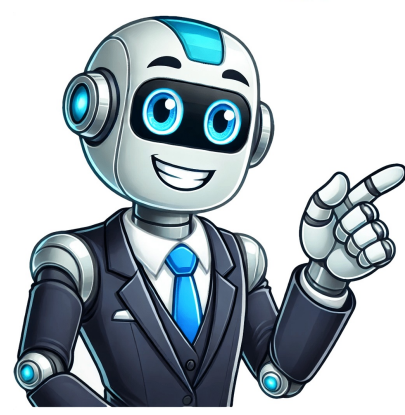


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for ME/CFS produced a prevalence rate of only 0.17%.[97] In England and Wales, over 250,000 people are estimated to be affected.[2]:92 These estimates are based on data before the COVID-19 pandemic. It is likely that numbers have increased as a large share of people with long COVID meet the diagnostic criteria of ME/CFS.[110]:228 A 2021–2022 CDC survey found that 1.3% of adults in the United States, or 3.3 million, had ME/CFS.[71] Women are diagnosed with ME/CFS about 1.5 to four times more often than men.[91]:38] The prevalence in children and adolescents is slightly lower than in adults,[9] and children have it less than adolescents.[72] The incidence rate (the onset of ME/CFS) has two peaks, one at 10–19 and another at 30–39 years.[4] and the prevalence is highest in middle age.[20] Main article: History of ME/CFSFrom 1934 onwards, there were multiple outbreaks globally of an unfamiliar illness, initially mistaken for polio. A 1950s outbreak at London's Royal Free Hospital led to the term "benign myalgic encephalomyelitis" (ME). Those affected displayed symptoms such as malaise, sore throat, pain, and signs of nervous system inflammation. While its infectious nature was suspected, the exact cause remained elusive.[1]:28–29 The syndrome appeared in sporadic as well as epidemic cases.[73] In 1970, two UK psychiatrists proposed that these ME outbreaks were psychosocial phenomena, suggesting mass hysteria or altered medical perception as potential causes. This theory, though challenged, sparked controversy and cast doubt on ME's legitimacy in the medical community.[1]:28–29 Melvin Ramsay's later research highlighted ME's disabling nature, prompting the removal of "benign" from the name and the creation of diagnostic criteria in 1986. These criteria included the tendency of muscles to tire after minor effort and take multiple days to recover, high symptom variability, and chronicity. Despite Ramsay's work and a UK report affirming that ME was not a psychological condition, skepticism persisted within the medical field, leading to limited research.[1]:28–29 In the United States, Nevada and New York State saw outbreaks of what appeared similar to mononucleosis in the middle of the 1980s. People suffered from "chronic or recurrent fatigue", among a large number of other symptoms.[1]:28–29 The initial link between elevated antibodies and the Epstein–Barr virus led to the name "chronic Epstein–Barr virus syndrome". The CDC renamed it chronic fatigue syndrome (CFS), as a viral cause could not be confirmed in studies.[74]:155–158 An initial case definition of CFS was outlined in 1988.[1]:28–29 the CDC published new diagnostic criteria in 1994, which became widely referenced.[75] In the 2010s, ME/CFS began to gain more recognition from health professionals and the public. Two reports proved key in this shift. In 2015, the US Institute of Medicine produced a report with new diagnostic criteria that described ME/CFS as a "serious, chronic, complex systemic disease". Following this, the US National Institutes of Health published their Pathways to Prevention report, which gave recommendations on research priorities.[76] Presentation of a petition to the National Assembly for Wales relating to ME support in South East Wales Main article: Controversies related to ME/CFS ME/CFS is a contested illness, with debates mainly revolving around the cause of the illness and treatments.[77] Historically, there was a heated discussion about whether the condition was psychological or neurological.[58] Professionals who subscribed to the psychological model had frequent conflicts with patients, who believed their illness to be organic.[78] While ME/CFS is now generally believed to be a multisystem neuroimmune condition,[58] a subset of professionals still see the condition as psychosomatic, or an "illness-without-disease".[78][79] The possible role of chronic viral infection in ME/CFS has been a subject of disagreement. One study caused considerable controversy by establishing a causal relationship between ME/CFS and a retrovirus called XMRV. Some with the illness began taking antiretroviral drugs targeted specifically for HIV/AIDS, another retrovirus,[80] and national blood supplies were suspected to be tainted with the retrovirus. After several years of study, the XMRV findings were determined to be the result of contamination of the testing materials.[81] Treatments based on behavioural and psychological models of the illness have also been the subject of much contention. The largest clinical trial on behavioural interventions, the 2011 PACE trial, concluded that graded exercise therapy and CBT are moderately effective. The trial drew heavy criticism.[77] The study authors weakened their definition of recovery during the trial: some participants now met a key criterion for recovery before the trial started. A reanalysis under the original clinical trial protocol showed no significant difference in recovery rate between treatment groups and the controls receiving standard care.[82][83] People with ME/CFS often face stigma in healthcare settings.[22] and the majority of individuals report negative healthcare experiences. They may feel that their doctor inappropriately calls their illness psychological or doubts the severity of their symptoms.[84] They may also feel forced to prove that they are legitimately ill.[85] Some may be given outdated treatments that provoke symptoms or assume their illness is due to unhelpful thoughts and deconditioning.[12]:2871 [19] Clinicians may be unfamiliar with ME/CFS, as it is often not fully covered in medical school.