maximal CPET to establish the individual's baseline performance and as a participant-referenced method to induce PEM[4]. A second maximal CPET is then conducted 24 h later to measure physiological and perceptual responses to exercise during the post-exertional state[4]. Standard objective criteria to evaluate effort are used to ensure maximal testing, including the respiratory exchange ratio at peak exertion[4]. This removes uncertainty related to effort. Meta-analyses involving participants with ME/CFS who have completed 2-day CPET indicate characteristic declines in the volume of oxygen consumed, work rate, and heart rate (HR) at submaximal exertion on the second CPET. These findings are reliably observed in people with ME/CFS but not deconditioned individuals[5–7]. Accordingly, the Institute of Medicine (IOM) cautioned that "a single CPET may be insufficient to document the abnormal response of ME/CFS patients to exercise."[1] (p. 106)

Using a single CPET introduces a threat to validity in Walitt et al.'s study[2], as it did not allow for the measurement of submaximal performance decrement in the post-exertional state[1,3–6]. This is important because deconditioning and PEM are not mutually exclusive. Special care must be taken when applying and interpreting CPET results[1]. Failure to use 2-day CPET prevented the authors from adequately testing their conclusion that PEM is related to participants' effort preference, as they did not evaluate physiological performance under conditions involving objective, standardized criteria for maximal exertion. Unfortunately, the use of a single CPET in this study contributed to the authors' misinterpretation that PEM is synonymous with reduced effort and deconditioning.

A common concern with CPET in ME/CFS research is the burden of PEM on participants. According to public comments, Walitt et al.[2] opted for a one-day CPET to reduce this burden[8]. However, risks must be balanced with the potential to generate valuable scientific knowledge for the broader society. The central benefit of 2-day CPET is providing valid, reliable data regarding PEM that cannot be obtained with one-day CPET. Given the controlled setting, Walitt et al.[2] could have explored and even mitigated the effects of PEM systematically to ensure all participants received the same procedure.

Furthermore, the study samples were not adequately matched using deconditioned control participants, which would be necessary to

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differentiate the effects of PI-ME/CFS from deconditioning. Healthy volunteers in this study demonstrated no cardiorespiratory impairment, but participants with PI-ME/CFS demonstrated a moderate to severe level of impairment[9]. Even the HR data from this study do not fully support the authors' hypothesis of deconditioning as a key driver of fatigue, because exercise HR was lower in people with PI-ME/CFS compared to healthy volunteers, whereas we would typically expect elevated HR in deconditioning[10,11]. Rather than supporting an 'effort preference and deconditioning' hypothesis, these data appear consistent with impaired oxidative metabolism and chronotropic incompetence—commonly observed in this population—which limit energy production and utilization and are key drivers of PEM.

Walitt et al.[2] characterized PEM as discomfort associated with exertion (p. 2) and the description of patients' behavioral adjustments as attempts to avoid discomfort (p. 10), which appears to downplay the severity of PEM. For individuals with ME/CFS, PEM is not merely discomfort. Rather, it involves a profound exacerbation of a whole host of signs and symptoms, further reduction in functioning, and inability to recover following even minor physical or cognitive exertion[1,12]. The 2015 IOM report proposed renaming the illness to systemic exertion intolerance disease to underscore the central importance of PEM, the worsening of symptoms and physical functioning after physical, cognitive, or emotional effort, and how it can lead to significant impairment[1,13]. The authors' characterization of PEM risks provides additional justification for clinicians, researchers, and policymakers to discount its severe and life-altering effects.

Walitt et al.[2] used the Effort-Expenditure for Rewards Task instrument[14], which has not previously been validated in participants with ME/CFS. This test requires all participants to be equally able to complete the test without becoming fatigued[15]. The increasing effect of PEM in participants with PI-ME/CFS during the test, because of the test itself, could impact the results and interpretation. Although the authors clearly stated that patients did not meet psychiatric diagnostic criteria, their framing of effort preference as the physiological basis of fatigue in PI-ME/CFS misattributes their symptoms to psychological and motivational factors. Walitt et al. also suggested participants with PI-ME/CFS uniquely received "strong encouragement"[2] (p.10) to achieve maximal criteria on the CPET tasks. It is standard practice in CPET to provide strong encouragement to all participants during the task[16], so the authors' statement may be misleadingly interpreted as supporting their conclusion that effort preference is a key driver of PEM. It is crucial that this study accurately notes the physiological basis of these symptoms to avoid reinforcing stigmas that have long been associated with this disease.

We are concerned that the analyses in this study are underpowered and lack ecological validity. Discrepancies between the findings of this study and other important ME/CFS studies[17–20] suggest that at least some of the participants with PI-ME/CFS may have had the mildest form of the disease or may represent a distinct clinical subgroup. Of the relatively small total sample size, only 8 PI-ME/CFS participants and 9 healthy volunteers undertook CPET. The detail that not all participants received all the outcome measures in the same order was omitted from the abstract and buried within the methods, where it may be overlooked. Yet, causal inference depicted in Figure 10 might lead a reader to conclude that all participants received the outcome measurements in the same order and prior exertion was carefully controlled. Prominently designating this project as a pilot or feasibility study could help clarify the scope and limitations of its findings.

Precisely identifying and evaluating PEM and its associated physiological underpinnings and biomarkers is vital for advancing the understanding and treatment of ME/CFS. Research communications must convey the legitimacy of ME/CFS as a medical disease and foster the development of future interventions. Considering these concerns, we urge the interpretation and dissemination of these findings with utmost caution, ensuring that they accurately reflect the complex and debilitating nature of ME/CFS[1].

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Author contributions

All authors drafted the manuscript, contributed to the revision, and editing of the manuscript.

Competing interests

The authors declare no competing interests.

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