Comorbidities and Less Studied Pathologies: A Comprehensive Approach to Infection-Associated Chronic Illnesses

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TAL RESEARCH GROUP

Disclosures

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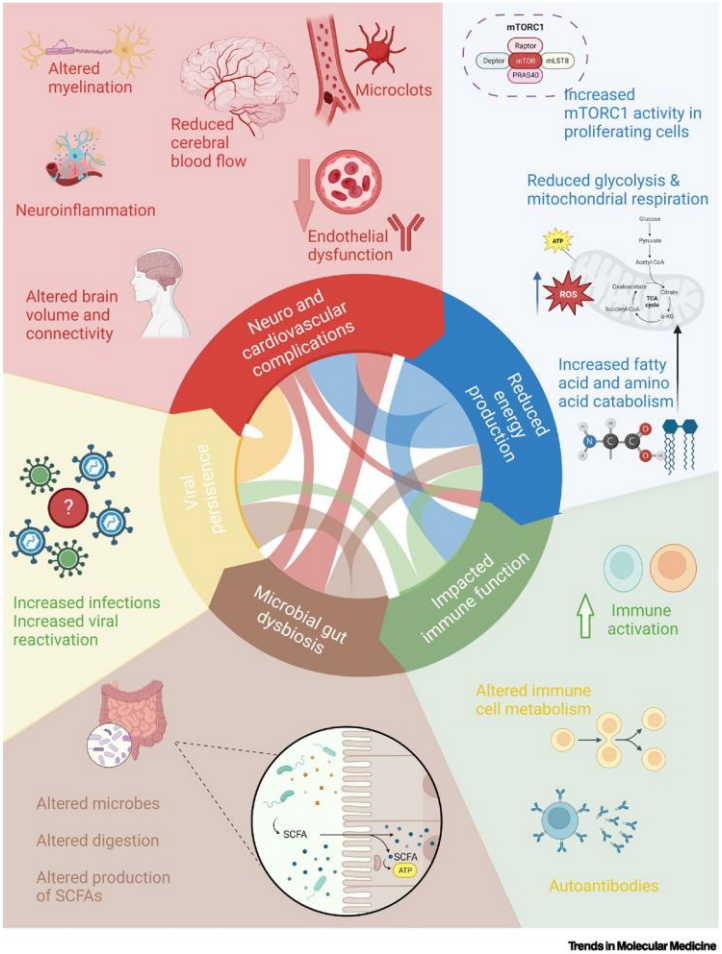
Long COVID and ME/CFS

- About half (43%-58%) of Long COVID patients meet criteria for ME/CFS after 6 months. (Bonilla et al., 2023; Jason et al., 2023).
- They share many overlapping features and symptoms.
- However, many patients develop a group of comorbid illnesses simultaneously, that also share many of these features and symptoms.

Symptom	ME/CFS	Long COVID	Symptom	ME/CFS	Long COVID
Fatigue	✓	✓	Poor appetite	✓	✓
Post-exertional malaise	✓	✓	Orthostatic intolerance	✓	✓
Headaches	✓	✓	Palpitations	✓	✓
Sleep disorder	✓	✓	Breathlessness	✓	✓
Impaired reasoning	✓	✓	Nausea and diarrhea	✓	✓
Impaired memory	✓	✓	Chills	✓	✓
Impaired attention	✓	✓	Cough	✓	✓
Secondary depression	✓	✓	Decreased smell and taste		✓
Secondary anxiety	✓	✓	Rash and hair loss		✓
Reduced activity	✓	✓	Painful lymph nodes	✓	
Myalgia/arthralgia	✓	✓	Chemical sensitivities	✓	
Muscle weakness	✓	✓	Tinnitus	✓	
Hot and cold spells	✓	✓			

ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome. Adapted from: Wong DJ (17).



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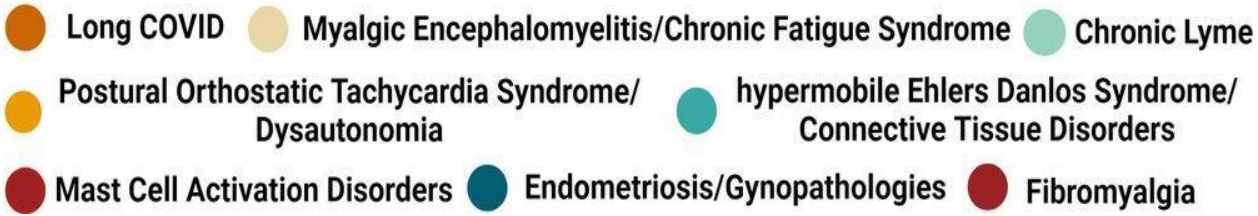
Annesley, Sarah J et al. "Unravelling shared mechanisms: insights from recent ME/CFS research to illuminate long COVID pathologies." *Trends in molecular medicine*, S1471-4914(24)00028-5. 4 Mar. 2024, doi:10.1016/j.molmed.2024.02.003

Understanding Comorbidity and Shared Pathobiology/Pathophysiology



Illnesses share overlapping:

- Triggers
- Risk Factors
- Symptoms
- Pathologies
- High rates of comorbidity

Common pathologies include
Neurological (including autonomic), immune neurocognitive, cardiovascular, mitochondrial and metabolic dysfunctions and more

Less studied pathologies include
mast cell activation, reproductive and gynecological, sleep, lymph pathologies, gastrointestinal issues, neuroendocrine dysfunction, connective tissue, and spinal disorders

ME/CFS and Comorbid Conditions

POTS

12% (n=75)**-70%** (n=23) of ME/CFS patients have POTS.