[19] Due to this unfamiliarity, people may go undiagnosed for years[12] or be misdiagnosed with mental health conditions.[19] As individuals gain knowledge about their illness over time, their relationship with treating physicians changes. They may feel on a more equal footing with their doctors and able to work in partnership. At times, relationships may deteriorate instead as the previous asymmetry of knowledge breaks down.[86] ME/CFS negatively impacts people's social lives and relationships. Stress can be compounded by disbelief in the illness from the support network, who can be sceptical due to the subjective nature of diagnosis. Many people with the illness feel socially isolated, and thoughts of suicide are high, especially in those without a supportive care network.[86] ME/CFS interrupts normal development in children, making them more dependent on their family for assistance instead of gaining independence as they age.[87] Caring for somebody with ME/CFS can be a full-time role, and the stress of caregiving is made worse by the lack of effective treatments.[88] Economic costs due to ME/CFS are significant.[89] In the United States, estimates range from \$36 to \$51 billion per year, considering both lost wages and healthcare costs.[90] A 2017 estimate for the annual economic burden in the United Kingdom was £3.3 billion.[13] The blue ribbon is used for ME/CFS awareness. Patient organisations have aimed to involve researchers via activism but also by publishing research themselves—similarly to AIDS activism in the 1980s, which also sought to combat underfunding and stigma. Citizen scientists, for example, helped start discussions about weaknesses in trials of psychological treatments.[77] ME/CFS International Awareness Day takes place on 12 May [91] The goal of the day is to raise awareness among the public and health care workers about the diagnosis and treatment of ME/CFS.[92] The date was chosen because it is the birthday of Florence Nightingale, who had an unidentified illness similar to ME/CFS.[91] Graph of ME/CFS papers published by year: Papers mentioning ME or CFS Papers whose title mentions ME/CFS Research into ME/CFS seeks to find a better understanding of the disease's causes, biomarkers to aid in diagnosis, and treatments to relieve symptoms.[1]:10 The emergence of long COVID has sparked increased interest in ME/CFS, as the two conditions may share pathology and treatment for one may treat the other.[26][14] Historical research funding for ME/CFS has been far below that of comparable diseases.[23][93] In a 2015 report, the US National Academy of Sciences said that "remarkably little research funding" had been dedicated to causes, mechanisms, and treatment.[1]:9 Lower funding levels have led to a smaller number and size of studies.[94] In addition, drug companies have invested very little in the disease.[95] The US National Institutes of Health (NIH) is the largest biomedical funder worldwide.[96] Using rough estimates of disease burden, a study found NIH funding for ME/CFS was only 3% to 7% of the average disease per healthy life year lost between 2015 and 2019.[97] Worldwide, multiple sclerosis, which affects fewer people and results in disability no worse than ME/CFS, received 20 times as much funding between 2007 and 2015.[93][23] Funding cuts to Columbia University during the second Trump administration forced the closure of a large research program dedicated to the disease.[98] Multiple reasons have been proposed for the low funding levels. Diseases for which society "blames the victim" are frequently underfunded. This may explain why COPD, a severe lung disease often caused by smoking, receives low funding per healthy life year lost.[99] Similarly, for ME/CFS, the historical belief that it is caused by psychological factors may have contributed to lower funding. Gender bias may also play a role; the NIH spends less on diseases that predominantly affect women in relation to disease burden. Less well-funded research areas may also struggle to compete with more mature areas of medicine for the same grants.[97] Many biomarkers for ME/CFS have been proposed. Studies on biomarkers have often been too small to draw robust conclusions. Natural killer cells have been identified as an area of interest for biomarker research as they show consistent abnormalities.[7] Other proposed markers include electrical measurements of blood cells and Raman microscopy of immune cells.[14] Several small studies have investigated the genetics of ME/CFS, but none of their findings have been replicated.[13] A larger study, DecodeME, is currently underway in the United Kingdom.[100] Various drug treatments for ME/CFS are being explored. Drugs under investigation often target the nervous system, the immune system, autotimmunity, or pain directly. More recently, there has been a growing interest in drugs targeting energy metabolism.[95] In several clinical trials of ME/CFS, rintalolomid showed a small reduction in symptoms, but improvements were not sustained after discontinuation.[101][95] Rintalolomid has been approved in Argentina.[102] Rituximab, a drug that depletes B cells, was studied and found to be ineffective.[14] Another option targeting autoimmunity is immune adsorption, which removes a large set of (auto)antibodies from the blood.[95] Symptoms and their severity can widely differ among people with ME/CFS. This poses a challenge for research into the cause and progression of the disease. Dividing people into subtypes may help manage this heterogeneity.[14] The existence of multiple diagnostic criteria and variations in how scientists apply them complicate comparisons between studies.[1]:53 Definitions also vary in which co-occurring conditions preclude a diagnosis of ME/CFS. 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