Incidence and Prevalence of Post-COVID-19 Myalgic Encephalomyelitis: A Report from the Observational RECOVER-Adult Study

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ABSTRACT

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may occur after infection. How often people develop ME/CFS after SARS-CoV-2 infection is unknown.

OBJECTIVE: To determine the incidence and prevalence of post-COVID-19 ME/CFS among adults enrolled in the Researching COVID to Enhance Recovery (RECOVER-Adult) study.

DESIGN, SETTING, AND PARTICIPANTS: RECOVER-Adult is a longitudinal observational cohort study conducted across the U.S. We included participants who had a study visit at least 6 months after infection and had no pre-existing ME/CFS, grouped as (1) acute infected, enrolled within 30 days of infection or enrolled as uninfected who became infected (n=4515); (2) post-acute infected, enrolled greater than 30 days after infection (n=7270); and (3) uninfected (1439).

MEASUREMENTS: Incidence rate and prevalence of post-COVID-19 ME/CFS based on the 2015 Institute of Medicine ME/CFS clinical diagnostic criteria.

RESULTS: The incidence rate of ME/CFS in participants followed from time of SARS-CoV-2 infection was 2.66 (95% CI 2.63–2.70) per 100 person-years while the rate in matched uninfected participants was 0.93 (95% CI 0.91–10.95) per 100 person-years: a hazard ratio of 4.93 (95% CI 3.62–6.71). The proportion of all RECOVER-Adult participants that met criteria for ME/CFS following SARS-CoV-2 infection was 4.5% (531 of 11,785) compared to 0.6% (9 of 1439) in uninfected participants. Post-exertional malaise was the most common ME/CFS symptom in infected participants (24.0%, 2830 of 11,785). Most participants with post-COVID-19 ME/CFS also met RECOVER criteria for long COVID (88.7%, 471 of 531).

LIMITATIONS: The ME/CFS clinical diagnostic criteria uses self-reported symptoms. Symptoms can wax and wane.

CONCLUSION: ME/CFS is a diagnosable sequela that develops at an increased rate following SARS-CoV-2 infection. RECOVER provides an unprecedented opportunity to study post-COVID-19 ME/CFS.

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) can be triggered following acute infection. A landmark prospective study followed patients from the time of acute infection with Epstein-Barr virus, *Coxiella burnetii*, or Ross River virus and found that 11% met ME/CFS criteria at 6 months post-infection.[1]

Researching COVID to Enhance Recovery (RECOVER) is a national initiative funded by the National Institutes of Health to conduct research on post-COVD-19 conditions, including postacute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID.[2] One component of RECOVER, the longitudinal observational adult cohort (RECOVER-Adult), reported that 85% of participants with PASC had fatigue.[3] Other symptoms that PASC patients experience include post-exertional malaise (PEM), brain fog, dizziness, and unrefreshing sleep. These are consistent with the core symptoms that are diagnostic for ME/CFS that include new onset of fatigue that has persisted for at least 6 months and is accompanied by a reduction in pre-illness activities, post-exertional malaise (PEM), and unrefreshing sleep plus either cognitive impairment or orthostatic intolerance (OI).[4]

We applied the ME/CFS clinical diagnostic criteria to (1) determine the incidence rate of post-COVID-19 ME/CFS among prospectively followed participants enrolled within 30 days of SARS-CoV-2 infection, and (2) compare the occurrence of new onset ME/CFS in participants with and without SARS-CoV-2 infection who were enrolled in the RECOVER-Adult study. We hypothesized that there would be an increased rate of ME/CFS in RECOVER-Adult participants infected with SARS-CoV-2 compared to matched uninfected participants.

METHODS

The study was approved by the institutional review board at NYU Grossman School of Medicine, serving as a single institutional review board. All participants provided written informed consent. The study is registered at NCT05172024.

Study Design RECOVER-Adult includes participants with and without SARS-CoV-2 infection.[2] Participants with SARS-CoV-2 infection met World Health Organization suspected, probable, or confirmed criteria for infection and were enrolled in RECOVER from 83 sites in 33 states plus Puerto Rico and Washington, DC.[5] Uninfected individuals did not meet any WHO criteria for infection and had a documented negative SARS-CoV-2 nucleic acid and nucleocapsid antibody test result at the time of enrollment.

Participants The RECOVER-Adult study included 15,181 people enrolled as (1) acute infected, enrolled within 30 days of infection; (2) post-acute infected, enrolled greater than 30 days after infection; or (3) uninfected. As SAR-CoV-2 infections continued to occur in study participants, participants who were initially enrolled as uninfected and then became infected during the study were reclassified as acute infected for post-infection visits (*n*=954) and were not included in the uninfected analyses. We excluded participants people who were hospitalized for COVID-19 (*n*=294), those who did not respond to the symptom questionnaires (*n*=640), any infected participant that did not undergo a study visit ≥6-month after incident SARS-CoV-2 infection (*n*=773), and those with pre-existing ME/CFS (*n*=198 infected, *n*=22 uninfected). The remaining 11,785 infected participants were assigned to three groups using the first qualifying visit at least 6 months from index infection: (1) post-COVID-19 ME/CFS participants, (2) ME/CFS-like participants, and (3) participants who did not report any ME/CFS symptoms.

The 1439 uninfected participants were classified to parallel the infected participant groups.

Exposure The exposure was SARS-CoV-2 infection.

Data Source Outcome measures were drawn from self-reported symptoms and comorbid medical conditions, as reported by participants at 3-month interval study visits.[2] All data were ascertained from the September 2024 data lock.

Outcome The primary outcome was new ME/CFS determined using the Institute of Medicine (IOM) ME/CFS clinical diagnostic criteria that require fatigue accompanied by physical impairment, PEM, unrefreshing sleep and either cognitive impairment or OI.[4] The first symptom survey response at least 6 months, or later from first infection was used to group infected participants as post-COVID-19 ME/CFS and ME/CFS-like; for uninfected participants, we included symptoms from any survey response.

