Proposed standardised disease criteria to facilitate ME/CFS research in adult populations

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Introduction

In the absence of biomarkers [1], well defined and commonly employed diagnostic criteria are critical to advance research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) [2][3]. Historically, lack of consensus and scepticism among the medical and allied professions has led to a paucity of research into ME/CFS and studies have been hampered by heterogeneous diagnostic criteria, selection bias, and small sample sizes [4], compounded by the lack of research funding for study validation [5]. Future studies will likely be further confounded by the inclusion of people with Long COVID labelled ME/CFS, when many of them may have concurrent organ damage or other non-ME/CFS related sequelae. Lack of commonly agreed inclusion criteria results in misclassification in research studies and the provision of inappropriate and occasionally harmful treatments [6].

The symptoms of ME/CFS point to multisystem impairments, which are common to other diseases (see Figure 1). As has been the case in some studies, broad clinical criteria can expand research study recruitment to include people mistakenly labelled as having ME/CFS [6]. When a treatment is offered to such an inclusive group, results can lead to erroneous conclusions around its benefit and other outcomes.
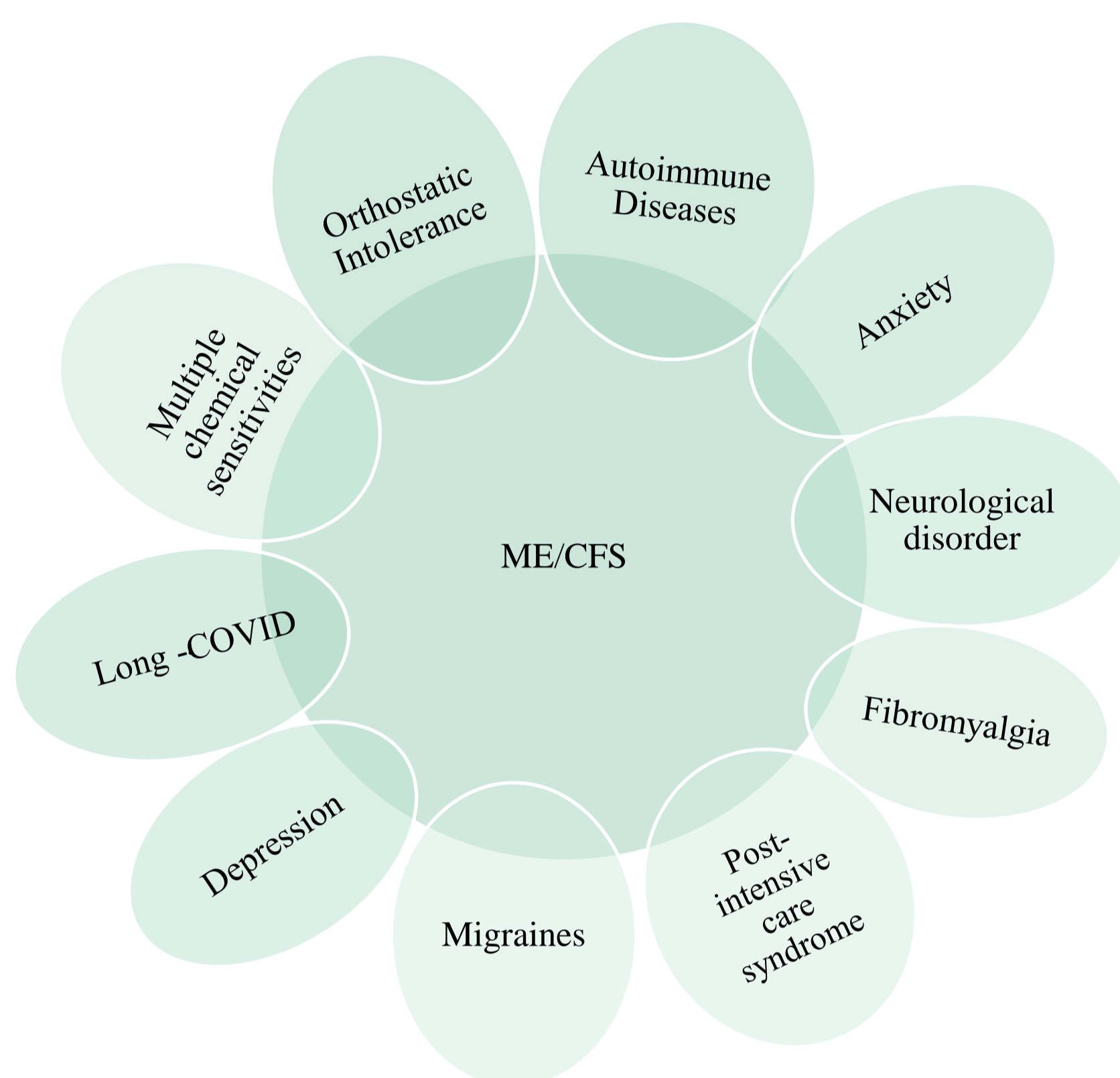

