

Recognition, research and respect: An agenda for change in ME

Executive summary

In this document we present a trans-national scientific position statement on Myalgic Encephalomyelitis (ME) that underpins the global advocacy led by the International Alliance for ME and affiliated individuals, and national professional organisations.

It builds on the national reports from the US (National Academy of Medicine¹, 2015), The Netherlands (The Health Council, 2018) and the global research scoping report in the UK (Radford & Chowdhury, 2016).

Our aims are three-fold:

1. To provide an overview of ME and the disease burden (pages 1 to 6)
2. To highlight barriers to progressing research in the ME field (pages 6 to 9)
3. To propose an agenda for change (page 9).

In doing so, we demonstrate why we are asking the World Health Organisation (WHO) to take leadership for people living with ME worldwide who continue to face poor access to healthcare and support. We ask the WHO to:

- recognise ME as a “serious, chronic, complex, and multisystem disease that frequently and dramatically limits the activities of affected patients” (National Academy of Medicine, 2015)
- produce a report that identifies current biomedical knowledge about ME and barriers to progress of recognition, research, clinical care and support
- adopt measures to address the barriers identified in the report below, providing a global and co-ordinated public health response to ME
- encourage the use of definitions that require hallmark symptoms of ME to increase the quality of biomedical research and expedite the process
- ensure that the disease continue to not be moved out of the neurological chapter of the ICD-11 until further research provides the scientific basis for that change.

This document is signed and supported by the individuals listed on page 10 onwards.

What is ME?

ME is a serious, chronic and fluctuating illness that affects many of the body’s systems causing debilitating symptoms that significantly impair an individual’s life. Diagnosing the disease remains a challenge and there are no approved treatments for ME. ME is a non-communicable disease and while the cause/s are yet unknown, in many cases, symptoms may be triggered by infection (National Academy of Medicine, 2015).

There remains a lack of consensus within the research and patient community with terms such as ME, CFS, ME/CFS and more recently, Systemic Exertion Intolerance Disorder (SEID). ME is not the same as chronic fatigue which is a symptom that occurs in a large number of

¹ Formerly known as Institutes of Medicine (IOM)

other illnesses. The term SEID was originally proposed in the US (National Academy of Medicine, 2015) but has not been adopted by the US government. For the purpose of this statement, the term ME has been used.

Who is affected?

ME is a global disease affecting people of all ages, and all socio-economic and ethnic backgrounds. It affects three to four times more women than men (National Academy of Medicine, 2015; Faro *et al*, 2015). The onset of the disease peaks at 10 to 19 years and 30 to 39 years (Bakken *et al*, 2014) with the average age of onset being 33 years (National Academy of Medicine, 2015). Although more people diagnosed are Caucasian, the illness may be more common in minority groups (Jason *et al*, 2011) and in lower socio-economic groups (Jason *et al*, 1999).

Incidence rates are not known to be routinely recorded in any country. As outlined below, there are variations in prevalence rates, which are expected due to differing study design and case definitions used (which do vary considerably). The rates vary significantly with an estimated prevalence of 0.1% using the Canadian² definition (Nacul *et al*, 2011b) 0.4 to 3.7% using the Oxford³ definition and 0.1 to 6.4% using the Fukuda⁴ definition (Brurberg *et al*, 2014). Furthermore, the International Consensus Criteria (Carruthers *et al*, 2011) notes that the US Centers for Disease Control and Prevention (CDC) prevalence estimates “increased tenfold” from 0.24% using the Fukuda criteria to 2.54% using the Reeves criteria.⁵

Variations in prevalence rates exist for children, although the above challenges are compounded by the use of self-report data and studies in which a child experienced fatigue only for three months or more. This means the prevalence rates are likely to be even less accurate than those for adults. Paediatric ME has been estimated by researchers in UK, The Netherlands and US populations with prevalence rates varying from 0.03% to 1.9% (Collin *et al*, 2016; Chalder *et al*, 2003; Crawley *et al*, 2011; Farmer *et al*, 2004; Jordan *et al*, 2006; Rimes *et al*, 2007; Nihof *et al*, 2011). A recent paediatric study in China (Shi *et al*, 2018) identified a 0.9% prevalence rate.

