



ME RESEARCH SUMMARY

2019

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General Information

Myalgic encephalomyelitis is a complex chronic disease that affects multiple body systems. While funding for research and clinical care remains a serious concern, there is now a growing body of literature that identifies and explicates dysfunction in the immune, neurological, and energy metabolism systems in people with ME. What follows is an abbreviated summary of ME research over the past ten years.

THE INSTITUTE OF MEDICINE REPORT, 2015

[Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness](#) is a literature review conducted by the National Academies of Medicine. A panel of experts reviewed over 9,000 separate studies and concluded that ME/CFS is a multi-system disease often preceded by an immune challenge.

Metabolism

Some metabolic pathways are favored over others in comparison to healthy controls, and there may be a pattern of hypometabolism overall in people with ME.

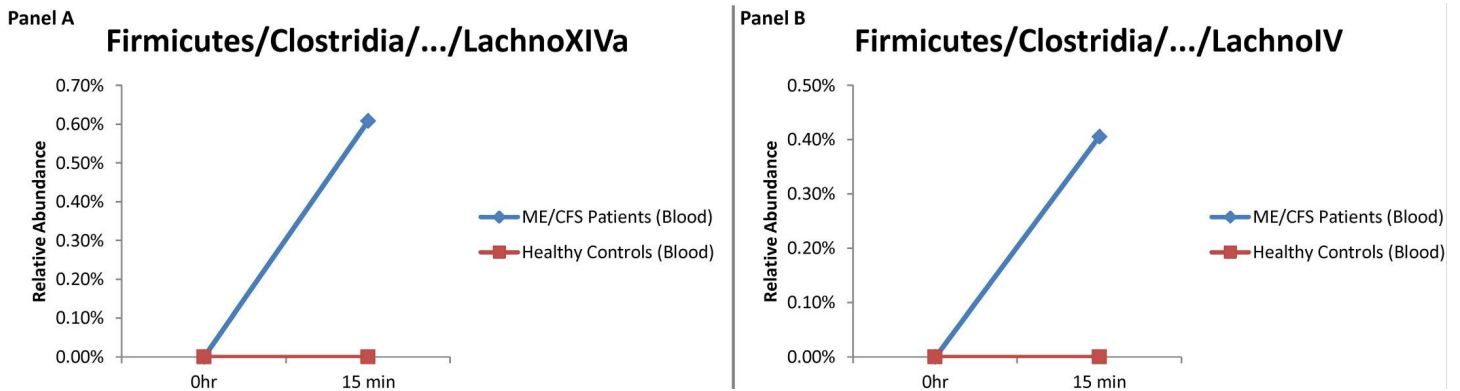
- **Amino acid metabolism** - [Fluge and Mella \(2016\)](#) and [Armstrong et al. \(2015\)](#) identified abnormalities in cellular energy production in people with ME, including an increased use of amino acids over sugars. Both papers cited perturbations in glycolysis, the process that breaks down carbohydrates and sugars, as a potential cause. Bathing normal cells in patient serum caused them to show the same metabolic abnormalities as patient cells.
- **Slowed cellular metabolism** - [Naviaux et al., 2016](#) found significant decreases in metabolites that indicate slowed metabolism in people with ME overall, as did [Armstrong \(2017b\)](#). Naviaux et al. also found changes in important cell membrane compounds, like sphingolipids and cholesterol.
- **Fatty acid processing** - Studies by [Germain et al. \(2017\)](#) and Nagy-Szakal et al. ([2017](#) & [2018](#)) confirm a dysregulation of fatty acid metabolism in people with ME. In addition, [Germain et al. \(2018\)](#) found 14 metabolites that were significantly altered in people with ME, including high heme levels; low cAMP (an important second messenger necessary to activate many proteins in cells); and several molecules associated with ketosis, the breakdown of fats in place of sugars.

Microbiome

Various cohorts of individuals with ME have been found to have abnormal microbiome populations. There is evidence that an altered microbiome may influence host metabolism, and that shifts in metabolic pathways may in turn lead to dysbiosis in people with ME.

- **Alterations in gut bacteria** - Cornell's team ([Giloteaux, 2016](#)) confirmed previous results showing that people with ME have different kinds of gut bacteria than healthy individuals, with specific kinds of bacteria elevated, including *Firmicutes* and *Bacteriodes*. Signs of microbial translocation, or movement of bacteria from the gut to the bloodstream, were also found by Giloteaux et al. [Mandarano et al. \(2018\)](#) found greater numbers of eukaryotic organisms associated with infection in people with ME, potentially implicating reduced immunocompetence.