Questionnaires to Assess ME/CFS Symptoms Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health 10 was used to assess (1) severity of fatigue over the past 7 days and (2) physical impairment by inability to carry out daily physical activities. PROMIS Sleep Disturbance question "My sleep was refreshing" was used to assess the severity of unrefreshing sleep over the past 7 days; responses of "Not at all" or "A little bit" were considered moderate to severe unrefreshing sleep. Cognitive impairment was determined by having a self-reported Neuro-QoL cognition T-score of ≤40 (1 SD below national mean) or a raw Neuro-QoL score of <24.[3,6] PEM and OI were assessed with a question asking if the participant had "post-exertional malaise (symptoms worse after even minor physical or mental effort)" (PEM) and "Feeling faint, dizzy, 'goofy'; difficulty thinking soon after standing up from a sitting or lying position" (OI), respectively. Responses that

indicated the presence of PEM or OI included "Yes, I have it NOW," or "Yes, and I STILL HAVE IT." Frequency and severity measures were not available for these symptoms; thus, all positive symptoms were considered qualifying.

ME/CFS was defined as reporting moderate to very severe fatigue over the past 7 days plus moderate to complete interference with ability to carry out every day physical activities, AND presence of PEM, AND not at all or a little bit of refreshing sleep over the past 7 days PLUS the presence of OI and/or a Neuro-QoL cognitive T-score of <40 or raw score of <24. Those having at least one ME/CFS symptom but not meeting all the above criteria were considered ME/CFS-like.

The RECOVER case definition for PASC identified four clusters composed of 44 symptoms among those with PASC.[3] Cluster 1 was characterized primarily by loss/change in smell or taste, and those participants had lowest symptom burden and quality of life impairment. Nearly all participants in cluster 2 had PEM (99%); half had dizziness and gastrointestinal symptoms; none had brain fog. Cluster 3 was defined by the presence of brain fog (100%) in addition to PEM (99%) and other symptoms. Cluster 4 participants had high levels of all symptoms, including PEM, dizziness, gastrointestinal symptoms, and brain fog, and overall had the worst quality of life. We determined which cluster post-COVID-19 ME/CFS and ME/CFS-like participants were assigned to in the study visit used for analysis.

Statistical Analysis RECOVER-Adult data collected between October 2021 and September 2024, and stored on the RECOVER analytic platform, Seven Bridges, were used in this analysis. Analytic groups were created using the ME/CFS criteria. Chi-square tests were used to assess differences in demographics between analytic groups and the two-sample *t*-test to test whether age at enrollment differed among the infected and uninfected groups. Fisher's exact test was used to determine differences in comorbid conditions between infected and uninfected participants. All analyses were conducted by restricting infected participants to those enrolled within 30 days of the first infection and then repeated the analyses with all participants regardless of time from SARS-CoV2 infection.

The incidence rate of post-COVID-19 ME/CFS was calculated among participants enrolled <30 days after acute SARS-CoV-2 infection compared to matched uninfected controls. We used propensity score matching with replacement to minimize selection bias given differences in baseline characteristics between infected and uninfected participants.[7] Propensity scores were estimated using logistic regression and adjusting for potential demographic and comorbidity condition confounders that were unrelated to SARS-CoV-2 infection but had features that were related to ME/CFS (Supplemental Material Table 1). We paired each uninfected participant with the acutely infected participant who had the closest propensity score that was within 0.2 standard deviations of the logit of propensity score ("greedy matching"). Among the 1439 uninfected participants, 847 (58.9%) had no matched acute infected participants, indicating substantial differences between the characteristics of the acutely infected and uninfected cohorts. After matching, the standard mean differences (SMD) were 0.036 meaning that the propensity score matching was successful. The demographic characteristics and comorbid conditions in the acute infected and uninfected groups before and after propensity matching are provided (Supplemental Material Tables 2 and 3). The hazard ratio for acute COVID-19 infection compared with no infection was calculated. Finally, we determined which PASC cluster the post-COVID-19 ME/CFS and ME/CFS-like participants were assigned to at their first qualifying visit. We considered a two-sided *P* value of less than 0.05 to be statistically significant. Analyses were conducted using SAS Studio, R, and Python 3.11 with scikit-learn (1.3.1; http://scikit-learn.org), lifelines (0.29.1; https://github.com/CamDavidsonPilon/lifelines), and pymatch (0.3.4; https://github.com/benmiroglio/pymatch) packages.

RESULTS

ME/CFS prevalence was determined among infected participants and uninfected participants (Fig. 1). Among the 11,785 infected participants, 531 (4.5%) met ME/CFS diagnostic criteria at the first study visit at least 6 months after acute SARS-CoV-2 infection; 4692 (39.8%) were ME/CFS-like, with at least one ME/CFS symptom; and 6562 (55.7%) did not report any ME/CFS symptoms. Of the 1439 uninfected participants, 9 (0.6%) met ME/CFS clinical diagnostic criteria, 232 (16.1%) had at least one ME/CFS symptom, and 1198 (83.3%) did not report any ME/CFS symptoms.

The 4515 acute infected participants provided the opportunity to estimate the incidence of new post-COVID-19 ME/CFS cases. The incidence rate of ME/CFS among acute infected participants was 2.66 (95% CI 2.63–2.70) per 100 person-years, which was significantly greater than the incidence rate in the propensity score-matched uninfected participants (0.93 per 100 person-years, 95% CI 0.91–0.95) (*p*<.0001). This is an attributable risk of 1.74 per 100 person-years with a significantly different incidence rate ratio test between SARS-CoV-2 infected and uninfected participants (*p* <.0001).[8] Furthermore, the hazard ratio for developing ME/CFS in acute infected participants compared to uninfected participants was 4.93 (95% CI 3.62–6.71) (*p*<.005).

Compared to those never meeting ME/CFS criteria in the infected cohort, those with post-COVID-19 ME/CFS were more likely to be White, female, between 46 to 65 years of age, and live in a rural area, and less likely to have been vaccinated at enrollment and to have completed college (Table 1). Since there were only nine participants that

met ME/CFS criteria in the uninfected cohort, the sample size was too small to compare to the other uninfected groups (Table 2).

Post-COVID-19 ME/CFS participants were more likely to report chronic pain syndrome or fibromyalgia, neuromuscular disease, chronic obstructive pulmonary disease, dementia or cognitive impairment, postural orthostatic tachycardia syndrome (POTS), dysautonomia or autonomic dysfunction, movement disorder, other mental health disorder, and use of oxygen at home compared to uninfected participants (Table 3). The remaining medical and psychiatric conditions occurred at similar or lower rates compared to those who did not meet ME/CFS criteria.