Figure 1 – Some diseases sharing symptoms with ME/CFS

In one survey [8], 95% of clinicians and researchers interviewed saw ME/CFS case definition as critical to research result comparability across studies. We propose that a requirement to meet common criteria would ensure such consistency in ME/CFS research.

Objectives

We aim: 1. to compare the consensus diagnostic criteria for ME/CFS recommended by the Mayo Clinic Proceedings (US) [9], the National Institute for Health and Care Excellence (NICE, UK) [10], and EUROMENE (Europe) [11] seeking consensus within the papers; 2. to elicit a set of required criteria for an ME/CFS research case definition to create homogeneity in the classification of individuals, and to identify co-morbid conditions which would exclude potential ME/CFS research participants.

Methods

We conducted a comparative analysis on the consensus diagnostic criteria recommended in the Mayo Clinic Proceedings (USA), The National Institute for Health and Care Excellence (NICE, UK), and EUROMENE (Europe); collectively considered were the Canadian Criteria, Institute of Medicine (IOM)/ National Academy of Medicine (NAM) [12,14], and the modified CDC-1994 [15]. We propose the common core symptoms identified in all three references as essential research diagnostic criteria for the recruitment of people with ME/CFS - aiming for specificity rather than inclusivity.

We also look to define conditions and diseases that are exclusionary for ME/CFS diagnosis by extrapolating from the three references considered; for heightened specificity, diseases considered exclusionary by any group have been included in the list.
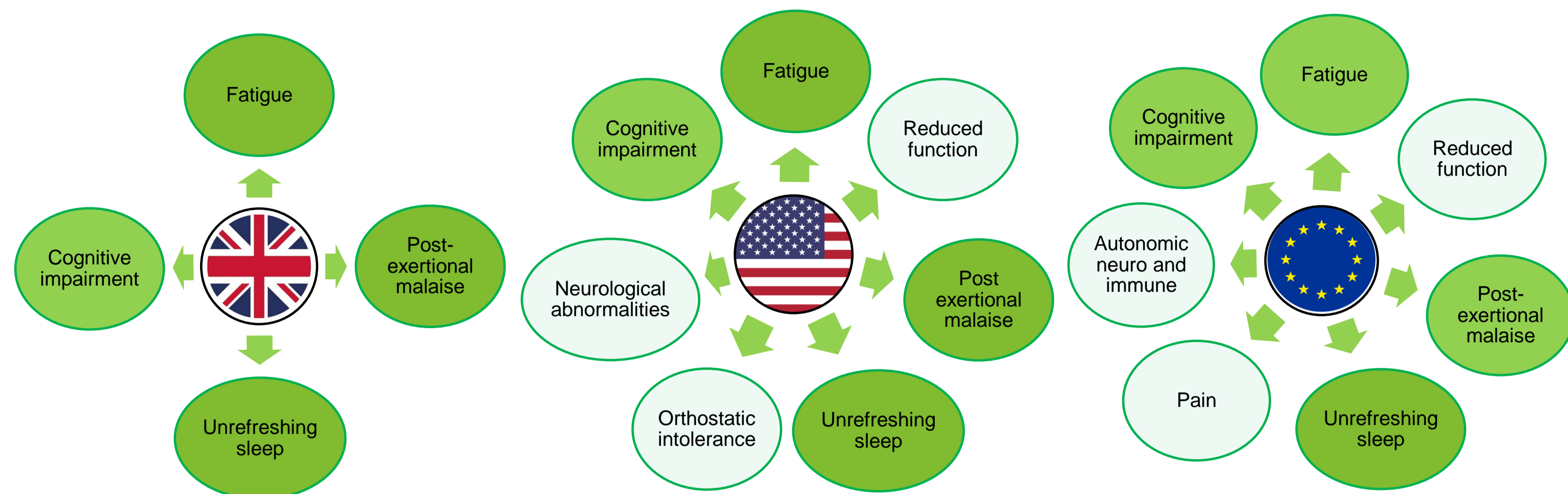
Results