- **Post-exercise pathogens in blood** – [Shukla et al., 2015](#) found that blood samples collected 15 minutes after exercise showed different bacteria in people with ME than in controls, and certain kinds of bacteria increased in the bloodstream in patients only. At least five studies have now shown dysregulated levels of *Clostridium* in people with ME ([Armstrong, 2017a](#); [Frémont, Coomans, Massart, & De Meirlier, 2013](#); [Nagy-Szakal et al., 2017](#); [Nagy-Szakal et al., 2018](#); [Shukla et al., 2015](#)).



([Shukla et al. 2015 -- Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\)](#))

- **The microbiome and metabolism** – [Armstrong et al. \(2017b\)](#) found evidence of higher amounts of SCFAs, a product of microbial metabolism, in people with ME, along with an overall slowed metabolism that may be due to an imbalance in gut bacteria. Increased SCFAs could illuminate a potential connection between gut dysbiosis and microglial activation. Reliance on amino acids for fuel as described in the previous section decreases the available pool to create proteins in the gut, which may lead to decreased production of digestive enzymes and mucins. What is not digested completely then may become food for microbes that can digest it, such as *Firmicutes*, which in turn may lead to dysbiosis [Armstrong et al. \(2017b\)](#). [Nagy-Szakal et al. \(2017 & 2018\)](#) also found that people with ME had dysregulated flora.

Cardiovascular & Autonomic

Measurable alterations in the functions of the cardiovascular system and autonomic nervous system have been observed in people with ME. Reduced blood volume and blood flow, issues with regulating heart rate and blood pressure, a lower VO₂ max during exercise testing, and an inability to replicate levels of exertion on successive days have been found in multiple studies.

BASELINE / AT REST:

- [Newton et al. \(2016\)](#), [Miwa & Fujita \(2011\)](#) and [van Campen, Rowe, and Visser, 2018](#) found **reduced blood volume** in people with ME. Newton found that this was unrelated to duration of illness and therefore unlikely to be due to deconditioning; van Campen's group (2018) found that reduced blood volume correlated to orthostatic intolerance.
- **Orthostatic intolerance, or unusual shifts in heart rate and blood pressure** on standing, are prevalent in people with ME. [Miwa et al. \(2017\)](#) found dysregulation in the hormones that control fluid balance (the renin-angiotensin system), which may in part explain low blood volume and orthostatic intolerance in ME. In a 2018 study, [Miwa et al.](#) found that 91% of people with ME had orthostatic intolerance, and that just under half of those studied couldn't complete a 10-min stand test.

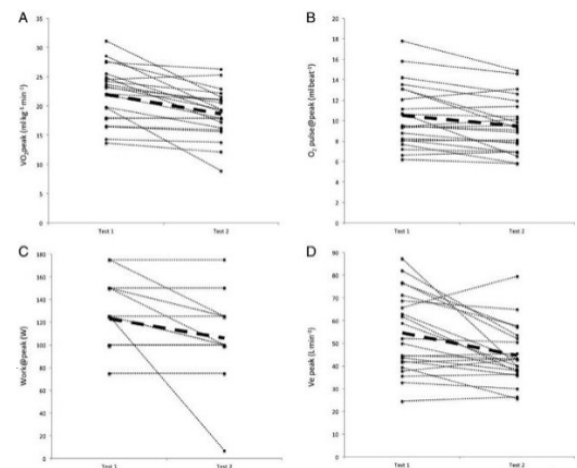
- [Van Campen, et al. \(2018\)](#) found that people with ME had **lower cardiac output and stroke volume** compared to controls during a tilt table test, the standard to determine orthostatic intolerance. There were differences between healthy controls and people with ME, but no differences between minor, moderate, or severe-presenting patients, indicating that it is unlikely these differences were related to deconditioning.
- Numerous studies have found **altered heart rate and blood pressure variability in ME** and CFS patients, including during sleep ([Boneva et al., 2007](#); [Hurum, Sulheim, Thaulow, & Wyller, 2010](#); [Meeus et al., 2013](#); [Togo, & Natelson, 2013](#)).

