

A Clearer Definition of PEM: *Why It Matters for Everyone*



Naomi D. Harvey,¹ Harriet A. Carroll^{2,3}, Ciara Wright⁴, Todd Davenport⁵
¹ Independent researcher ² Lund University, Malmö, Sweden ³ Long Covid Scientific Consultancy, Aberdeen, UK
⁴ Positive Nutrition, Dublin, Ireland ⁵ Department of Physical Therapy, School of Health Sciences, University of the Pacific, Stockton, CA, USA



The statement: PEM is the defining feature and is unique to Myalgic Encephalomyelitis ME/CFS

Myalgic encephalomyelitis or ME/CFS is commonly characterised with four main features:

- o profound fatigue
- o unrefreshing sleep
- o cognitive impairments
- o post-exertional malaise (PEM)

(NICE, 2021)

But PEM is the defining feature of ME/CFS and is unique to ME/CFS

Introduction

History: The Origins of Post-Exertional Malaise (PEM)
Post-exertional malaise (PEM) as the hallmark symptom of ME/CFS has been recognised since the earliest descriptions of the disease. Following the 1955 Royal Free Hospital outbreak, Dr. Melvin Ramsay identified **prolonged muscle fatigability and delayed recovery after exertion** as the **defining feature of the illness**, describing recovery as taking **three to five days or longer**. He considered this feature essential for diagnosis.

PEM is synonymous with PENE
While **PEM** is the most widely used term in research and by the patient community, many patients feel that *malaise* does not adequately reflect the severity of their symptoms. Additionally, in ME/CFS, *exertion* refers not only to exercise but also to physical, cognitive, emotional, sensory, or social activity, which may provoke a disproportionate worsening of symptoms, even after minimal effort. The **International Consensus Criteria (2011)** proposed the alternative term **post-exertional neuroimmune exhaustion (PENE)** to emphasise the multisystem nature of this response; however, **PEM** is the most commonly used term in the ME literature worldwide and is well-established within the patient community.

PEM = PENE

Measuring PEM by Cardiopulmonary Exercise Testing



Day 1 CPET
Target: reach maximum effort and exhaust anaerobic capacity



Day 2 CPET
Repeat Day 1 protocol
Inability to reproduce Day 1 aerobic performance

Deconditioning versus PEM: Key Differences

- **Beyond normal recovery:** Symptoms such as brain fog, pain, and problems affecting multiple body systems last **for days to weeks**, rather than being just prolonged muscle soreness
- **Different from deconditioning:** **severe fatigue and additional systemic symptoms can start 12–48 hours later**, rather than only immediate tiredness after exercise

Limitations

- Inaccessible to most except patients with the mildest disease state
- Major risk of inducing PEM, prolonged recovery and permanent functional decline

The problem...

Despite being the hallmark symptom of ME/CFS, **PEM is frequently misrepresented and inconsistently defined** in both research and clinical practice.
PEM is increasingly conflated with post-exertional symptom exacerbation (PESE) which describes symptom worsening in a range of fatigue-related conditions, despite important differences in its characteristics, severity, recovery profile, and objectively measurable changes.

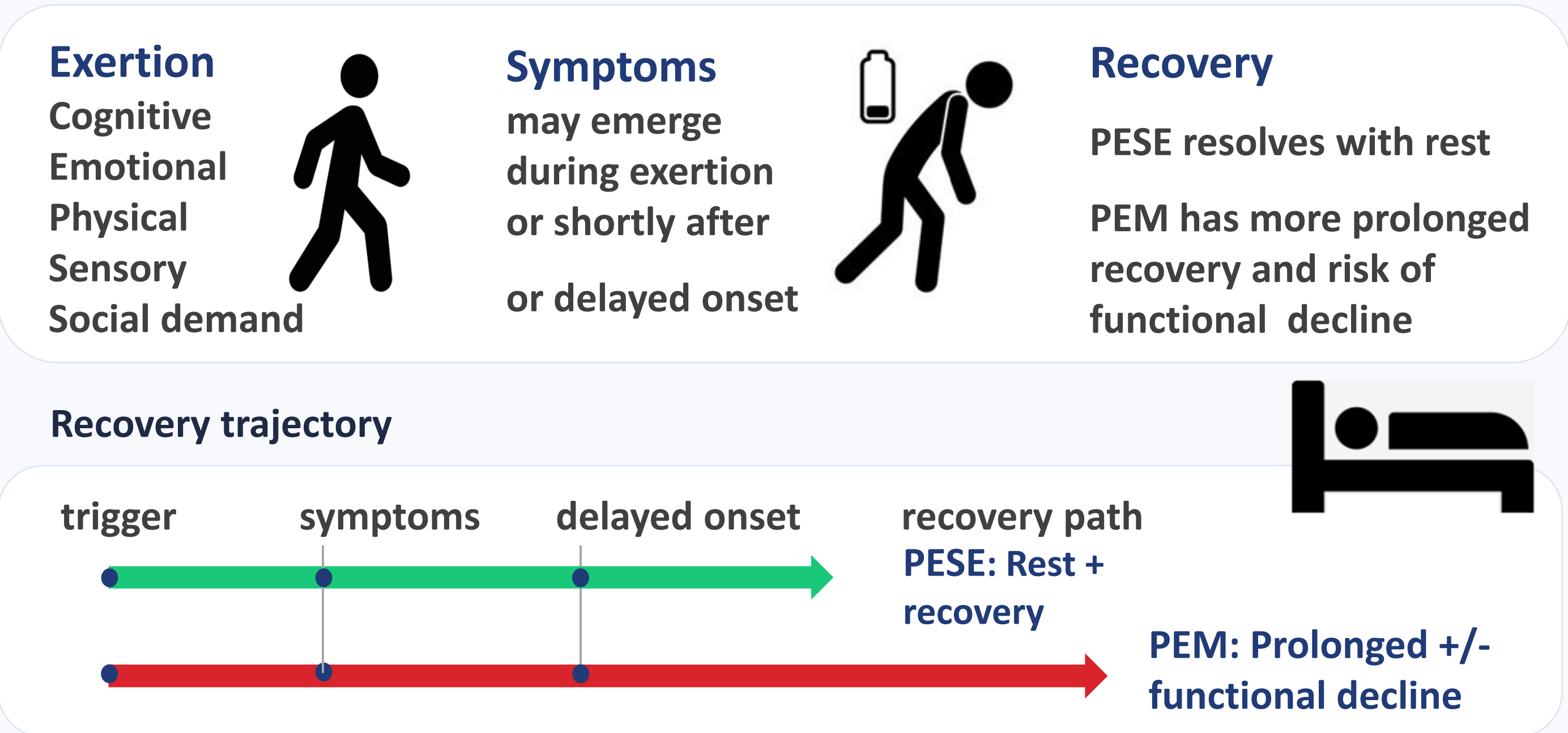
Research definitions often fail to capture true PEM, relying on broad fatigue measures (e.g., the Chalder Fatigue Questionnaire) or older diagnostic criteria (e.g., Fukuda, 1994) that do not require PEM for diagnosis. This has resulted in **heterogeneous study populations** and findings that are difficult to interpret or compare.

