The Stockholm Declaration

Response to Chronic fatigue syndromes: real illnesses that people can recover from, Scandinavian Journal of Primary Health Care, DOI: 10.1080/02813432.2023.2235609)

The authors initially claim that the current public narrative on severe, persistent fatigue conditions are "most commonly expressed by campaigners concerned with chronic fatigue syndrome (CFS/myalgic encephalomyelitis (ME/CFS)), but more recently by those writing about post-covid-19 condition". These "campaigners" include the Institute of Medicine and their 400-page review of ME/CFS[1] and the recent guidelines by the National Institute for Health and Care Excellence[2]. The prognosis of ME is not a question of "narratives" but of good, transparent, and reproducible empiric evaluation. The results of research are consistent, suggesting low rates of full recovery of between 5-10 % for adults[3-6].

In claiming a lack of specificity in the newer criteria including post exertional malaise (PEM) as a mandatory symptoms[2,7], the authors are unaware of recent research, finding lower thresholds for lactate production[8] and lower oxygen extraction[9] during exercise in ME/CFS-patients as contributors to ME/CFS exertional intolerance-and thus to PEM. Other publications have identified mitochondrial dysfunction to be a likely explanation for PEM[10] and have shown a correlation between severity and mitochondrial damage[10,11].

The authors propose an alternative explanation based on questionable scientific evidence that purports to offer realistic hope of improvement and recovery. This scientific evidence comprises a study in 19 female CFS patients and 21 normal healthy controls showing significant changes in a single measure of heart rate variability after cognitive therapy[12], and a study of long-term follow-up in children and young adults[13] that may have a much better prognosis. However, the latter study relies on limited data and is contradicted by a more recent and larger study[14]. Cognitive treatment plays a limited role in ME/CFS as pointed out in the NICE-guidelines[2]. In lumping patients with a diagnosis of ME/CFS in to one non-specific group of patients with fatigue clearly demonstrates the authors' limited clinical and scientific experience in ME/CFS and the

fact that several of the manifestations of this disease may be alleviated by targeted treatment[15-17].

The authors state that the approach often recommended by the public narrative of inactivity, isolation, and sensory deprivation, risks worsening symptoms and associated disability. Firstly, such a statement discloses the authors' lack of clinical experience with the range of severity and phenotypes in ME/CFS requiring modifications in the therapeutic approach. Secondly, it is an unsubstantiated claim (no references) and for the potential risks, the authors refer to a meta-analysis on bed rest as a primary treatment in conditions such as acute low back pain, preeclampsia, and myocardial infarction[15] and to an unpublished study on long-term sensory deprivation related to space flights[16]. Sensory deprivation is not a choice but a necessity in ME/CFS-patients due to the general increased sensitivity of the nervous system to afferent input secondary to neuro-inflammation. Symptoms of neuroinflammation are essential in the diagnosis of ME/CFS and different imaging techniques have shown neuroinflammation to be present in several studies[17,18] and that neuroinflammation is a common denominator in ME/CFS and long-COVID[19].

In the "Oslo Declaration's" justification for a new perspective, the authors refer to chronic pain, fibromyalgia, and post COVID syndrome for support, but recent advances do not support their narrative.

The "Oslo Declaration" is flawed, and the dismissal of biological evidence as non-specific associations is bewildering, with the authors seeking to replace it with a biopsychosocial model entirely based on associations. A recent study in fibromyalgia has demonstrated that patient autoantibodies mediate the sensory, motor, and anatomical symptoms and signs that patients present with[20]. Similarly, studies have revealed pathophysiological mechanisms including immune cell dysregulation and altered cortisol levels in post COVID patients[21]. The authors claim "After 40 years of research into CFS/ME … neither a specific biological defect or pathology, nor a specific biomarker, has been identified". It is estimated that at least 10,000 scientific papers have been published on ME/CFS and several distinct biological changes have been discovered resulting in targeted interventions and thorough descriptions of the pathobiology of ME/CFS[22,23]. In opposition to the vast amount of biopathological evidence, the authors refer to a publication where the initial part of the summary reads: "The basic assumption underlying the model presented here is that the brain makes sense of the internal state of the body by being sensitive to statistical regularities in its own neural activity"[24]. the publication title seems to state the validity

of this concept by “Taking the inferential leap” perhaps not knowing that inferring denotes either a conclusion based on known facts or the act of passing from statistical sample data to generalization. The authors fail to provide any of these.

Conclusion: The “Oslo Declaration” epitomises the dangers of extrapolating findings from a small under-powered, narrowly focused study with data from unrelated studies (disorders) to explain a complex multi-factorial disease comprising different clinical subtypes that ME/CFS represents. To quote the American literary critic HL Mencken: “For every complex problem there is an answer that is clear, simple, and wrong.”

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