POST EXERCISE

- Both [Neary et al., 2008](#); and [Peterson et al., 1994](#) found **reduced blood flow to the brain and heart** in people with ME.
- **Reduced oxygen uptake in hemoglobin** ([Miller et al., 2015](#)) and reduced oxygen use on second-day exercise testing ([Jones et al., 2012](#); [Keller, Pryor, & Giloteaux, 2014](#)) were found in people with ME.
- People with ME showed **differences in maximal oxygen use** not caused by a general lack of physical activity/deconditioning ([Vermeulen, & Vermeulen van Eck, 2014](#))
- There were notable **differences in VO₂** on two-day CPET between people with multiple sclerosis, people with ME, and healthy controls. ([Hodges, Nielsen & Baken, 2017](#)).
- **Reduction in absolute heart rate recovery** after single-day cardiopulmonary exercise testing was found in people with ME ([Moneghetti et al., 2018](#))

Note that exercise studies are performed on minor or minor-moderate-presenting people with ME. Severe patients may be incapable of exercise. Metabolism is measured via the products of respiration during testing, and some clinicians or researchers may gather additional information about energy metabolism through venous or arterial blood sampled at intervals during the test. Cardiopulmonary exercise testing (CPET) is an objective measure that cannot be 'fooled' by low effort on the part of the patient.

Keller's work shows the difference in ME/CFS patient function on their first exercise test versus their second, 24 hours later (Keller et al., 2014 -- [Inability of myalgic encephalomyelitis/ chronic fatigue syndrome patients to reproduce VO₂ peak indicates functional impairment](#))



- **Gene expression post-exercise** – [Light et al., 2009](#): Light's group found different gene function after exercise in patients, including in genes related to immunity, metabolism, and the nervous system. Genes with increased expression included those responsible for regulating function of the heart, cell death, and inflammation. In order to carry out the same actions, people with ME may have to exert themselves far more than healthy individuals. Genes activated during exercise, effort, or as a result of painful sensations may be activated significantly more in people with ME than in healthy controls performing these same activities.
- **Second-day CPET and VO₂** – [Snell et al., 2013](#), [Keller et al., 2014](#), and [Vermeulen & Vermeulen, 2014](#): Post-exertional malaise, or a worsening of all symptoms after exertion with delayed recovery, is considered the cardinal feature of ME/CFS. However, patients do not always experience the consequences of PEM right away; they may experience a 'crash' 8, 24, or 48 hours after the initial exertion.

[Snell et al. \(2013\)](#) found that, while a single exercise test showed no noticeable differences between CFS patients and controls, a second test performed 24 hours later showed significant abnormalities in oxygen use and how hard patients were able to work. [Keller \(2014\)](#) also found significant differences in ability to perform during a second test.

[Vermeulen et al. \(2014\)](#) compared sedentary controls (active less than 1 hour / week) to ME/CFS patients to show that these findings were not merely a matter of low activity level (deconditioning). O₂ extraction in people with ME was still found to be less than half that of inactive controls.

A two-day cardiopulmonary exercise test can be used to objectively identify post-exertional malaise, the cardinal symptom of ME.

- **PACE trial and refutations** -- The PACE trial was a trial of graded exercise therapy for ME/CFS initially heralded as a success. Patients, researchers and clinicians were skeptical of these claims, as the National Academy of Medicine describes exercise intolerance as one of the distinguishing features of the disease.

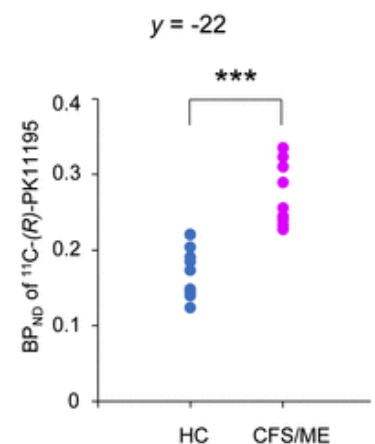
Numerous issues with the trial were identified. Most significantly, the original authors found no difference between activity levels on follow-up with the original participants ([Sharpe et al., 2015](#)): even subjective improvements dissipated within a few months. The same null result was found in their similar FINE trial on long-term follow-up ([Wearden et al., 2010](#)). *The Lancet* has not yet retracted the study, but [PLOS ONE has flagged it](#) and issued an [expression of concern](#). AHRQ downgraded the evidence for the use of GET and CBT in people with ME, and in 2018, the US CDC removed recommendations for graded exercise and cognitive behavioral therapy from its pages on ME.

There have been a series of articles discussing the flaws of the PACE trial, notably David Tuller's series [Trial By Error](#), posed on Racaniello's Virology Blog. Additionally, the Journal of Health Psychology released a [series of solicited opinions on PACE](#).

Neuroendocrine

ME is classified as a disease of the central nervous system by the World Health Organization. Many of the most dominant symptoms are neurological in presentation.