We assessed the proportion of acute infected, post-acute infected, and uninfected participants who reported each ME/CFS symptom (Fig. 2). PEM was the most frequently reported symptom in both acute infected participants

(15.9%, 717/4515) and post-acute infected participants (29.1%, 2113/7270). OI was the next most common symptom, reported in 14.4% (652/4515) of acute infected participants and in 25.0% (1815/7270) of post-acute infected participants. Unrefreshing sleep (11.0%, 498/4515), cognitive impairment (10.1%, 457/4515), and fatigue (9.3%, 418/4515) were reported at similar rates in acute infected participants. Cognitive impairment occurred in 23.7% (1725/7270) of post-acute infected participants followed by fatigue (20.7%, 1508/7270) then unrefreshing sleep (19.8%, 1436/7270). All ME/CFS symptoms were lower in uninfected compared to infected participants.

Eighty-nine percent (471/531) of post-COVID-19 ME/CFS participants met PASC criteria and most (45.0%, 239/531) were assigned to PASC cluster 4, the cluster with the highest frequency of all symptoms including ME/CFS symptoms (Fig. 3). Twenty-nine percent (156/531)

Table 1 Demographic Characteristics of *Infected* Participants of the RECOVER-Adult Study

	Infected groups (number (%))			P value	
	Post-COVID-19 ME/CFS	ME/CFS-like	Never met criteria	Post-COVID-19 ME/CFS vs never	ME/CFS-like vs never
Enrollment age				<0.001	0.076
Median (IQR)	48 (18)	45 (24)	43 (26)		
N	531	4692	6562		
Age category at enrollment (*n*, %)				<0.001	<0.001
18–45	223 (42.0)	2367 (50.5)	3512 (53.5)		
46–65	275 (51.8)	1757 (37.5)	2080 (31.7)		
>65	33 (6.1)	566 (12.1)	968 (14.8)		
Missing (<18)	0 (0)	2 (0.04)	2 (0.03)		
Sex at birth				<0.001	<0.001
Female	422 (79.5)	3552 (75.7)	4626 (70.5)		
Intersex	0 (0)	1 (0.02)	3 (0.05)		
Male	107 (20.2)	1114 (23.8)	1913 (29.2)		
Missing	2 (0.4)	25 (0.5)	20 (0.3)		
Race				<0.001	<0.001
Asian, non-Hispanic	15 (2.8)	211 (4.5)	464 (7.1)		
Black, non-Hispanic	45 (8.5)	630 (13.4)	941 (14.3)		
Hispanic	77 (14.5)	673 (14.3)	871 (13.3)		
Multiracial/ethnic	49 (9.2)	402 (8.6)	457 (7.0)		
White, non-Hispanic	328 (61.8)	2646 (56.4)	3661 (55.8)		
Other	15 (28)	106 (2.3)	144 (2.2)		
Missing	2 (0.4)	24 (0.5)	24 (0.4)		
Vaccine at enrollment				<0.001	0.068
Yes	459 (86.4)	4203 (89.6)	5945 (90.6)		
No	58 (10.9)	356 (7.6)	440 (6.7)		
Don't know	0 (0)	2 (0.04)	4 (0.1)		
Missing	11 (2.1)	107 (2.3)	150 (2.3)		
Prefer not to answer	3 (0.6)	24 (0.5)	23 (0.4)		
Education				<0.001	<0.001
Bachelors/advanced degree	291 (54.8)	2832 (60.4)	4602 (70.1)		
High school/some college	217 (40.9)	1659 (35.4)	1716 (26.2)		
Not complete high school	15 (2.8)	151 (3.2)	186 (2.8)		
Missing	3 (0.6)	30 (0.6)	35 (0.5)		
Prefer not to answer	5 (1.0)	20 (0.4)	23 (0.4)		
Rural				<0.001	<0.001
No	493 (92.8)	4421 (94.2)	6324 (96.4)		
Yes	38 (7.2)	271 (5.8)	238 (3.6)		
Medically underserved area				0.616	<0.001
No	407 (76.7)	3384 (72.1)	4966 (75.7)		
Yes	124 (23.4)	1308 (27.9)	1596 (24.3)		

Table 2 Demographic Characteristics of *Uninfected* Participants of the RECOVER-Adult Study

	Uninfected groups (number (%))			*P* value	
	ME/CFS	ME/CFS-like	Never met criteria	ME/CFS vs never	ME/CFS-like vs never
Enrollment age				0.758	0.653
Median (IQR)	44 (21)	51 (27)	49 (27)		
N	9	232	1198		
Age category at enrollment (*n*, %)				0.826	0.882
18–45	5 (55.6)	104 (44.8)	554 (46.2)		
46–65	3 (33.3)	89 (38.4)	439 (36.6)		
>65	1 (11.1)	39 (16.8)	205 (17.1)		
Missing (<18)	0 (0)	0 (0)	0 (0)		
Sex at birth				<0.001	0.258
Female	4 (44.4)	145 (62.5)	815 (68.0)		
Male	4 (44.4)	86 (37.1)	378 (31.6)		
Missing	1 (1.1)	1 (0.4)	5 (0.4)		
Race				0.589	0.911
Asian, non-Hispanic	0 (0)	15 (6.5)	75 (6.3)		
Black, non-Hispanic	1 (11.1)	46 (19.8)	238 (19.8)		
Hispanic	0 (0)	24 (10.3)	109 (9.1)		
Multiracial/ethnic	0 (0)	21 (19.1)	88 (7.4)		
White, non-Hispanic	7 (77.8)	121(52.2)	657 (54.8)		
Other	0 (0)	4 (1.7)	26 (2.2)		
Missing	1 (1.1)	1 (0.4)	5 (0.4)		
Vaccine at enrollment				0.550	0.654
Yes	7 (77.8)	208 (89.7)	1,098 (91.7)		
No	0 (0)	9 (3.9)	56 (4.7)		
Don't know	0 (0)	1 (0.4)	0 (0)		
Missing	2 (22.2)	13 (5.6)	43 (3.6)		
Prefer not to answer	0 (0)	1 (0.4)	1 (0.1)		
Education				0.726	<0.001
Bachelors/advanced degree	4 (44.4)	123 (53.0)	772 (64.4)		
High school/some college	3 (33.3)	88 (37.9)	372 (31.2)		
Not complete high school	0 (0)	19 (8.2)	47 (3.9)		
Missing	2 (22.2)	1 (0.4)	6 (0.5)		
Prefer not to answer	0 (0)	1 (0.4)	1 (0.1)		
Rural				0.515	0.203
No	9 (100.0)	217 (93.5)	1144 (95.5)		
Yes	0 (0)	15 (6.5)	54 (4.5)		
Medically underserved area				0.068	0.138
No	9 (100.0)	158 (68.1)	873 (732.9)		
Yes	0 (0)	74 (31.9)	325 (27.1)		