Given the significant variations in prevalence rates due to differing study designs and applied case definitions, the more conservative 0.1% to 0.42% range (Nacul *et al*, 2011b; Jason *et al*, 1999) can be applied to establish worldwide estimates of people with ME. Assuming a global population of 7.6 billion (United Nations, 2017), this gives a range between 7.6 and 34.96 million people.

What are the symptoms?

² Carruthers BM, Anil Kumar J, De Meirleir KL, et al. (2003) ‘Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols’, *Journal of Chronic Fatigue Syndrome*, 11(2), pp. 7-115.

³ Sharpe MC, Archard LC, Banatvala JE, et al. (1991) ‘A report – chronic fatigue syndrome: guidelines for research. *J R Soc Med*, 84(2), pp. 118–121.

⁴ Fukuda K, Straus SE, Hickie I, et al. (1994) ‘The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study’, *Annals of Internal Medicine*, 121, pp. 953-959.

⁵ Reeves WC, Wagner D, Nisenbaum R et al. (2005) ‘Chronic fatigue syndrome – a clinically empirical approach to its definition and study’, *BMC Med*; 3:19.

ME is a heterogeneous, multi-system illness. As stated by National Academy of Medicine and required by the more recent definitions, the defining feature of the illness is post-exertional malaise (PEM), defined as the often “delayed and prolonged worsening of symptoms and loss of stamina after physical, cognitive or emotional activity leading to a reduction in functional ability” (Carruthers *et al*, 2003).

The onset of PEM can be delayed by a day or more, the symptom severity and duration is often disproportionate to activity, and the return to baseline can take days, weeks or longer. For example, a walk downstairs may result in an individual being in bed for the rest of the day or longer. Maes *et al* (2012) state that there are different profiles of biological markers for patients who meet Fukuda criteria with PEM compared to those without. More recent studies identify that PEM was 10.4 times more likely to be associated with ME than with controls (Brown & Jason, 2018) and Chu *et al* (2018) further describes symptoms and timing associated with PEM.

Other symptoms can include ongoing flu-like symptoms (sore throat, swollen and/or tender lymph nodes), unrefreshing sleep, cognitive dysfunction (sometimes called ‘brain fog’), immune dysfunction, pain, hypersensitivity to light, sound and/or touch, orthostatic intolerance, gastrointestinal issues, and a number of other symptoms.

What is the disease burden?

At least one in four people are so severely ill they are housebound, and often bedbound (Pendergrast *et al*, 2016; Marshall *et al*, 2011; National Institutes of Health, 2011; Shepherd and Chaudhuri, 2001). A Japanese patient survey (Shinohara, 2015) commissioned by the Japanese Ministry for Health, Labour and Welfare found that 30% of people were severely ill.

ME is at least as disabling as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, congestive heart failure and other chronic conditions (Komaroff *et al*, 1996). Quality of life research suggests that someone with well-characterised ME may experience on average greater disability than those with a range of illnesses including type 2 diabetes, congestive heart failure, back pain/sciatica, lung disease, osteoarthritis, multiple sclerosis and even most cancers (Hvidberg *et al*, 2015; Twisk, 2014; Nacul *et al*, 2011a; Jason & Richman, 2008). People with ME are “measurably more disabled” than those with MS, work fewer hours and have lower income (Kingdon *et al*, 2018).

Many people report significant barriers to accessing a range of support and healthcare and this has substantial health and financial implications (Lin *et al*, 2009; Thanawala & Taylor, 2007). ME symptoms are severely debilitating and impact on ability to work or attend school part- or full-time (Action for ME, 2014; Crawley *et al*, 2011; Taylor & Kielhofner, 2010; Solomon *et al*, 2003; Twemlow *et al*, 1997). Furthermore, family members may need to leave their own education or employment to care for the person with ME.

A significant number of people with ME are unable to work as a result of the illness. For example, the US Centers for Disease Control and Prevention (CDC) reported that only 25% of the people in its five-year multi-site study were able to work (Unger *et al*, 2016). There is no universally agreed cost to the global economy but country-specific amounts have been estimated, including at least £3.3 billion in the UK (2020 Health, 2017), and \$17 to 24 billion

in the US (National Academy of Medicine, 2015). The US estimate includes both direct medical costs and lost productivity.