90% (n=429) of adults with ME/CFS have reduced cerebral blood flow on a tilt.

96% (n=26) and (n=55)-**100%** (n=25) of adolescents with ME/CFS have orthostatic intolerance on a tilt.

Fibromyalgia

22% (n=160)**-76%** (n=229) of ME/CFS patients have fibromyalgia.

A meta analysis revealed a **47.3%** diagnostic overlap between fibromyalgia and ME/CFS patients.

MCAS

7% (n=160) of ME/CFS patients have MCAS (though this is thought to be higher)

Small Fiber Neuropathy

31% (n=160) of ME/CFS patients have SFN.

hEDS and joint hypermobility

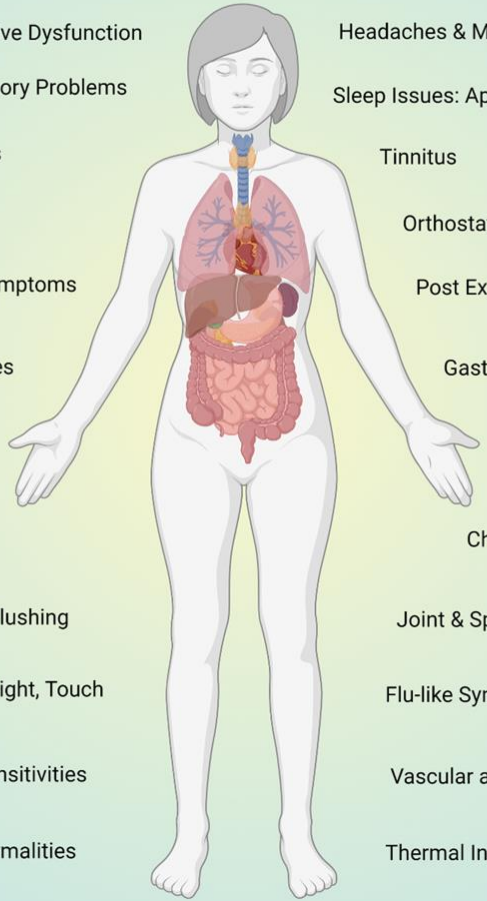
12% (n=100)**-19%** (n=229) of ME/CFS patients have hEDS.

50% (n=229)**-81%** (n=63) of people with ME/CFS have GJH or JHS respectively.

Long COVID

43% (n=134) **-58%** (n=465) of Long COVID have ME/CFS.

Overlapping Symptoms Across the Illness Group



Neurocognitive Dysfunction

Brain Fog & Memory Problems

Neuropsychiatric Symptoms

Fatigue

Cardiovascular & Respiratory Symptoms

New Food Allergies

Prickling, Tingling, & Burning eg.Paresthesia

Muscle Pain & Weakness

Skin: Dermographism, Rashes, Flushing

Increased Sensitivities to: Noise, Smell, Sound, Light, Touch

Environmental, Mold, & Chemical Sensitivities

Neuromotor Abnormalities

Headaches & Migraine

Sleep Issues: Apnea, Insomnia, Hypersomnia, Unrefreshing Sleep

Tinnitus

Orthostatic Intolerance & Dizziness

Post Exertional Malaise & Exertional Intolerance

Gastrointestinal: Digestion, Constipation, Diarrhea

Genitourinary & Gynecological Symptoms

Chronic Widespread Pain

Joint & Spine Pain

Flu-like Symptoms: Fever, Sweats, Chills, Tender lymph nodes

Vascular and Circulatory Symptoms

Thermal Instability & Cold/Heat Intolerance

Common Triggers & Onset Patterns

Infection

Infection is the #1 trigger

- **20%-50%** of POTS patients report a viral infection preceding illness.
- **23%-75%** of ME/CFS patients report infectious triggers.
- **100%** of Long COVID and long Lyme patients.
- **5.6%** of fibromyalgia patients report infectious triggers in a survey

Injury

Injury is the #2 most common trigger

e.g., car accidents, falls, surgery, concussion, pregnancy, giving birth

- These account for **79.3%** of fibromyalgia patients who can identify an illness trigger (27% could identify a trigger out of 939 patients).
- **31%** of POTS patients
- **~24%** of ME/CFS patients (cumulatively)

Onset Patterns

Illness onset can be gradual with multiple triggers, or sudden:

- **POTS**: Over time, 44% of POTS patients report their symptoms worsening “a lot”; 10% report no change; and 42% of patients experience symptoms improving a little, with 1/3 of these patients crediting medication. (n=4,835)
- **ME/CFS:** Symptom onset was insidious in 23% of ME/CFS patients (n=40). Among adolescents with ME/CFS, 45.5% (25/55) had abrupt onset, 40% (22/55) had gradual onset, 14.5% (8/55) had a mixture of abrupt and gradual.