of post-COVID-19 ME/CFS participants were assigned to cluster 3, 10% (52/531) were assigned to cluster 2, and 5% (24/531) were assigned to cluster 1. Eleven percent of post-COVID-19 ME/CFS participants were PASC indeterminant. In contrast, most ME/CFS-like participants were PASC indeterminant with only 8% (377/4692) assigned to cluster 4, 9% (410/4692) assigned to cluster 3, 6% (300/4692) assigned to cluster 2, and 10% (471/4692) assigned to cluster 1 (Fig. 3).

DISCUSSION

Because ME/CFS can be a consequence of acute infection with viral and non-viral agents,[1,9,10] we hypothesized it would be a sequela of SARS-CoV-2 infection. The prospective design of the RECOVER-Adult study provided the opportunity to estimate the incidence and prevalence of ME/CFS after infection with SARS-CoV-2. Of the 4515

participants that enrolled in RECOVER Adult within 30 days of their acute SARS-CoV-2 infection and were followed more than 6 months, 2.66 per 100 person-years vs. 0.93 per 100 person-years in matched uninfected participants met the IOM clinical diagnostic criteria for ME/CFS for an attributable risk of ME/CFS after SARS-CoV-2 exposure of approximately 1.74 per 100 person-years. A pre-COVID pandemic study conducted by the CDC estimated the incidence rate of ME/CFS at 0.18 per 100 person-years.[11] This low incidence rate may reflect the focus on fatigue as the main outcome rather than the full constellation of ME/CFS symptoms. An electronic health record study found the incidence of post-COVID-19 chronic fatigue was 1.8 per 100 person-years.[12] This is between the rate of ME/CFS we found in the acutely infected and uninfected cohorts and is likely an underestimate because the study relied on ICD coding and, prior to a 2023 update to ICD-10, there was not a specific code for ME/CFS.[13] Our results provide evidence that the rate and

Table 3 Comorbidities in Post-COVID-19 ME/CFS and ME/CFS-like Compared to those Who Never Met ME/CFS Criteria and Total Infected and Uninfected

	Post-COVID-19 ME/CFS (n=531)	ME/CFS-like (n=4692)	Never Met Criteria (n=6562)	P value	Infected (n=11,785)	Uninfected (n=1439)	P value
Anxiety, depression or PTSD	68 (12.8%)	891 (19%)	908 (13.8%)	<.0001	1867 (15.8%)	531 (36.9%)	<.0001
Cardiovascular disease	43 (8.1%)	492 (10.5%)	774 (11.8%)	.0063	1309 (11.1%)	389 (27%)	<.0001
Obesity	52 (9.8%)	659 (14%)	831 (12.7%)	.0064	1542 (13.1%)	351 (24.4%)	<.0001
Asthma	49 (9.2%)	429 (9.1%)	544 (8.3%)	.2428	1022 (8.7%)	237 (16.5%)	<.0001
Other mental health disorder	21 (4%)	215 (4.6%)	175 (2.7%)	<.0001	411 (3.5%)	233 (16.2%)	<.0001
Rheumatologic, autoimmune or connective tissue disease	32 (6%)	262 (5.6%)	309 (4.7%)	.0697	603 (5.1%)	161 (11.2%)	<.0001
Diabetes and specific type	17 (3.2%)	210 (4.5%)	306 (4.7%)	.2932	533 (4.5%)	140 (9.7%)	<.0001
Immunocompromised condition	23 (4.3%)	139 (3%)	185 (2.8%)	.1434	347 (2.9%)	143 (9.9%)	<.0001
Chronic pain syndrome or fibromyalgia	37 (7%)	169 (3.6%)	76 (1.2%)	<.0001	282 (2.4%)	102 (7.1%)	<.0001
Neuromuscular disease	16 (3.0%)	125 (2.7%)	79 (1.2%)	<.0001	220 (1.9%)	85 (5.9%)	<.0001
Other chronic lung disease	10 (1.9%)	58 (1.2%)	61 (0.9%)	.0592	129 (1.1%)	67 (4.7%)	<.0001
Active cancer	5 (0.9%)	61 (1.3%)	116 (1.8%)	.0823	182 (1.5%)	61 (4.2%)	<.0001
Schizophrenia or bipolar disorder	9 (1.7%)	75 (1.6%)	61 (0.9%)	.0032	145 (1.2%)	82 (5.7%)	<.0001
Chronic obstructive pulmonary disease	14 (2.6%)	77 (1.6%)	56 (0.9%)	<.0001	147 (1.3%)	62 (4.3%)	<.0001
Kidney disease	4 (0.8%)	84 (1.8%)	92 (1.4%)	.0875	180 (1.5%)	53 (3.7%)	<.0001
Polycystic ovary disease	5 (0.9%)	99 (2.1%)	126 (1.9%)	.1675	230 (2%)	54 (3.8%)	<.0001
Chronic liver disease	6 (1.1%)	38 (0.8%)	51 (0.8%)	.6118	95 (0.8%)	38 (2.6%)	<.0001
Stroke or bleed	9 (1.7%)	40 (0.9%)	55 (0.8%)	.1337	104 (0.9%)	38 (2.6%)	<.0001
Dementia or cognitive impairment	9 (1.7%)	62 (1.3%)	35 (0.5%)	<.0001	106 (0.9%)	32 (2.2%)	<.0001
Movement disorder	6 (1.1%)	38 (0.8%)	25 (0.4%)	.0021	69 (0.6%)	29 (2.0%)	<.0001
POTS, dysautonomia or autonomic dysfunction	9 (1.7%)	45 (1.0%)	21 (0.3%)	<.0001	75 (0.6%)	25 (1.7%)	<.0001
Seizure disorder	5 (0.9%)	38 (0.8%)	34 (0.5%)	.0908	77 (0.7%)	16 (1.1%)	.0635
Use of oxygen at home	9 (1.7%)	22 (0.5%)	23 (0.4%)	.0011	54 (0.5%)	22 (1.5%)	<.0001
Sickle cell anemia	2 (0.4%)	9 (0.2%)	7 (0.1%)	.1411	18 (0.2%)	16 (1.1%)	<.0001
CNS infection, inflammatory or demyelinating disease	3 (0.6%)	23 (0.5%)	18 (0.3%)	.0974	44 (0.4%)	10 (0.7%)	.0787