Prognosis can be poor, leaving patients sick for years or even decades. Studies on natural history and prognosis are limited but one review by Cairns and Hotopf (2005) reported a median full recovery rate of 5%.

How is ME treated?

There is no pharmaceutical treatment specifically approved for ME and no cure, despite the efforts of dedicated scientists and clinicians around the world to move the field forward. Medications licensed for other indications have been used 'off-license' sometimes as a disease-modifying treatment but more often to treat symptoms and comorbidities.

For a number of years, two behavioural approaches – cognitive behavioural therapy (CBT) and graded exercise therapy (GET) – have been recommended in many countries as safe and effective treatments for ME/CFS (Wilshire et al, 2018). These treatments are based on the theory that the debility of the disease is the result of deconditioning which is the result of a fear of activity, symptom focusing, and unhelpful cognitions.

The largest study to support this was the PACE trial (White et al, 2011), a randomised controlled trial that indicated 59 to 61% improvement, and 22% recovery, for patients who used CBT and/or GET compared to pacing and/or standard medical care (White et al, 2013). A Cochrane Review (Larun et al, 2017) identified that “moderate-quality evidence showed exercise therapy was more effective at reducing fatigue compared to ‘passive’ treatment or no treatment. Exercise therapy had a positive effect on people’s daily physical functioning, sleep and self-ratings of overall health.”

The 2014 evidence review by the Agency for Healthcare Research and Quality (AHRQ) in the US also found that GET “improved measures of fatigue, function, and clinical global impression of change compared with controls” (Smith et al, 2014). But like Cochrane, that review included studies using the Oxford definition, which the AHRQ said could include patients with other fatiguing conditions. In 2016, the AHRQ reanalysed the evidence after excluding the Oxford studies and found insufficient evidence of effectiveness for GET (Smith et al, 2016), noting that studies using definitions requiring hallmark criteria such as PEM were “blatantly missing.”

Further, a re-analysis of the data from the trial has found that the original study did not consistently follow protocol procedures, that in fact rates of recovery were consistently low and not significantly different across treatment groups, and that “the modest treatment effects obtained on self-report measures in the PACE trial do not exceed what could be reasonably accounted for by participant reporting biases” (Wilshire et al, 2018)

More than 110 international researchers and clinicians have since written to The Lancet, which published the PACE trial paper, asking it to “commission an independent re-analysis of the individual-level trial data, with appropriate sensitivity analyses, from highly respected reviewers with extensive expertise in statistics and study design” (Tuller *et al*, 2018).

The CDC states that “ME/CFS is a biological illness, not a psychologic disorder” (CDC, 2018) and has removed its recommendation that ME patients be treated with CBT and GET (Rehmeier & Tuller, 2017). The UK National Institute for Health and Care Excellence (NICE) in the UK is reviewing 2007 guideline for ME (NICE, 2017).

Instead of CBT and GET, we know that disease experts recommend that patients manage their activities to stay within their “energy envelope” to prevent crashes and possible long-term worsening from PEM. They also recommend pharmaceutical and non-pharmaceutical therapies to treat the symptoms, which can help improve the quality of life.

Disease pathophysiology

The cause of ME is not yet known, which is unsurprising given the lack of investment in biomedical research. However, the National Academy of Medicine report (2015) provided substantial evidence of neurological, immunological, autonomic and energy metabolism impairment.

Evidence suggestive of neurological impairment includes reduction in gray matter volume, reduction in blood flow in the brain, increases in brain lactate levels, changes on MRI and EEG, evidence of autonomic dysfunction, the presence of abnormal proteins in the spinal fluid, neuroendocrine dysfunction, neurocognitive changes that include deficits in attention, memory and reaction time (Komaroff & Cho, 2011; Komaroff, 2018b) and impaired functional connectivity in the brain (Komaroff *et al*, 2018a).

