RECOVER
Researching COVID to Enhance Recovery

FACT SHEET

FAQs: Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS)

This fact sheet contains commonly asked questions and answers about ME/CFS, the RECOVER Initiative, and Long COVID. This content is compiled from inquiries received by RECOVER and includes references to peer-reviewed research and other public sources of information. The information shared here may change and be updated as we learn more about these topics.

What is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute sequelae of SARS-CoV-2 infection (PASC)?

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, chronic, complex, and systemic disease associated with neurological, immunological, autonomic, and energy metabolism dysfunction[1]. Individuals with ME/CFS experience a range of symptoms, some of which can be similar to those suffering from post-acute sequelae of SARS-CoV-2 infection (PASC), also known as Long COVID. Those working within RECOVER believe this research could benefit not only people with Long COVID but also shed light upon other post-acute infection syndromes like ME/CFS.

What research is NIH doing on PASC/Long COVID that could help to better understand ME/CFS given the common symptoms of both conditions?

Symptoms of PASC can be similar to those of ME/CFS, and many people suffering from PASC or Long COVID may even meet established criteria for a diagnosis of ME/CFS. Scientists suspect that many cases of ME/CFS develop following an infection, but so far research has not found a specific virus that causes the disease[2,3,4]. Research on PASC/Long COVID is unique because many individuals experienced infection with SARS-CoV-2, albeit different variants, at a known point in time and tracked their symptoms and health status from when they found out they were infected with the virus. Due to the number of people experiencing the same infection and the heightened public awareness of COVID, this situation enables researchers the opportunity to understand how these syndromes develop, and potentially how to treat and prevent them.

Research awards through RECOVER are made on a competitive basis in response to open solicitations. When the NIH released the first Research Opportunity Announcements (ROAs) for RECOVER in February 2021, investigators with expertise in ME/CFS and other post-infection illnesses were encouraged to apply.

The RECOVER Initiative held a RECOVER Research Review (R3) webinar on April 12, 2022, about commonalities shared by PASC/Long COVID with other disorders and post-infection illnesses. You can find information about this webinar on the R3 Webinar Series webpage and watch the recording on YouTube.

In addition to RECOVER studies, clinicians at the NIH National Institute of Neurological Disorders and Stroke (NINDS), Dr. Avindra Nath and Dr. Brian Walitt have developed a clinical study modeled on the NIH intramural ME/CFS protocol. The goal of the study is to observe and describe the range of medical syndromes that occur after an acute SARS-CoV-2 infection. This protocol will include tele-interviews and online questionnaires, as well as long-term follow-up.

In 2017, the NIH awarded four grants to establish a coordinated scientific research effort on ME/CFS. This initiative supported the creation of a consortium made up of three Collaborative Research Centers (CRC) and a Data Management Coordinating Center (DMCC). The CRCs each conduct independent research but also collaborate on several projects. Together, this consortium forms the ME/CFS Research Network to help advance knowledge on ME/CFS. The NIH recently recompeted the funding to support this research network.

The NIH remains committed to supporting critical research on both ME/CFS and PASC/Long COVID. We believe that people affected by ME/CFS may benefit from insights gained from research on PASC/Long COVID, and vice versa.

Has NIH included ME/CFS as a control arm in RECOVER research studies?

There is no ME/CFS cohort used as a control arm in RECOVER studies. However, post-infection illness experts contribute to RECOVER in a variety of ways. View the list of post-infection illness experts working on RECOVER.

Can I participate in RECOVER research studies if I have other diagnoses, including a post-infection condition diagnosis like ME/CFS, dysautonomia, or postural orthostatic tachycardia syndrome (POTS)?

Yes, RECOVER is enrolling people with and without other diagnoses. People with other conditions like ME/CFS, dysautonomia, and POTS may participate in RECOVER research. You also do not need to have COVID or Long COVID to participate in RECOVER research.

As an individual with ME/CFS, will I receive treatment if I participate in a RECOVER study (for example, receive Paxlovid)?

RECOVER is not currently testing possible interventions for Long COVID.
As announced recently, the RECOVER initiative plans to launch clinical trials in 2023. Participating in clinical trials will include receiving treatments or therapies.