risk of developing ME/CFS following SARS-CoV-2 infection is significantly increased and is supported by other studies that have implicated infectious agents such as Epstein Barr Virus and Ross River Virus and non-viral diseases such as Q fever and giardiasis in the etiology of ME/CFS.[1,9,10]

The 4.5% post-COVID-19 ME/CFS prevalence rate we found in the RECOVER-Adult study is similar to the 3–4% ME/CFS prevalence rate in people with acute infection-like illness suggestive of SARS-CoV-2 infection reported by the Innovative Support for Patients with SARS-CoV-2 Infections
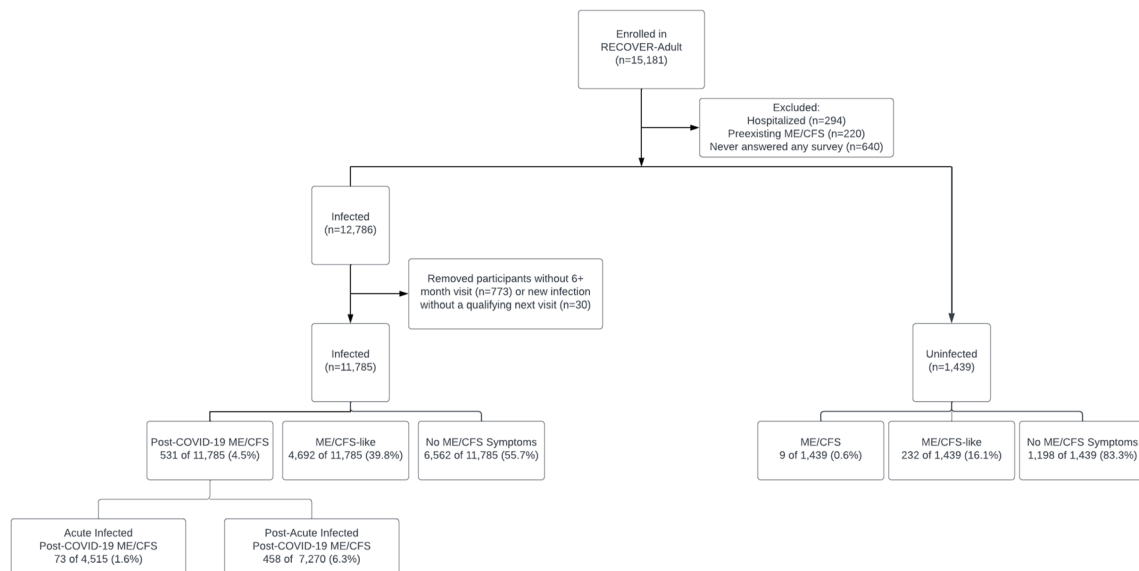
Figure 1 The ME/CFS clinical diagnostic criteria was applied to both infected and uninfected participants in the RECOVER Adult study group
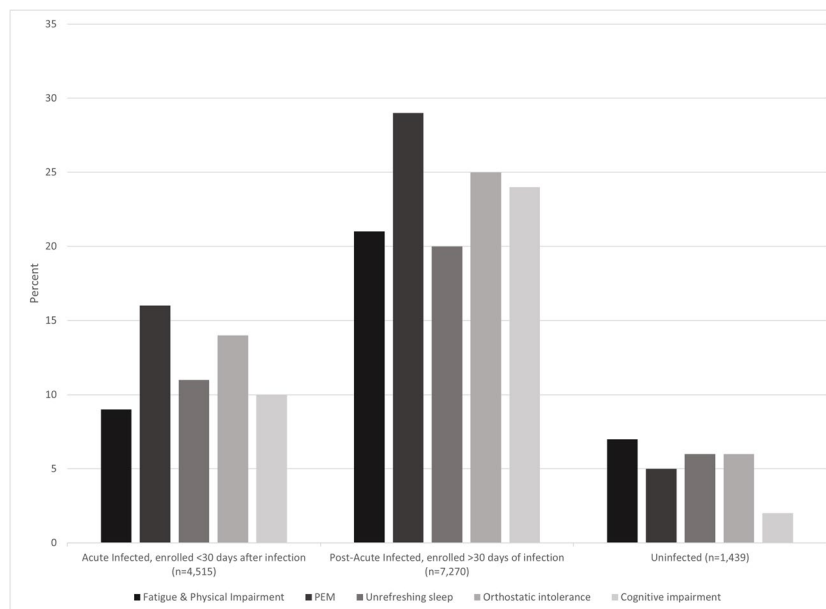
Figure 2 Percent of infected and uninfected participants with ME/CFS symptoms
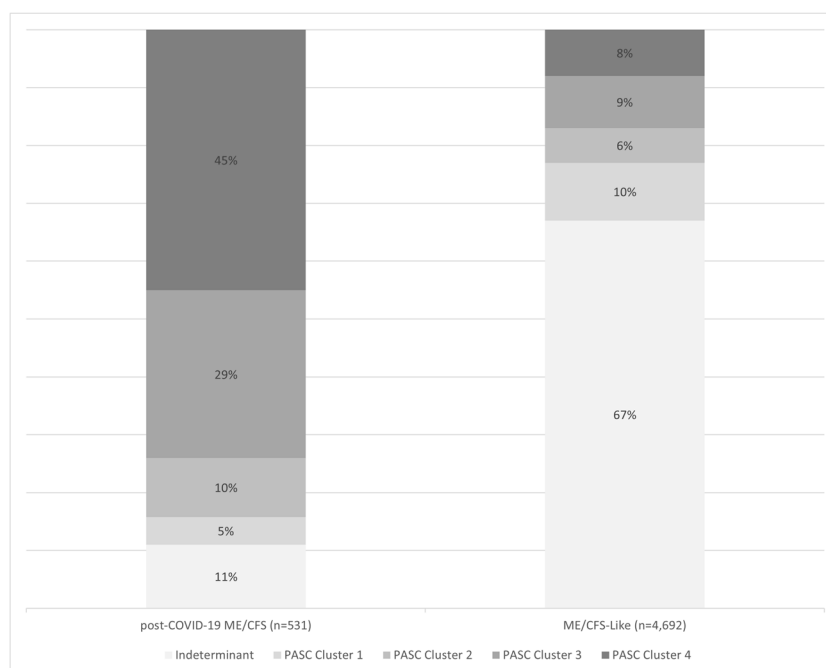