References: Verino et al., 2021; Van Campen et al., 2022; Choutka et al., 2022; Juan et al., 2015; Shaw et al., 2019; Chu et al., 2019; Roma et al., 2019.

Some Shared Risk Factors

Sex

- **63%-83% of patients are female** (Long COVID, chronic Lyme, ME/CFS, Fibromyalgia, MCAS, dysautonomia, EDS)
  - Sex differences in immune responses to infection may partially explain this.
  - Males are at higher risk for more severe acute COVID (and other infections), and females are at higher risk for long-term illness.

Hereditary

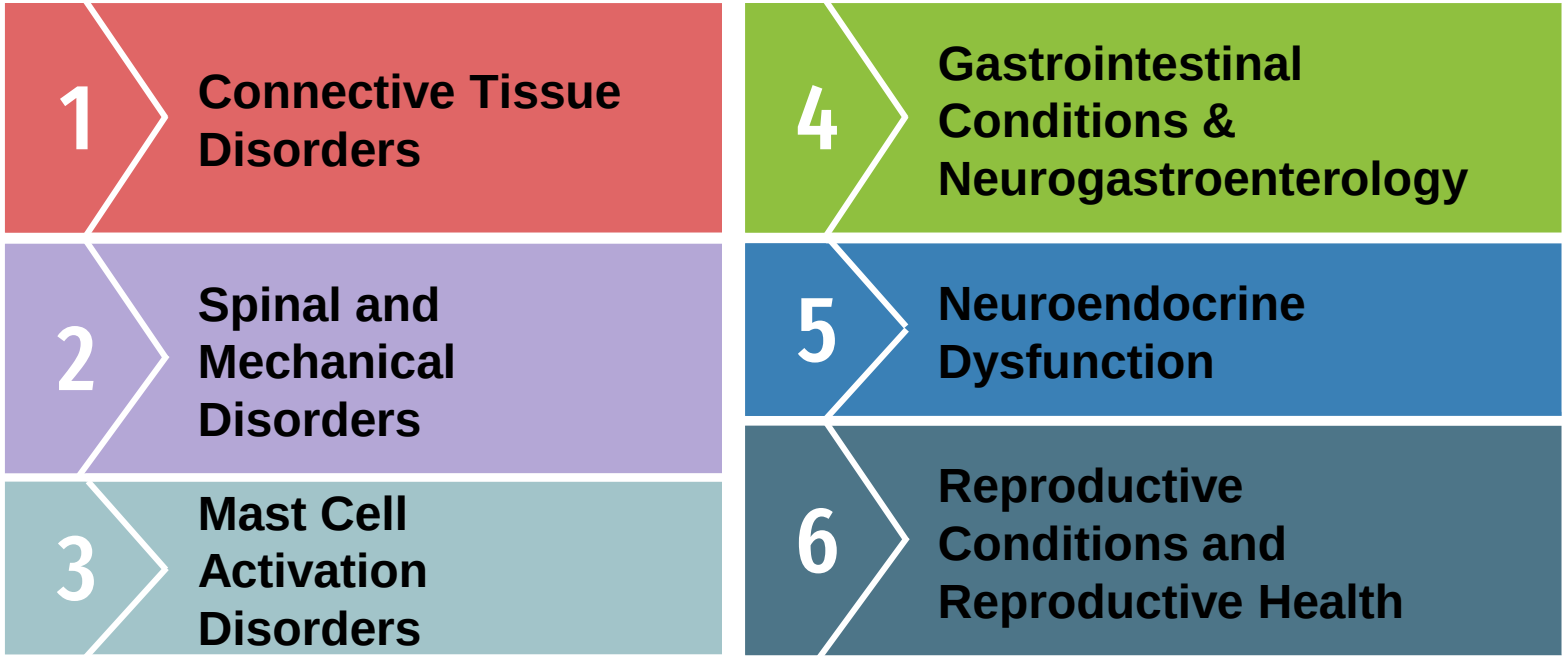
- **Hereditary and genetic risk factors**
  - Research suggests that ME/CFS, fibromyalgia, dysautonomia, MCAS, and hEDS are suspected of sometimes being familial.

Medical Conditions & Infections

- **Pre-existing conditions and a history of infection:**
  - Severity of acute illness and pre-existing conditions increases likelihood of Long COVID.
  - A history of frequent infectious illnesses like colds increases risk for ME/CFS.
  - In long Lyme, not treating acute lyme with antibiotics increases risk.

