



Research Summary: CFS #1

As featured in Dr. Kenny Mittelstadt's video:
The Real Reason ME/CFS Crashes After Exercise (Chronic Fatigue Syndrome)
Date of Publication: 06/23/2026

Research Context:

For years, the standard advice for ME/CFS included graded increases in physical activity, built on the assumption that fatigue in this condition works the same way it does in other illnesses: that the body, given consistent exercise signals, will adapt and build tolerance over time. The research below helped shift that assumption entirely. What these studies reveal is that something specific is happening in the recovery process itself in ME/CFS patients, and that understanding this pattern changes both how we interpret the symptom of crashing after activity and what a thoughtful next step actually looks like.

Key Findings from the Research:

Study 1 (PMID 35358096):

Germain et al. tracked 1,157 plasma metabolites (the molecules in the bloodstream that reflect what the body's chemistry is doing) in 60 ME/CFS patients and 45 healthy sedentary controls across four time points: before and after two separate maximal exercise tests separated by 24 hours. In healthy controls, the gap between day-one and day-two metabolic patterns was minimal. The body responded, recovered, and came back ready. In ME/CFS patients, the opposite happened. The differences between the two exercise sessions grew larger, not smaller. The metabolic patterns moved further apart during the recovery window, pointing to a disruption in how the body processes and recovers from physical effort at the chemical level. One of the most consistent patterns involved glutamate metabolism, a pathway connected to energy production and nervous system signaling. This was a pilot study involving a relatively small number of participants, so the findings are best understood as a meaningful signal that warrants further investigation rather than a definitive conclusion.

Study 2 (PMID 38965566):

Keller et al. conducted the largest two-day cardiopulmonary exercise test (CPET) study in ME/CFS to date, involving 84 ME/CFS patients and 71 healthy sedentary controls. A CPET measures how the heart, lungs, and metabolism respond to maximum physical effort. In healthy people, performance on day two holds steady or improves. In the ME/CFS group, researchers found significant measurable drops on day two across heart rate, oxygen consumption, cardiovascular output, and several other markers. Critically, when researchers matched ME/CFS patients to healthy controls by fitness level, the patients still declined while the controls held steady. This directly challenges the explanation that the problem is simply deconditioning or being out of shape.

Study 3 (PMID 35628033):

Vink and Vink-Niese published a review examining the evidence that had previously supported graded exercise therapy (GET) as a treatment for ME/CFS, in the context of the British National Institute for Health and Care Excellence (NICE) updating its 2021 guidelines. NICE concluded, after a comprehensive review of the literature, that GET was not supported by adequate evidence and should no longer be recommended. This review analyzed the specific design problems in the trials that had underpinned GET: reliance on subjective outcomes in non-blinded studies, mismatched patient groups, selective reporting, and a failure to account for objective measures. The authors found that when objective markers of improvement were applied, the evidence for GET collapsed. The NICE reversal was not a softening of a recommendation.



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Functional Medicine Connections:

Here is how these findings connect as a pattern rather than isolated facts. In a healthy system, exertion draws on energy reserves, the body detects the deficit, and recovery mechanisms kick in to restore and sometimes expand capacity. That cycle of stress and adaptation is the basis for why exercise generally helps most fatigue conditions.

In ME/CFS, that cycle appears to be interrupted. The metabolic data from Germain et al. shows that the recovery period itself is where the divergence between patients and healthy controls is most pronounced. The CPET data from Keller et al. shows that this disruption is measurable at the level of heart, lung, and oxygen function, and that it persists even when fitness level is accounted for. Together, these patterns point toward a system where the mechanism that should be refilling the energy account is not functioning predictably.

From a systems perspective, this connects to several upstream questions: What is the state of the autonomic nervous system, which regulates how the body shifts between output and recovery? What is happening at the mitochondrial level, where ATP (the body's energy currency) is produced? Is there ongoing immune activation that is keeping the system in a state of heightened demand?

Practical Reflections & Takeaways:

When you think about the times your symptoms have worsened after physical, cognitive, or emotional effort, what patterns have you noticed about how long it takes to recover and what seems to affect that recovery window?

If you have received the advice to gradually increase activity and found that it made things worse rather than better, what did that experience tell you about how your body is currently responding, and how have you adjusted your approach since?

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