Figure 3 PASC cluster assignments at the first qualifying visit for post-COVID-19 ME/CFS and ME/CFS-like participants

Registry (INSPIRE).[14] However, these post-pandemic prevalence rates are in contrast to pre-pandemic ME/CFS prevalence estimates, which ranged from 0.2 to 1.0% of people in the U.S. and is in line with what we found in uninfected participants.[15–17] The 2021–2022 wave of the National Health Interview Survey conducted during the pandemic found that 1.3% of adults reported being diagnosed with ME/CFS by a doctor, suggesting that post-COVID ME/CFS might already be increasing national prevalence rates.[18] Our finding that 4.5% of infected RECOVER-Adult participants met criteria

for ME/CFS based on IOM diagnostic criteria is higher than any pre-pandemic prevalence estimate. While this prevalence is confounded by individuals who enrolled up to 18 months after infection and may be differentially less likely to have fully recovered from COVID, when combined with our incidence estimates from those enrolled within 30 days of SARS-CoV2 infection these data provide further evidence of the post-infectious nature of ME/CFS and confirm that it is one of the diagnosable sequelae that occurs after SARS-CoV-2 infection.[19]

Detection and diagnosis of a true positive ME/CFS case is complicated as symptoms vary in frequency and severity over the course and duration of illness.[20–22] Furthermore, the symptom(s) must be recognized as part of the ME/CFS manifestation. For example, PEM is the worsening of symptoms following physical or cognitive exertion and is an unusual phenomenon, particularly to people who are unfamiliar with the onset, experience, and triggers of exertional intolerance.[23] PEM is the cardinal feature of ME/CFS. It is the exacerbation of ME/CFS signs and symptoms that can be triggered by daily activities such as showering, driving, reading, cleaning, cooking, or conversing.[23,24] In this study, PEM was the most common symptom among acute and post-acute infected participants in RECOVER-Adult. PEM has also been identified as one of the most common and debilitating symptoms of long COVID in several studies.[3,25–27]

Cognitive impairment and OI symptoms fluctuate and are exacerbated by being in upright postures.[28–30] They were the next most common symptoms in RECOVER-Adult study infected participants. While the mechanisms driving these symptoms are not known, there are pathophysiological findings in ME/CFS that help explain these symptoms. Structural, metabolic, and inflammatory abnormalities have been found in the brain of ME/CFS patients.[31–33] Peripheral neurovascular dysregulation and reduced cerebral blood flow is characteristic of ME/CFS.[34,35] There is immune dysfunction in both the innate and adaptive immune system in ME/CFS.[36,37] Before the COVID-19 pandemic, ME/CFS was characterized as a multisystemic metabolic-inflammatory disorder showing altered bioenergetics associated with disease severity, physical exertion, and illness duration.[38–53]

Four PASC subgroups have been identified using cluster analysis in the RECOVER study.[3] Cluster 1 symptoms include loss or change in smell and taste; cluster 2 includes PEM and fatigue; cluster 3 includes brain fog, PEM, and fatigue; and cluster 4 includes fatigue, PEM, dizziness, brain fog, gastrointestinal, and palpitations.[3] Cluster 4 is the most symptomatic PASC subgroup with the highest frequency of ME/CFS defining symptoms. This study found that 90% of post-COVID-19 ME/CFS participants met PASC criteria and aligned with the cluster 4 PASC subgroup.[3] This may indicate that post-COVID-19 ME/CFS represents a severely ill subset of PASC. A careful examination of the pathophysiology in both these groups and, as appropriate, modification, and updating of the ME/CFS diagnostic criteria should be considered.

There are limitations to this study that may have contributed to an overestimation of the number post-COVID-19 ME/CFS participants in RECOVER-Adult. We excluded people with a formal diagnosis of ME/CFS prior to infection but may have missed participants who both had pre-existing qualifying symptoms and were not previously diagnosed, mischaracterizing them as new. There may be recall bias where participants were uncertain whether they had symptoms before or only after infection. We included participants with pre-existing medical and psychiatric conditions that might cause ME/CFS-like symptoms, causing a misattribution of ME/CFS. Severity of PEM and OI were not assessed which might have allowed more participants to qualify. There may be a selection bias since with PASC may be more likely to enroll in RECOVER. These issues are mitigated by the enrollment of participants within 30 days of infection.

Conversely, there are also factors that might have contributed to an underestimation of participants with post-COVID-19 ME/CFS. Hospitalized RECOVER participants were excluded and therefore were not included in the prevalence and incidence estimate of post-COVID-19 ME/CFS. The waxing/waning nature of symptoms might have caused us to miss cases. The 2015 IOM ME/CFS diagnostic criteria mostly reflect severely ill ME/CFS of many years duration and may not be ideal for identifying short duration ME/CFS. Participants might not be familiar with the concept of PEM and may not have reported it. The most severely affected individuals may have been unable to enroll in RECOVER or to have been differentially lost to follow-up because of study burden. Participants were mostly enrolled in the Omicron era, limiting our ability to assess ME/CFS frequency after earlier, more severe variants. Most participants were vaccinated, so incidence and severity may be lower and less than in an unvaccinated population.