Less Studied Pathologies in ME/CFS Research Webinar

- First of its kind, 4-hour NIH research webinar on Less Studied Pathologies January 5, 2024. Now posted on YouTube. NIH report to be published May 2024.
- Webinar focused on ME/CFS, but these pathologies are seen across this group of illnesses. https://www.youtube.com/watch?v=A-RN1yjwtIs



Less Studied Pathologies: Environmental Sensitivities

Environmental exposure as a common trigger of ME/CFS:

- Between 16% (n=75) and 44% (n=258) of ME/CFS patients report that environmental toxin exposures, including chemicals and mold, triggered their illness.
- Infection remains the most studied trigger of ME/CFS; chemical and mold triggers remain poorly understood and understudied (Chu et al., 2019).

Chemical sensitivity in ME/CFS: Two of the diagnostic criteria for ME/CFS include chemical sensitivity. It is an incredibly common but very understudied symptom, often thought to be connected to chronic mast cell activation as one possible mechanism.

- International Consensus Criteria: lists sensitivities to food, medications, odors or chemicals as an optional criteria for diagnosis, under Section C. Immune, gastrointestinal and genitourinary impairments.
- Canadian Consensus Criteria:sensitivities to food, medications, odors, or chemicals (under immune, GI, and genitourinary symptom).

Mold and ME/CFS: In a preliminary study of ME/CFS patients who report mold as an illness trigger (n=236), urinalysis revealed that 92.4% of patients had at least one aspergillus mycotoxin including Ochratoxin, Aflatoxin, and Gliotoxin, though limitations include lack of a control group (Wu et al., 2022).

Toxic Chemical Exposures

Pesticides/
Organophosphates

Solvents

Mold exposure

Less Studied Pathologies: Connective Tissue Disorders

Connective Tissue Disorders like hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorders (HSD) are commonly comorbid with ME/CFS, POTS, and fibromyalgia.

ME/CFS

- **12%-19%** of ME/CFS patients have hEDS.
- **50%-81%** of people with ME/CFS are hypermobile.

POTS

- **18%-31%** of POTS patients have hEDS.
- **41%-90%** of hEDS and EDS patients respectively have POTS.

Fibromyalgia

- A meta study found the association prevalence (how frequently they co-occur) of hEDS/HSD and fibromyalgia ranges from **68%-88.9%**.

Long COVID can cause tissue and organ damage; emerging evidence on association with connective tissue disorders

- 23.35% of Long COVID patients in an EHR study fit within a phenotype characterized in part by having a higher prevalence CTDs.
- COVID-19 is associated with a substantial risk for autoimmune and autoinflammatory connective tissue disorders in a retrospective cohort study (n=354, 527)
- Case studies document Long COVID patients developing joint hypermobility post COVID-19.
- ICD-10 Code introduced in 2021 for other specified systemic involvement of connective tissue (M35.89).

Comorbidity is significantly higher than general population prevalence

- EDS: 0.02%-0.2% of the population may have EDS or EDS/JHS (pre-pandemic), 3.4% may have symptomatic hypermobility (joint hypermobility with widespread pain), 12%-28% have hypermobility.

Less Studied Pathologies: Spinal Conditions

Connective tissue laxity can contribute to disabling spinal conditions. More research is needed on spinal conditions in ME/CFS, and associated illnesses like EDS, and their roles in pathophysiology.

Spinal Conditions include:

- Upper Cranial Instability (including Craniocervical instability and Atlantoaxial instability)
- Tethered Cord Syndrome
- Chiari Malformation

- Can result in neuropathy, brainstem/vascular/nerve compression, cord stretch injury, and cerebral hypoperfusion.
- Symptoms overlap with ME/CFS including neurological, orthostatic and cognitive symptoms, fatigue, and pain.

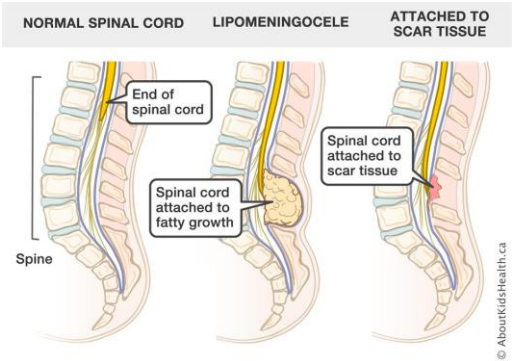


Image credits: Shutterstock and AboutKidsHealth.ca

Less Studied Pathologies: Spinal Conditions

Statistics

- **ME/CFS**: MRI study, **80%** (n=205) of ME/CFS patients have disc bulging or hernias in the cervical spine; **83%** have signs of intracranial hypertension; **64%** have obstructions in C1–T2; **53%** have spinal cord compressions at C5–C6, and **28%** at C6–C7.
- **ME/CFS: 26.5%** (n=913) of ME/CFS patients have severe spine problems in an EHR study of ME/CFS clinics.
- **EDS: 21%** of EDS patients have craniocervical instability and **40%** of EDS patients have tethered cord syndrome in an EHR study of EDS clinics.
- **Fibromyalgia**: Studies have found spinal conditions in fibromyalgia patients. **71%** (n=49) of fibromyalgia patients have cervical cord compression; **83%** (n=129) have straight neck; **46%** (n=270) have cervical myelopathy; **20%** (n=270) have chiari malformation; **91%** (n=42) have short filum terminale (indicative of cord stretch injury).