Studies have long noted that many cases followed an infection and displayed immunological abnormalities that suggest an activated immune system. This includes reduced NK-cell functioning, elevated viral titres, elevated cytokines that are correlated with disease severity, differences in cytokines in spinal fluid and an immune response following exercise, different to that seen in healthy patients (National Academy of Medicine, 2015; Komaroff 2018b). While not approved specifically for ME, some patients have seen improvement on anti-virals (National Academy of Medicine, 2015) and the experimental, immune-modulating Rintatolimod (Ampligen) (Smith *et al*, 2014). Recent research has demonstrated the presence of neural adrenergic antibodies (Loebel *et al*, 2016) and improvement following plasmapheresis (Scheibenbogen *et al*, 2018).

Abnormalities have also been reported in energy physiology and metabolism. Metabolomics studies have reported disturbed metabolite profiles in ME (Naviaux *et al*, 2016; Germain *et al*, 2016). Studies using a two-day cardiopulmonary test have demonstrated an impaired aerobic energy metabolism and lowered anaerobic threshold that are associated with the hallmark symptom of PEM (National Academy of Medicine, 2015; Keller *et al*, 2014; Snell *et al*, 2013). People with ME cannot reproduce their performance on a maximal exercise test 24 hours later, despite showing maximal effort, unlike healthy controls, those who are deconditioned (National Academy of Medicine, 2015), those who have cardiopulmonary diseases (Keller *et al*, 2014), or those with multiple sclerosis (Hodges *et al*, 2017). This suggests that the theory underlying CBT and GET studies that the debility of ME is a result of deconditioning is flawed.

There is evidence that ME can develop after a range of severe microbial infections (Hickie *et al*, 2006; National Academy of Medicine, 2015) and some evidence for the development of a fatigue syndrome following infectious mononucleosis (Katz, 2009).

Studies have also demonstrated significant heterogeneity in well-characterised patients. For instance, there is a wide range of severity with some patients able to work and others needing total care. Hornig *et al* (2015) demonstrated differences in cytokines based on the duration of the disease. Naviaux *et al* (2016) demonstrated differences in metabolomics based on gender, while expert clinicians have noted subsets in their patients who respond differently to treatments. The presence of comorbidities can also influence the presentation of the disease (National Academy of Medicine, 2015).

Disease classification

The World Health Organization (WHO) added ME to the neurological chapter of the International Classification of Diseases (ICD) in 1969. In the ICD-10, ME is an inclusion term under post-viral fatigue syndrome (code G93.3). Following two outbreaks in the mid-1980s, the US coined the alternative term “chronic fatigue syndrome,” which the WHO added to ICD-10 and indexed to “post-viral fatigue syndrome.” In its version of the ICD-10 (the ICD-10-CM), the US reclassified CFS to be equivalent to the symptom of “chronic fatigue, unspecified” while leaving ME in the neurological chapter.

In the ICD-11, the terms “ME” and “CFS” are in the neurological chapter following the precedent set in ICD-10. But WHO staff have submitted an ICD-11 proposal to reclassify the terms to the Signs and Symptoms chapter under the musculoskeletal system section based on the claim that there is no evidence of neurological impairment and that the disease is perpetuated by psychological processes (Dua, 2017). These claims are not supported by the evidence of neurological, immunological, and energy metabolism impairment. (National Academy of Medicine 2015; Komaroff & Cho, 2011; Komaroff *et al*, 2018a). The WHO has stated that no decision will be made on proposals to change the classification until they complete a systematic review.

While not formally classified as such, ME and CFS have often been grouped with Medically Unexplained Symptoms, Functional Somatic Syndrome, Somatic Symptom Disorder, Bodily Distress Syndrome, and similar terms (Improving Access to Psychological Therapies, 2014; Fink, 2017). This continues to put ME at high risk of being treated erroneously as a psychological illness.

What are the barriers?

Naming/terminology/definition

The 2015 National Academy of Medicine report acknowledges that “ME and CFS often are used interchangeably to refer to an illness characterized by profound fatigue and autonomic and neurocognitive symptoms.” But there are more than 20 sets of CFS and ME case definitions and diagnostic criteria (Brurberg *et al*, 2014) which vary on specificity and sensitivity (Nacul *et al*, 2011b).