- **Increased ventricular lactate** -- Mathew et al., [2009](#); [2010](#); [2012](#); [2017](#): Several imaging studies show increased [ventricular](#) lactate in people with ME as compared to various control groups. This is significant because lactate is produced by cells when oxygen is low. This may be due to poor blood flow in people with ME.
- **Neuroinflammation** -- [Nakatomi et al., 2014](#) : Nakatomi et al. (2014) performed an imaging study using ¹¹C-(R)PK11195, a marker for microglial and astrocyte activation. The ¹¹C-(R)-PK11195 levels found in people with ME were between 1.5 and 3 times as high as that of healthy people, and correlated to symptom severity.



(Right: [Nakatomi et al., 2014](#) -- [Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis](#):

An ¹¹C-(R)-PK11195 PET Study : BPND of ME/CFS patients versus healthy controls)

[Encephalomyelitis: An ¹¹C-\(R\)-PK11195 PET Study](#) : BPND of ME/CFS patients versus healthy controls)

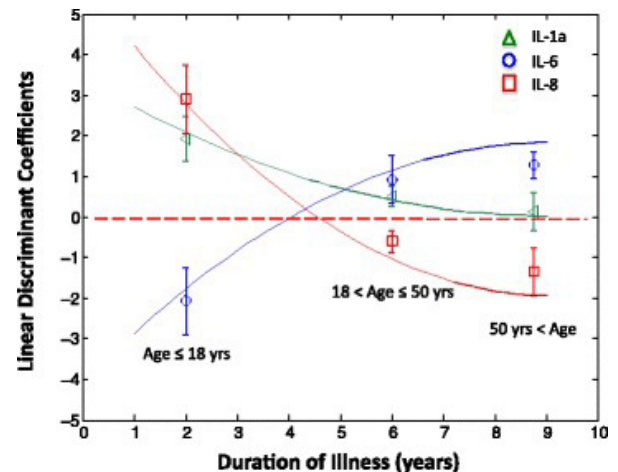
- **Brain changes on MRI**: [Shan et al. \(2016\)](#) found that white matter volume (WMV) had decreased in some regions of the brain, and that the grey matter volume (GMV) had decreased in others. These changes correlated to symptoms. In a 3T MRI study, [Puri et al., \(2012\)](#) also found reduced grey and white matter in areas that support patient reports of impaired memory and visual processing, and discrepancies between intended actions and consequent movements.

- **MRI abnormalities post-exertion** – [Cook et al., 2017](#) and [Staud et al., 2018](#) : Cook found that patients and healthy controls had similar physiological responses to an initial exercise test, but they could not replicate the level of effort of healthy controls, and they experienced greater pain and fatigue on exertion. Patient response to other tasks was then examined post-exercise. People with ME performed significantly worse in difficult mental tasks post-exercise; this impairment correlated to changes on fMRI. Staud found that, while people with ME showed no differences in cerebral perfusion (blood flow to the brain) from healthy controls at rest, people with ME showed a significant decrease in perfusion following a strenuous task.
- **ME vs multiple sclerosis** – [Jain et al., 2017](#): People with ME were found to have more severe problems with cognition and sleep than those with MS in a cross-sectional study of approximately 400 UK ME/CFS biobank participants.
- **Glucocorticoid receptors** – [de Vega et al., 2017, 2018a, 2018b](#): These studies found dysregulated glucocorticoid receptor function in people with ME. While glucocorticoids are anti-inflammatory in the periphery, they can be inflammatory to the central nervous system. Increased sensitivity to input from glucocorticoids may amplify this effect in people with ME.
- **Review** – [VanElzakker et al., 2019](#) produced a useful review of neuroimaging techniques and cytokine studies in people with ME

Immunological

The search for a single infectious organism that causes ME has not been successful to date. However, there is evidence that immune challenges such as infections can trigger the disease in susceptible individuals, including viruses such as Epstein-Barr and other herpes viruses; and echovirus, coxsackie and other enteroviruses ([Institute of Medicine, 2015](#))¹. ME/CFS may appear in epidemic outbreaks², further implicating an infectious agent or agents in onset, and many people report onset after an acute infection or other immune challenge. Several studies show that cytokines, substances secreted by immune cells that affect immune function, are different in people with ME versus healthy controls.