Possible Roles of Infection, Inflammation, and Mast Cell Activation?

- Mast cell mediators like histamine and tryptase can damage collagen.
- Klinge et al found inflammatory cell invasion (including mast cells) in the filum terminale of hEDS tethered cord surgical patients, and their filum was half as elastic as non-hEDS tethered cord surgical patients, increasing risk for cord stretch injury.
- HHV-6 viral miRNA was found in the brain and spinal cords of ME/CFS patients, including cervical, lumbar, and sacral nerve roots (Kasimir et al., 2022).

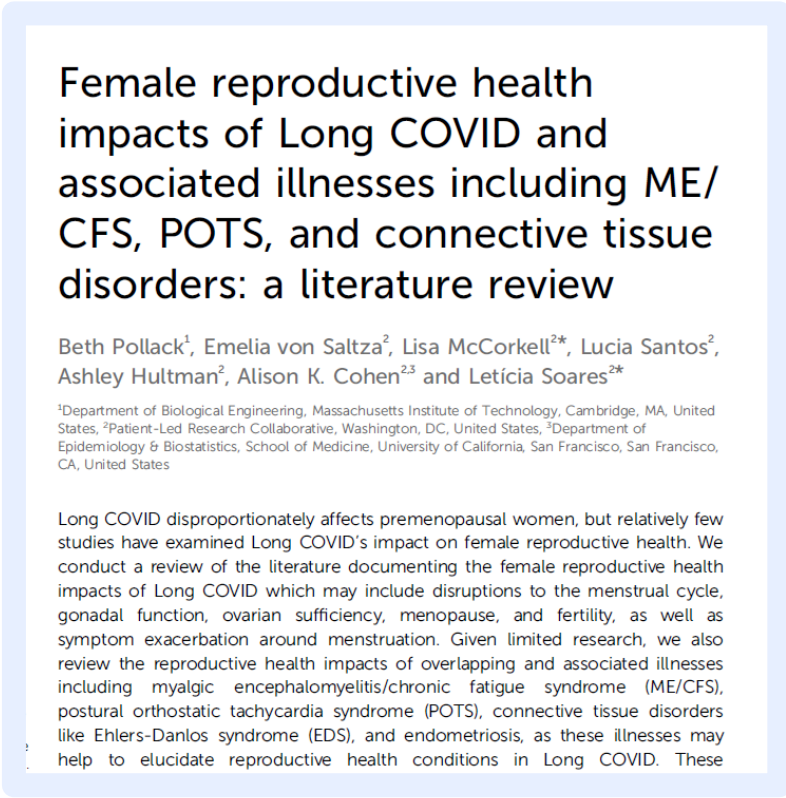
First Review of Reproductive Impacts of Long COVID; Contextualizes with Findings in ME/CFS, POTS, and EDS

Reproductive impacts of both Long COVID and ME/CFS include disruptions to:

- Menstrual cycle
- Gonadal function and ovarian sufficiency
- Menopause
- Fertility
- Symptom exacerbation around menstruation

Sex differences:

- **Female sex as a risk factor**: ME/CFS impacts ~70% female patients. Long COVID impacts 2x female patients as male, and may disproportionately impact transgender patients as well.
- **Age as a risk factor:** Pre-menopausal women have an increased risk for Long COVID compared to age-matched men. Premenopausal women may also have a higher risk for ME/CFS, particularly age 30-39.
- **Sex hormones and immunity:** Findings Suggest that sex hormones and sex differences in immune responses to infection may play a role in ME/CFS and Long COVID development.



Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review

Beth Pollack[1], Emelia von Saltza[2], Lisa McCorkell[2*], Lucia Santos[2], Ashley Hultman[2], Alison K. Cohen[2,3] and Letícia Soares[2*]

[1]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, United States, [2]Patient-Led Research Collaborative, Washington, DC, United States, [3]Department of Epidemiology & Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, CA, United States

Long COVID disproportionately affects premenopausal women, but relatively few studies have examined Long COVID's impact on female reproductive health. We conduct a review of the literature documenting the female reproductive health impacts of Long COVID which may include disruptions to the menstrual cycle, gonadal function, ovarian sufficiency, menopause, and fertility, as well as symptom exacerbation around menstruation. Given limited research, we also review the reproductive health impacts of overlapping and associated illnesses including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), connective tissue disorders like Ehlers-Danlos syndrome (EDS), and endometriosis, as these illnesses may help to elucidate reproductive health conditions in Long COVID. These

ME/CFS: Key Female Reproductive Health Findings

1. ME/CFS and the Menstrual Cycle

- Women with ME/CFS (compared to controls) disproportionately report irregular menstrual cycles, amenorrhea, dysmenorrhea, excessive menstrual bleeding, and bleeding between periods.
- **53%-67%** of female ME/CFS patients say their symptoms increase before menstruation.