You can read more at this announcement on the RECOVER website. Please continue to check the website for more news and announcements about RECOVER clinical trials.

Are people with ME/CFS more likely to get Long COVID than people without ME/CFS?

We don't know yet. As the CDC's webpage on the long-term effects of COVID-19 explains, researchers, including those who are part of RECOVER, are working to understand which people or groups of people are more likely to have post-COVID conditions (also called Long COVID), and why. Studies have shown that some groups of people—including people who had underlying health conditions before COVID-19—may be more likely to develop post-COVID conditions[5,6].

Should people with Long COVID and/or ME/CFS also be tested for mitochondrial dysfunction?

RECOVER has not published research findings on this topic to date. However, RECOVER's adult study protocol lists the many questions and tests that research participants take part in. Not all participants take all tests; that is, some advance to different tiers of the study to take different types of tests. See Appendix 2 on page 53 of the adult study protocol for a list of laboratory tests, Appendix 3 on page 54 for a list of Tier 2 tests, and Appendix 4 on page 56 for a list of Tier 3 tests.

Why would RECOVER plan clinical trials that test exercise and forms of cognitive behavioral therapy (CBT) as treatments for Long COVID as opposed to testing much needed drugs?

We understand concerns about the use of these interventions in clinical trials as they could be harmful to the health of people with post-acute infection syndromes like ME/CFS. However, these therapies might be beneficial to many other individuals with Long COVID. As is the case for all RECOVER studies, no clinical trial participant will

have to undergo a test or procedure that could worsen their health. RECOVER clinical trials will test a variety of therapies and interventions – including pharmaceuticals, to prevent and treat Long COVID and trial participants will be able to select the trial that is most appropriate for their health condition and medical history.

Are there other ways for people living with ME/CFS, their families or caregivers, or patient advocates to get involved with NIH research on ME/CFS?

The National Advisory Neurological Disorders and Stroke (NANDS) Council recently created the ME/CFS Research Roadmap Working Group to identify research priorities to move the field of ME/CFS research toward translational studies and clinical trials. The Working Group will include ME/CFS experts from the basic science and clinical research community, leaders of ME/CFS non-profit advocacy and research organizations, and people living with ME/CFS, those with a family history of ME/CFS, and those who are caregivers or care partners for people living with ME/CFS, as well as people who identify as ME/CFS patient advocates. The Working Group will be coordinated by members of the Trans-NIH ME/CFS Working Group, together with staff from the National Institute of Neurological Disorders and Stroke (NINDS) Office of Science Policy and Planning and the NINDS Office of Neuroscience Communications and Engagement. Visit the ME/CFS Research Roadmap Working Group page to learn more. For more information about NIH's research efforts on ME/CFS, please visit www.nih.gov/mecfs.

[1] Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): National Academies Press (US); 2015 Feb 10. PMID: 25695122.

[2] Komaroffj, A. L., Lipkin, W. I. (2021). Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. Trends in Molecular Medicine, 27 (9), 895-906.

[3] Hornig, M., Montoya, J. G., Klimas, N. G., Levine, S., Felsenstein, D., Bateman, L., ... & Lipkin, W. I. (2015). Distinct plasma immune signatures in ME/CFS are present early in the course of illness. Science advances, 1(1), e1400121.

[4] Centers for Disease Control and Prevention. (2018). Myalgic Encephalomyelitis/Chronic Fatigue Syndrome – Possible Causes. Division of High-Consequence Pathogens and Pathology (DHCPP), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention. Atlanta, GA. Available at: https://www.cdc.gov/me-cfs/about/possible-causes.html

[5] Subramanian, A., Nirantharakumar, K., Hughes, S., Myles, P., Williams, T., Gokhale, K. M., ... & Haroon, S. (2022). Symptoms and risk factors for long COVID in non-hospitalized adults. *Nature medicine, 28*(8), 1706-1714.

[6] Hastie, C. E., Lowe, D. J., McAuley, A., Winter, A. J., Mills, N. L., Black, C., ... & Pell, J. P. (2022). Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. *Nature communications, 13*(1), 1-9.