The CFS definitions focus on medically unexplained fatigue and do not require hallmarks of the disease such as PEM. The 2014 evidence review by the AHRQ reports that the Oxford CFS definition has a “high risk of including patients who may have an alternate fatiguing illness, or whose illness resolves spontaneously with time” (Smith *et al*, 2014).

The National Academy of Medicine report (2015) also states that 1994 Fukuda and 2005 Reeves CFS definitions do not require hallmark symptoms of ME and as a result include patients with other conditions. Based on its comparison of definitions, it concludes that “the diagnostic criteria for ME have required the presence of specific or different symptoms from those required by the diagnostic criteria for CFS; thus, a diagnosis of CFS is not equivalent to a diagnosis of ME.”

Lack of investment in research

There is an acute lack of investment in ME research funding. A scoping report (Radford & Chowdhury, 2016) found that only 0.02% of active grants recorded on the Dimensions Database are awarded to research ME, which is comparatively very low given the estimated prevalence of the condition and disease burden. Using Disability Adjusted Life Years, one study (Dimmock *et al*, 2016) estimated that, to be commensurate with disease burden compared to other funded diseases, National Institutes of Health (NIH) funding in the US would need to be \$188m per year compared to the \$14m per year currently spent.

Compounding the lack of funding, the National Academy of Medicine (2015) noted a relative lack of biomedical research stating, there had been only “limited research efforts to study ME in fields other than psychiatry and psychology.”

Misperceptions, lack of medical knowledge and inadequate medical care

There remains a lack of knowledge of disease mechanisms and disease progression, a lack of effective biomarkers and diagnostic markers, and there is a dearth of appropriate treatments (National Academy of Medicine, 2015).

Misunderstandings and disbelief of patients among the medical community result in 84% to 91% of individuals being undiagnosed and patients subjected to “treatment strategies that exacerbate their symptoms” (National Academy of Medicine 2015). Misdiagnosis of other conditions as ME is also a significant problem (Newton *et al*, 2010). Furthermore, many people with ME report being subjected to “hostile attitudes” by health care providers, and the “healthcare community generally still doubts the existence or seriousness of this disease” (National Academy of Medicine, 2015). The CDC reported that 85% of clinicians think that ME is in part or entirely a psychiatric illness (Unger *et al*, 2011).

Walter Koroshetz, Director of US National Institute of Neurological Disorders and Stroke and Chair of the Trans-NIH ME/CFS Working Group, acknowledges that ME “has been completely under-investigated” (SolveCFS, 2017). Both society and the medical profession have contributed to the ignorance and neglect experienced by patients with ME, who are often treated with “skepticism, uncertainty, and apprehension and labeled as deconditioned or having a primary psychological disorder” (Green *et al*, 2015).

As a result of the stigma and misunderstanding, all countries experience a critical lack of knowledgeable clinicians. For instance, in the US, there are an estimated 12 to 15 expert clinicians in the entire country, and many of those are approaching retirement. Compounding this problem, no medical specialty has taken responsibility for this disease. This not only affects access to clinical care for people with ME but also impedes the advancement of research.

Research methodology

A fundamental issue is the use of overly broad criteria and the lack of commonly agreed research criteria and associated assessment methods, backed up by data, to accurately recruit patients. Accurate prevalence estimates are hindered by a lack of consensus over inclusion and exclusion criteria for core symptoms and for comorbid and psychiatric conditions (Johnston et al, 2013). Studies often fail to stratify ME cohorts in order to formally test inclusion criteria.

Numerous studies, such as those referred to in this statement, including some of the largest, have used overly broad inclusion criteria such as the Oxford and the Fukuda, which did not require hallmark symptoms of ME and have included patients with other fatiguing conditions. This has resulted in inconsistent results, which have impeded progress. For this reason, the NIH (2014) and AHRQ in the US recommended that the Oxford criteria be retired; some researchers have done so while biomedical researchers have typically not used it. Moreover, the Fukuda criteria should not be used as a single instrument for diagnosis in either research or clinical care but can be used as an aid to screen for cases, followed by a full clinical evaluation using criteria that require hallmark symptoms such as post exertional malaise (PEM).