2. Reproductive Health Conditions in ME/CFS

- ME/CFS patients report increased rates of polycystic ovarian syndrome; ovarian cysts, pelvic pain, gynecological surgery, and endometriosis compared to controls.

3. Early Onset Menopause in ME/CFS

- Onset of menopause occurred earlier in women with ME/CFS (37.6 y) compared to healthy controls (48.6 y) in a longitudinal case control study.
- Menopause exacerbated symptoms in **38%** of perimenopausal and postmenopausal women with ME/CFS.

4. Pregnancy as a Risk Factor for ME/CFS

- Pregnancy is reported as a trigger for ME/CFS in **3%-10%** of cases.
- A study found that women who had been pregnant in the previous year were ***over 31 times more likely*** to develop ME/CFS than women who had not been pregnant.
- Studies vary regarding how pregnancy affects symptoms in pre-existing ME/CFS, with some finding that nearly equal subsets see symptoms improve, stay the same, or worsen.

All references found in: Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci*. 4:1122673. doi: 10.3389/fresc.2023.1122673

Long COVID: Key Female Reproductive Health Findings

1. **Common menstrual cycle irregularities**: worsening of premenstrual symptoms and changes to the length of the cycle and duration and intensity of menses.
    - 33% to 62% of pre-menopausal Long COVID patients report an exacerbation of their Long COVID symptoms in the days before menses. (n=1,792 and n=460)
    - 34% of menstruating Long COVID patients (n=1,800) reported menstrual issues, which included subsets experiencing abnormally irregular cycles (26%) and heavy periods (19.7%)

2. **Ovarian health:** Case reports suggest COVID-19 infection may be associated with long-term decline of ovarian health, including premature ovarian insufficiency.

3. **Premature menopause:** May be more prevalent among Long COVID patients in their 40s than in the general population (3% vs 1%).

4. **Critical to further study COVID in pregnant people:** A small control matched prospective cohort study in Brazil followed pregnant women after testing positive for COVID-19 (n=84) and 76% developed Long COVID.

All references found in: Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci*. 4:1122673. doi: 10.3389/fresc.2023.1122673

Female Reproductive Conditions in Long COVID, ME/CFS, POTS, and EDS*

Menstrual

- Menstrual cycle irregularities [LC, ME/CFS]
- Excessive menstrual bleeding [LC, ME/CFS, EDS]
- Symptom exacerbation around periods [LC, ME/CFS, POTS]
- Amenorrhea and Oligomenorrhea [LC, ME/CFS, POTS]
- Premenstrual syndrome symptoms [LC]
- Dysmenorrhea [EDS]
- Bleeding between periods [ME/CFS, EDS]

Gynepathologies

- Premature ovarian insufficiency [LC]
- Endometriosis [LC, ME/CFS, POTS]
- Ovarian dysfunction [LC]
- Dyspareunia [EDS]
- Vulvodynia [EDS]
- Ovarian cysts and polycystic ovarian syndrome [ME/CFS, POTS]
- Uterine fibroids and bleeding [POTS]
- Pelvic congestion syndrome [POTS]
- Non-menstrual pelvic pain [ME/CFS]

Fertility and Pregnancy

- Fertility issues [LC, EDS]
- Higher risk of maternal mortality from childbirth [EDS]
- Higher risk of premature birth, miscarriage, stillbirths, placenta previa, preterm premature rupture of membranes, cervical incompetence, antepartum hemorrhage, intra-uterine growth restriction, delivery by C-section, spontaneous abortions, and longer postpartum hospital stays [EDS]
- Pregnancy can trigger and/or alter the course of illness [ME/CFS, POTS]

Menopause

- Premature menopause [LC, ME/CFS]
- Postmenopausal bleeding [LC]
- Symptom exacerbation in perimenopause and postmenopause [ME/CFS]

Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci.* 4:1122673. doi: 10.3389/fresc.2023.1122673

Endometriosis

Approximately **10%** of women and people with uteruses develop endometriosis.
Average time to diagnosis: **7-10 years**

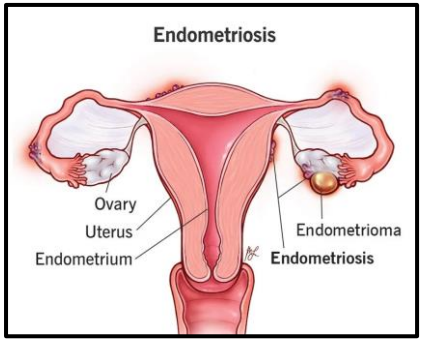


Image source: Cleveland Clinic, 2021

ME/CFS

- **20.1%** of 726 ME/CFS patients at 4 specialty clinics have an endometriosis diagnosis..
- About **36%** of women with ME/CFS (n=36) report endometriosis.