Poorly defined cohorts and inconsistent measurement of PEM have contributed to conflicting evidence, **limiting progress in understanding the pathophysiology of ME/CFS and the development of effective treatments**.

Misunderstanding PEM has contributed to **inappropriate clinical recommendations, including graded exercise therapy (GET)**, which can exacerbate symptoms and lead to prolonged deterioration in people with ME/CFS.

A clear, evidence-based definition of PEM is essential for accurate diagnosis, robust research, and safe clinical care

PESE ≠ PEM PESE ⊂ PEM



Typical Features	PESE	PEM
Extreme, out of proportion and rapid physical and/or cognitive fatiguability to minimal activities	✓	✓
Involve immediate symptom exacerbation following triggering exertion	✓	✓
Involve delayed symptom exacerbation following triggering exertion, by hours or days	✓	✓
Low threshold for triggering physical and mental fatiguability, to a substantial degree compared to pre-illness activity levels	✓	✓
Can be debilitating and cause a long lasting relapse of the patients condition reducing their baseline level of function	✗	✓
Recovery period is prolonged , always taking more than 24 hours but commonly lasting multiple days. It may take weeks, months or cause lasting decline.	✗	✓
Loss of function is such that the patient is unable to repeat the previous days triggering exertion to the same level, and additionally loses ability to function in other aspects of life	✗	✓
May also be triggered by cognitive exertion or other forms of exertion. The worsening of condition is systemic in nature, affecting multiple body systems, both physical and cognitive , irrespective of the trigger	✗	✓

Recommendations: Why it matters for EVERYONE

A clear, consistent definition of **PEM** is essential to improve research, clinical care, and outcomes across multiple health conditions

Screen for PEM routinely in both clinical practice and research

Use validated, PEM-specific outcome measures (e.g., **FUNCAP**) rather than generic fatigue scales

Define study populations accurately, ensuring people with ME/CFS are correctly identified and only included when appropriate (e.g., not all Long COVID cohorts)

Differentiate PEM from post-exertional symptom exacerbation (PESE) to support safe rehabilitation and ensure interventions such as graded exercise are applied only where appropriate

Provide evidence-based clinical advice that minimises the risk of PEM and functional decline

Improve healthcare experiences for people with ME/CFS and support informed care for families and carers

Improve research across fatigue-related conditions by distinguishing true PEM from other forms of post-exertional symptom worsening, enabling more accurate participant stratification, meaningful outcome measures, and the development of targeted treatments

A clearer definition of PEM benefits everyone - not only people with ME/CFS, but also clinicians, researchers, and patients with other fatigue-related conditions by improving diagnostic accuracy, research validity, and the safety of clinical care

References

1. NICE. *Myalgic encephalomyelitis (or encephalopathy) / chronic fatigue syndrome: Diagnosis and management*. 2021.
2. Ramsay AM. *Myalgic encephalomyelitis and postviral fatigue states: The saga of Royal Free disease*. London: Gower Medical Publishing; 1988.
3. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med*. 2011;270:327-338.
4. Davenport TE, Stevens SR, Stevens J, et al. Properties of measurements obtained during cardiopulmonary exercise testing in individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Work*. 2020;66:247-256. doi:10.3233/WOR-203170.