ME/CFS is a diagnosable sequela of SARS-CoV-2 infection. RECOVER provides the opportunity to identify objective biomarkers and to study the biology, mechanisms, and natural history of post-COVID-19 ME/CFS.

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REFERENCES

1. **Hickie I, Davenport T, Wakefield D et al.** Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006;333(7568):575. https://doi.org/10.1136/bmj.38933.585764.AE

2. **Horwitz LI, Thaweethai T, Brosnahan SB et al.** Researching COVID to Enhance Recovery (RECOVER) adult study protocol: Rationale, objectives, and design. Reyes LF ed. Plos One. 2023;18(6):e0286297. https://doi.org/10.1371/journal.pone.0286297

3. **Thaweethai T, Jolley SE, Karlson EW et al.** Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023;329(22):1934. https://doi.org/10.1001/jama.2023.8823

4. Institute of Medicine. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Published online 2015.

5. *WHO COVID-19: Case Definitions.* World Health Organization; 2022. WHO/2019-nCoV/Surveillance_Case_Definition/2022.1

6. **Cella D, Lai JS, Nowinski CJ et al.** Neuro-QOL: Brief measures of health-related quality of life for clinical research in neurology. Neurology. 2012;78(23):1860-1867. https://doi.org/10.1212/WNL.0b013e318258f744

7. **Rosenbaum PR, Rubin DB.** The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55. https://doi.org/10.1093/biomet/70.1.41

8. **Sahai H, Khurshid A.** On analysis of epidemiological data involving a 2×2 contingency table: an overview of fisher's exact test and yates' correction for continuity. J Biopharm Stat. 1995;5(1):43-70. https://doi.org/10.1080/10543409508835098

9. **Levine PH, Jacobson S, Pocinki AG et al.** Clinical, epidemiologic, and virologic studies in four clusters of the chronic fatigue syndrome. Arch Intern Med. 1992;152(8):1611-1616.

10. **White PD, Thomas JM, Amess J et al.** Incidence, risk and prognosis of acute and chronic fatigue syndromes and psychiatric disorders after glandular fever. Br J Psychiatry. 1998;173(6):475-481. https://doi.org/10.1192/bjp.173.6.475

11. **Reyes M, Nisenbaum R, Hoaglin DC et al.** Prevalence and Incidence of Chronic Fatigue Syndrome in Wichita, Kansas. Arch Intern Med. 2003;163(13):1530. https://doi.org/10.1001/archinte.163.13.1530

12. **Vu Q, Fitzpatrick A, Cope J et al.** Estimates of Incidence and Predictors of Fatiguing Illness after SARS-CoV-2 Infection. Emerg Infect Dis J. 2024;30(3). https://doi.org/10.3201/eid3003.231194

13. ICD-10-CM Codes.

14. **Unger ER, Lin JMS, Wisk LE et al.** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome After SARS-CoV-2 Infection. JAMA Netw Open. 2024;7(7):e2423555. https://doi.org/10.1001/jamanetworkopen.2024.23555

15. **Jason LA, Richman JA, Rademaker AW et al.** A Community-Based Study of Chronic Fatigue Syndrome. Arch Intern Med. 1999;159(18):2129. https://doi.org/10.1001/archinte.159.18.2129

16. **Reyes M, Nisenbaum R, Hoaglin DC et al.** Prevalence and Incidence of Chronic Fatigue Syndrome in Wichita, Kansas. Arch Intern Med. 2003;163(13):1530. https://doi.org/10.1001/archinte.163.13.1530

17. **Valdez AR, Hancock EE, Adebayo S et al.** Estimating Prevalence, Demographics, and Costs of ME/CFS Using Large Scale Medical Claims Data and Machine Learning. Front Pediatr. 2019;6:412. https://doi.org/10.3389/fped.2018.00412

18. **Vahratian A, Lin JMS, Bertolli J, Unger ER.** *Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Adults: United States, 2021-2022.* National Center for Health Statistics (U.S.). National Health Interview Survey (NHIS); 2023. https://doi.org/10.15620/cdc:134504

19. Committee on Examining the Working Definition for Long COVID, Board on Health Sciences Policy, Board on Global Health, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine. *A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences.* (Fineberg HV, Brown L, Worku T, Goldowitz I, eds.). National Academies Press; 2024:27768. https://doi.org/10.17226/27768

20. **Chu L, Valencia IJ, Garvert DW, Montoya JG.** Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Pediatr. 2019;7:12. https://doi.org/10.3389/fped.2019.00012

21. **Bateman L, Bested AC, Bonilla HF et al.** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. Mayo Clin Proc. 2021;96(11):2861-2878. https://doi.org/10.1016/j.mayocp.2021.07.004

22. **Rowe PC, Underhill RA, Friedman KJ, et al.** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. Front Pediatr. 2017;5:121. https://doi.org/10.3389/fped.2017.00121

23. **Vernon SD, Hartle M, Sullivan K et al.** Post-exertional malaise among people with long COVID compared to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Mooney A, ed. Work. 2023;74(4):1179-1186. https://doi.org/10.3233/WOR-220581

24. **Hartle M, Bateman L, Vernon SD.** Dissecting the nature of post-exertional malaise. Fatigue Biomed Health Behav. 2021;9(1):33-44. https://doi.org/10.1080/21641846.2021.1905415

25. **Tokumasu K, Honda H, Sunada N et al.** Clinical Characteristics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Diagnosed in Patients with Long COVID. Medicina (Mex). 2022;58(7):850. https://doi.org/10.3390/medicina58070850

26. **Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG.** Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. Phys Ther. 2022;102(4):pzac005. https://doi.org/10.1093/ptj/pzac005

27. **Bonilla H, Quach T, Tiwari A, et al.** *Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Is Common in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC): Results from a Post-COVID-19 Multidisciplinary Clinic.* Infectious Diseases (except HIV/AIDS); 2022. https://doi.org/10.1101/2022.08.03.22278363

28. **Day H, Yellman B, Hammer S et al.** Cognitive impairment in post-acute sequelae of COVID-19 and short duration myalgic encephalomyelitis patients is mediated by orthostatic hemodynamic changes. Front Neurosci. 2023;17:1203514. https://doi.org/10.3389/fnins.2023.1203514