POTS

- 20% of women with POTS (n=65) report endometriosis.

Reproductive health conditions as risk factors for Long COVID

- **Endometriosis**: Endometriosis patients may have an increased risk of developing Long COVID (based on a population-based retrospective cohort-matched study using data from electronic health records of non-hospitalized Long COVID patients.) More research is needed to understand contributing factors.
- **PCOS:** People with PCOS have a **28%** increased risk for COVID-19 infection, after adjusting for adjusting for risk factors (e.g. age, BMI, hypertension and cardiovascular disease)

Overlapping Immune and Endocrine Dysfunction: Reduced natural killer cell cytotoxic function, macrophage alterations, lowered cortisol, elevated oxidative stress, and allergies may be implicated in both endometriosis and ME/CFS.

Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci*. 4:1122673. doi: 10.3389/fresc.2023.1122673

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Lucinda Bateman, Salima Darakjy, Nancy Klimas, Daniel Peterson, Susan M. Levine, Ali Allen, Shane A. Carlson, Elizabeth Balbin, Gunnar Gottschalk & Dana March (2015) Chronic fatigue syndrome and co-morbid and consequent conditions: evidence from a multi-site clinical epidemiology study, Fatigue: Biomedicine, Health & Behavior, 3:1, 1-15, doi: 10.1080/21641846.2014.978109

Endometriosis and Infection Research

Tal Research Group at MIT

Could infection, such as pathogenic bacteria, contribute to the development of endometriosis?

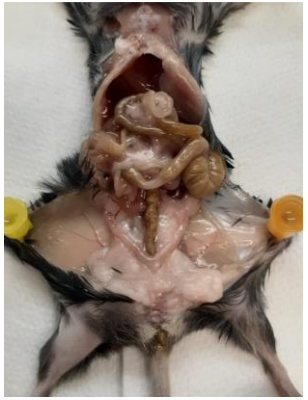
Muraoka et al found fusobacterium in endometrial tissue of 64% (n=79) of women with endometriosis and 7% of healthy controls (n=76).

In mouse models of endometriosis, mice inoculated with fusobacteria had increased and larger endometrial lesions.

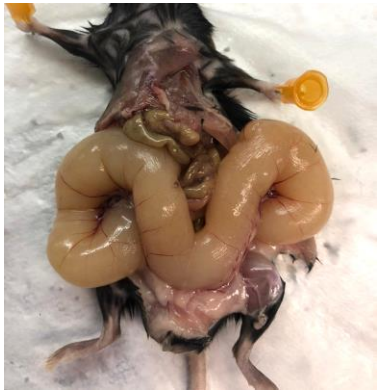
Antibiotic treatment (metronidazole and chloramphenicol) reduced fusobacterium and the number and size of endometrial lesions in mice.

Ayako Muraoka et al. (2023), Fusobacterium infection facilitates the development of endometriosis through the phenotypic transition of endometrial fibroblasts.*Sci. Transl. Med.*15, eadd1531. doi:10.1126/scitranslmed.add1531

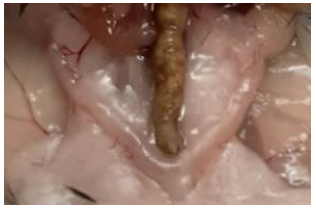
Preliminary Findings: Infection-induced Reproductive Tract Pathologies in Mouse Models

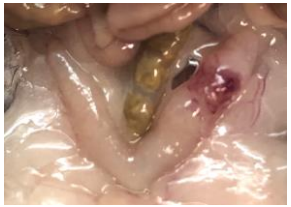


Uninfected:
Normal Uterus and Ovaries



18-Month Infected
Uterus and Ovaries

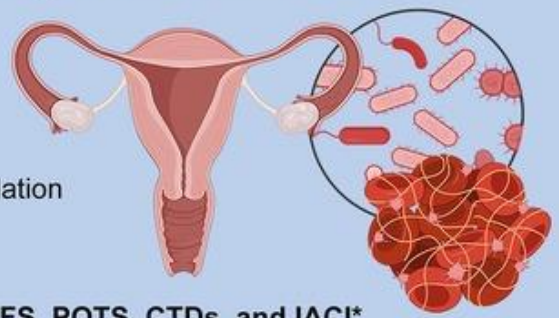




Source: Tal Research Group at MIT, Grace Blacker, Sarah Galloway, Paige Hansen, Michal Tal

Research Priorities for Female Reproductive Health in Long COVID, ME/CFS, POTS, and EDS