- **Epstein-Barr studies** – [Halpin et al.\(2017\)](#) and [Lerner et al. \(2012\)](#) found that people with ME showed high antibodies to an enzyme produced by the Epstein-Barr virus and other herpes viruses. Higher antibody levels correlated to lower patient-reported fatigue, according to Lerner, suggesting that an active immune response may lead to fewer symptoms. This runs counter to the idea of an 'overactive' immune system keeping patients sick.
- **Cytokine studies** – Many cytokines related to the inflammatory response have been found to be elevated in patient serum. Some researchers have discovered a general pattern of increased inflammation early in the disease and an immune exhaustion state after long-term illness ([Hornig et al., 2015](#); [Russell et al., 2016](#)). A second set of researchers found that these cytokines fluctuated with severity rather than over time ([Montoya et al., 2017](#)). People with ME also showed a significantly different cytokine profile after single-day cardiopulmonary exercise testing when compared to that of sedentary controls ([Moneghetti et al., 2018](#)).



Right: Russell et al., 2016 – [Illness progression in chronic fatigue syndrome: a shifting immunebaseline](#). Patterns of cytokine expression over disease progression

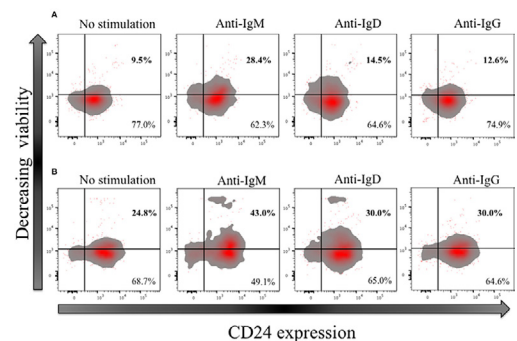
¹You can find a patient-created list of enteroviral research with links [here](#).

²You can find a list of outbreaks of myalgic encephalomyelitis 1934-1980 with attendant references [here](#).

- **Natural killer cells (NKCs)** – Natural killer cells are a type of white blood cell that combats cancer and viral infection. A summary by [Strayer et al. \(2015\)](#) found that out of 17 studies in ME/CFS studying natural killer cell function, 15 found lower NK cell function in people with ME. [Rivas et al., 2018](#) and [Fletcher et al., 2010](#) showed a significant difference between NK cell function in healthy controls and people with ME as well. Rivas et al. also demonstrated that people with ME with a post-infectious onset had lower numbers of NKCs. Both [Huth et al. \(2014\)](#) and [Brenu et al. \(2014\)](#) found increased degranulation, a process to break down infected or cancerous target cells in NKCs. Brenu found depleted Granzyme B activity with increased CD57 expression – a mature-cell surface marker in NK cells.
- **Ion channels** – Nguyen et al. ([2016a](#); [2016b](#)) found low expression of transient receptor potential melastatin subfamily 3 (TRPM3) ion channels to be associated with ME. These channels are essential for immune cell activation, and may in part explain poor NK cell function.
- **T cells** -- Curriu and colleagues found elevated T cell exhaustion markers PD-1 and CD95 ([2013](#)). Both [Ono et al., 2017](#) and [Rivas et al., 2018](#) found fewer T regulatory cells, cells that help control the cytotoxic T cell population. Rivas also correlated NKT (natural killer T cell) levels to severity of symptoms in people with ME. At least four studies have found genetic markers associated with T cell dysregulation in people with ME ([de Vega et al., 2018a](#); Nguyen et al. [2016a](#); [2016b](#); [Schlauch et al., 2016](#)).
- **B cells** – High numbers of naïve B cells have also been found in people with ME ([Bradley et al., 2013](#); [Ono et al., 2017](#)), and [Mensah et al. \(2018\)](#) found alterations in B cells that indicate poor survival and provide evidence for dysfunctional metabolism in the immune system.
- **Altered immune responses to infection** - has recently been identified in ME in several studies, including a deficiency in EBV-specific B- and T-cell memory responses in CFS patients ([Lerner et al., 2012](#)).

Autoantibody studies -- Multiple studies have found signs of autoimmunity in ME/CFS patients, including elevated levels of:

- Anti-cholinergic muscarinic antibodies ([Loebel et al., 2016](#))
- Anti-B-adrenergic antibodies ([Loebel et al., 2016](#))
- Anti-serotonin antibodies ([Maes et al., 2013](#))
- Anti-P_i (phosphatidylinositol) antibodies ([Maes et al., 2007](#))
- Anti-human nuclear dUTPase ([Halpin et al., 2017](#))



In one, small study, immunoadsorption, the process of removing autoantibodies, produced lasting symptomatic improvement in the majority of people with ME tested ([Scheibenbogen, 2018](#)).

(Right: B cells from people with ME before and after stimulation, [Mensah et al. 2018](#)).

THANKS TO OUR REVIEWERS:

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To learn about these and other studies, visit [me-pedia.org](#), the [myalgic encephalomyelitis wiki](#).
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