29. **Vernon SD, Funk S, Bateman L et al.** Orthostatic Challenge Causes Distinctive Symptomatic, Hemodynamic and Cognitive Responses in Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Med. 2022;9:917019. https://doi.org/10.3389/fmed.2022.917019

30. **Palombo T, Campos A, Vernon SD, Roundy S.** Accurate and objective determination of myalgic encephalomyelitis/chronic fatigue syndrome disease severity with a wearable sensor. J Transl Med. 2020;18(1):423. https://doi.org/10.1186/s12967-020-02583-7

31. **Kimura Y, Sato N, Ota M et al.** Brain abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: Evaluation by diffusional kurtosis imaging and neurite orientation dispersion and density imaging: Microstructural Abnormalities in CFS. J Magn Reson Imaging. 2019;49(3):818-824. https://doi.org/10.1002/jmri.26247

32. **Murrough JW, Mao X, Collins KA, et al.** Increased ventricular lactate in chronic fatigue syndrome measured by 1H MRS imaging at 3.0 T. II: comparison with major depressive disorder. NMR Biomed. 2010;23(6):643-650. https://doi.org/10.1002/nbm.1512

33. **Nakatomi Y, Mizuno K, Ishii A et al.** Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An [11] C-(*R*)-PK11195 PET Study. J Nucl Med. 2014;55(6):945-950. https://doi.org/10.2967/jnumed.113.131045

34. **Joseph P, Arevalo C, Oliveira RKF et al.** Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Chest. 2021;160(2):642-651. https://doi.org/10.1016/j.chest.2021.01.082

35. **van Campen C (Linda) MC, Verheugt FWA, Rowe PC, Visser FC.** Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography. Clin Neurophysiol Pract. 2020;5:50-58. https://doi.org/10.1016/j.cnp.2020.01.003

36. **Cliff JM, King EC, Lee JS et al.** Cellular Immune Function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Front Immunol. 2019;10:796. https://doi.org/10.3389/fimmu.2019.00796

37. **Klimas NG, Salvato FR, Morgan R, Fletcher MA.** Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol. 1990;28(6):1403-1410. https://doi.org/10.1128/jcm.28.6.1403-1410.1990

38. **Maes M, Twisk FN.** Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS. Neuro Endocrinol Lett. 2009;30(6):677-693.

39. **Xiong R, Gunter C, Fleming E et al.** Multi-'omics of gut microbiome-host interactions in short- and long-term myalgic encephalomyelitis/chronic fatigue syndrome patients. Cell Host Microbe. 2023;31(2):273-287.e5. https://doi.org/10.1016/j.chom.2023.01.001

40. **Guo C, Che X, Briese T et al.** Deficient butyrate-producing capacity in the gut microbiome is associated with bacterial network disturbances and fatigue symptoms in ME/CFS. Cell Host Microbe. 2023;31(2):288-304.e8. https://doi.org/10.1016/j.chom.2023.01.004

41. **Germain A, Barupal DK, Levine SM, Hanson MR.** Comprehensive Circulatory Metabolomics in ME/CFS Reveals Disrupted Metabolism of Acyl Lipids and Steroids. Metabolites. 2020;10(1):34. https://doi.org/10.3390/metabo10010034

42. **McGregor NR, Armstrong CW, Lewis DP, Gooley PR.** Post-Exertional Malaise Is Associated with Hypermetabolism, Hypoacetylation and Purine Metabolism Deregulation in ME/CFS Cases. Diagnostics. 2019;9(3):70. https://doi.org/10.3390/diagnostics9030070

43. **Naviaux RK, Naviaux JC, Li K et al.** Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci. 2016;113(37). https://doi.org/10.1073/pnas.1607571113

44. **Glass KA, Germain A, Huang YV, Hanson MR.** Urine Metabolomics Exposes Anomalous Recovery after Maximal Exertion in Female ME/CFS Patients. Int J Mol Sci. 2023;24(4):3685. https://doi.org/10.3390/ijms24043685

45. **Tomas C, Elson JL, Strassheim V, Newton JL, Walker M.** The effect of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity on cellular bioenergetic function. Zhang J, ed. PLOS ONE. 2020;15(4):e0231136. https://doi.org/10.1371/journal.pone.0231136

46. **Che X, Brydges CR, Yu Y et al.** Metabolomic Evidence for Peroxisomal Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Int J Mol Sci. 2022;23(14):7906. https://doi.org/10.3390/ijms23147906

47. **Nagy-Szakal D, Williams BL, Mishra N et al.** Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome. 2017;5(1):44. https://doi.org/10.1186/s40168-017-0261-y

48. **Hoel F, Hoel A, Pettersen IKN et al.** A map of metabolic phenotypes in patients with myalgic encephalomyelitis/chronic fatigue syndrome. JCI Insight. 2021;6(16):e149217. https://doi.org/10.1172/jci.insight.149217

49. **Fernandez-Guerra P, Gonzalez-Ebsen AC, Boonen SE et al.** Bioenergetic and Proteomic Profiling of Immune Cells in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients: An Exploratory Study. Biomolecules. 2021;11(7):961. https://doi.org/10.3390/biom11070961

50. **Kitami T, Fukuda S, Kato T, et al.** Deep phenotyping of myalgic encephalomyelitis/chronic fatigue syndrome in Japanese population. Sci Rep. 2020;10(1):19933. https://doi.org/10.1038/s41598-020-77105-y

51. **Germain A, Giloteaux L, Moore GE et al.** Plasma metabolomics reveals disrupted response and recovery following maximal exercise in myalgic encephalomyelitis/chronic fatigue syndrome. JCI Insight. 2022;7(9):e157621. https://doi.org/10.1172/jci.insight.157621

52. **Germain A, Ruppert D, Levine S, Hanson M.** Prospective Biomarkers from Plasma Metabolomics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Implicate Redox Imbalance in Disease Symptomatology. Metabolites. 2018;8(4):90. https://doi.org/10.3390/metabo8040090

53. **Germain A, Ruppert D, Levine SM, Hanson MR.** Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism. Mol Biosyst. 2017;13(2):371-379. https://doi.org/10.1039/C6MB00600K