A second issue is that a number of studies on risk, prognosis, and the use of CBT and GET as treatment have been based on a psychogenic-deconditioning theory that the disease debility can be reversed by CBT and GET. This theory focuses on personality, psychological and behavioural issues as factors that predispose and perpetuate the disease. But no study has provided scientific evidence to support this theory. Furthermore, this disease theory cannot be reconciled with what is known about the biological impairment of ME or the reports from the National Academy of Medicine (2015) and patient surveys (Geraghty et al, 2017) that exertion can cause harm.

Another problem is the lack of sick controls in some studies to show that changes are unique to ME rather than generic ill-health markers. The appropriate use of sick controls in more studies would allow us to distinguish potentially similar-looking conditions (such as multiple sclerosis, early rheumatoid arthritis and depression) from ME. Additionally, due to a lack of funding, study designs often suffer from being under-powered to detect true, reproducible effects, and pivotal studies have not been replicated.

Finally, even when properly characterised, and when patients with other conditions are excluded, ME is still a complex disease and likely to be heterogeneous. Careful study design and sub-setting is needed that accounts for the progression and remission of the disease, the presence of comorbidities and differences such as gender, duration of disease, genetics, level of sedentariness, and differences in the metabolome. One increasingly important

approach being incorporated into study design is the use of exertion challenges to provoke the hallmark PEM and the associated impairment in aerobic energy metabolism.

What can be done to address the barriers?

We call upon the WHO to take action to:

- recognise ME as a “serious, chronic, complex, and multisystem disease that frequently and dramatically limits the activities of affected patients” (National Academy of Medicine, 2015)
- produce a report that identifies current biomedical knowledge about ME and barriers to progress of recognition, research, clinical care and support
- adopt measures to address these barriers, providing a global and co-ordinated public health response to ME
- encourage the use of definitions that require hallmark symptoms of ME to increase the quality of biomedical research and expedite the process
- continue to ensure that the disease not be moved out of the neurological chapter of the ICD-11 until further research provides the scientific basis for that change.

The fundamental issues of stigma, misperception and miseducation lead downstream to the barriers we have identified. Appropriate education for professionals working with people living with ME is essential to improve care, support and diagnosis. There is little teaching in medical schools and a limited presence in medical resources (National Academy of Medicine, 2015).

Worse still, the medical resources available to medical providers in practice are inadequate, incorrect and sometimes harmful as they too often have been based on studies that included people who did not have ME. Governments must fund and support medical education campaigns, using updated medical information, to reverse the misinformation and stigma and teach doctors how to properly care for people with ME.

To really address this disease, it is essential that governments provide sufficient funding and other incentives to rapidly accelerate research, using agreed criteria, in order to validate existing findings and to dramatically expand upon what we know about the disease and its appropriate diagnosis and treatment.

Until this has been achieved, definitions should only be used that recognise the disease’s hallmark criteria: post-exertional malaise. The Oxford criteria should be retired, and findings from Oxford studies not be used to support recommendations in clinical guidance. ME should not be conflated with and treated as Medically Unexplained Symptoms (MUS), Functional Somatic Syndrome, Somatic Symptom Disorder (SSD), Bodily Distress Syndrome (BDS), or similar terms. Treatments, such as CBT and GET, tested using the criteria which does not require post-exertional malaise, should not be recommended for people with ME.

In recent years, there has been increasing recognition of the value of patient and public involvement in research and health care systems (Sacristán *et al*, 2016). We request that a transparent, consultative process involving people living with ME, national ME organisations and the scientific community be established to agree upon research and clinical criteria.

Signatories

On behalf of the International Alliance for M.E. (IAFME)

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Action for M.E., United Kingdom
The American ME and CFS Society, United States
Associated New Zealand ME Society, New Zealand
Emerge Australia, Australia
Forward ME, United Kingdom (a House of Lords-led collaboration of ten M.E. charities)
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UK CFS/ME Research Collaborative: a national collaboration of leading UK researchers, patient advisory group and charities working with mainstream research funders
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