Figure 2 – Core symptoms described in the three sources showing those required for diagnosis (in green)

We postulate that the key symptoms (in green-filled circles), i.e., fatigue, post-exertional malaise, unrefreshing sleep and cognitive impairment are necessary for ME/CFS diagnosis in research. Symptoms in the white-filled circles (pain, reduced function, neurological abnormalities, orthostatic intolerance, autonomic, immune) are significant but not critical to the recruitment of research participants with ME/CFS.

Conditions that may exclude ME/CFS	
• Active malignant disease • Auto-immune disease • Diabetes mellitus • Endocrine disorders • Heart disease • Hepatitis and liver disease • Illnesses related to toxic substance exposure • Infectious diseases including HIV/AIDS and TB • Inflammatory bowel diseases • Major psychiatric disease • Multiple sclerosis, and other neuro-immunological diseases	• Narcolepsy • Neurological injury and disease • Post-concussion syndrome, post-ICU syndrome (COVID-19) • Renal failure • Serious neurodegenerative diseases and stroke • Severe anaemia, haemochromatosis • Severe respiratory disease • Uncontrolled thyroid disease • Alcohol or substance abuse • BMI>40 • Pregnancy and lactation

For more detail, please consult EUROMENE [11], p11, Box 7

Table 1

ME/CFS Categories	Description
Mild	• Ability to maintain employment/study (even with reduced hours)
Moderate	• Restricted in all activities of daily living • Frequent periods of rest needed • Difficulties with mobility
Severe	• Virtually house-bound
Very severe	• Virtually bed-bound

Table 2

Discussion

Core symptoms and disease duration:
The proposed research criteria require that participants with ME/CFS have the four key symptoms observed across all three references: fatigue, post-exertional malaise, sleep dysfunction and cognitive impairment. Their suggested use in all studies involving people with ME/CFS could foster international homogeneity in their recruitment, which in turn would allow for better comparability and interpretation of treatment studies and could accelerate the search for a biomarker.

It has been accepted that clinical criteria and research criteria for ME/CFS do not have to be identical [16]; for instance, orthostatic intolerance may be critical in a clinical setting but need not be a prerequisite for ME/CFS case definition in research. Similarly, although it may be clinically important for people with ME/CFS to receive a diagnosis at 3 months, for research purposes a minimum symptom duration of **at least 6 months** is required to ensure that there is no error in the diagnosis.

Exclusion criteria:
The additional application of rigorous exclusion criteria is critical to prevent potential participants with other conditions or diseases that present with similar symptoms (see Figure 1) being inappropriately included in research studies as people with ME/CFS (misclassification bias).

Disease severity
Challenges in categorising the disease state of ME/CFS as mild or moderate stem from dynamic symptom fluctuation and the absence of clear boundaries between these two categories including the intermittent ability to work; this may make it difficult to rigidly classify patients as mild or moderate into distinct severity levels, particularly at the early stage of the disease. It is also important to acknowledge that the proposed research criteria may not incorporate adjustments for gender or age-related fluctuations.

Conclusion

We recommend that a universally accepted set of research criteria based on the four core symptoms would strengthen future research and serve to accelerate investigations into the aetiology and treatment of this complex and debilitating disease. Furthermore, the inclusion of specific exclusion criteria plays a vital role by eliminating confounding factors such as coexisting diseases that may impede our understanding of the underlying causes and mechanisms. Additionally, agreement around the subgrouping research participants with ME/CFS would enable better comparisons between research findings, which may result in a more comprehensive understanding of this disease, helping to unravel its multifaceted nature and pave the way for more targeted interventions.

References

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