- **How menstruation, pregnancy, sexual function, and menopause impact and are impacted by LC* and comorbidities**
  - Flaring at different times of the menstrual cycle
  - Menstrual cycle impacts on CTD* laxity and CTD related symptoms
  - Fluctuations of MCA* throughout the menstrual cycle
  - Reproductive microbiomes and their impact on RH*
  - Whether sex hormones in the menstrual cycle may increase microclotting and hypercoagulation
- **Sex differences and the role of sex hormones in disease mechanisms and trajectories**
- **Health inequities and underrepresentation in RH research**
- **Rates and mechanisms of RH conditions in LC and associated illnesses including ME/CFS, POTS, CTDs, and IACI***



*LC = Long COVID
*CTD = Connective Tissue Disorder
*MCA = Mast Cell Activation
*RH = Reproductive Health
*IACI = Infection Associated Chronic Illnesses

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Figure from: Pollack B, von Saltza E, McCorkell L, Santos L, Hultman A, Cohen AK and Soares L (2023) Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front. Rehabil. Sci*. 4:1122673. doi: 10.3389/fresc.2023.1122673

Towards a Comprehensive Approach (Clinical)

Earlier Diagnosis, Screening for Comorbidities and Common Pathologies, Collaborative Care

- Need to screen patients for common comorbidities and pathologies.
    - Reduce diagnostic delays
    - Patients commonly see multiple doctors over many years before being diagnosed.
- Increased awareness of lesser known and lesser studied pathologies.

Studies on promising meds

- Case studies and pilot studies on promising off-label meds prescribed in specialty clinics.

More Specialist Clinicians

- We need more physicians specializing in complex chronic illnesses:
    - ~21 specialist clinicians in ME/CFS clinician coalition for ~2.5 million patients in the US.
    - The Mast Cell Disease Society US directory lists only 33 specialist physicians for an estimated up to 56 million Americans with MCAS.
    - The American Academy of Neurologists membership includes ~27 autonomic neurologists (less than 1% of members) for an estimated ~3.1 million Americans with POTS.

Clinical Research Collaboration

- Ongoing dialogue between clinicians and researchers to inform research (e.g. slack community?)
- Research collaborations on EHR analysis, clinical studies, and clinical trials between specialty clinics and academic research labs

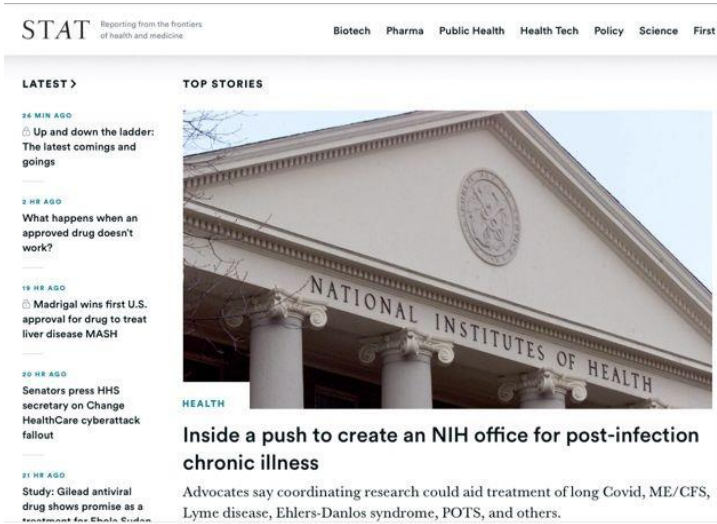
Towards a Comprehensive Approach (Research)

Cross Illness Research and Mechanistic Understanding of Pathologies

- Need for cross-illness research with multiple illness comparator cohorts
    - Need funding for clinical trials and clinical studies with multiple illness cohorts
    - Need standards, models, and protocols for effective cross illness research
- Need for research to comprehensively screen participants for comorbidities (medical history, validated instruments, diagnostic criteria)
- Mechanistic research on the many pathologies in these illnesses - both commonly studied and understudied!

Research on Severe and Highly Complex Patients

- Need for research focusing on the most severe and complex patients.
    - This includes developing standards and protocols for research methodology.
    - Need to understand and be able to predict/prevent/treat severe illness trajectories and phenotypes of severe patients.



Working Groups to Establish Research Priorities for Understudied Topics

- Collaborative working groups
    - To develop research priorities and next steps for the field, especially focusing on less studied pathologies across illnesses (CTDs/spine, reproductive health, lymph pathologies etc)
    - Working groups on drug priorities for clinical trials for each illness, and identifying opportunities for cross-illness trials.

Screening for Comorbidities in ME/CFS Research
Example: PLRC Biomedical Research Fund

Scientific panel where we allocated nearly **$5 million in grant funding** to support innovative research on Long COVID, ME/CFS, and associated illnesses. All grantees were required to screen for comorbid illnesses via diagnostic and validated surveys to help characterize their cohort and possibly identify phenotypes

1. **ME/CFS**
   - CCC and IOM
   - Bell CFIDS disability scale to assess illness severity
1. **POTS/Dysautonomia**
   - Malmö POTS symptom score
   - Or COMPASS-31
1. **hEDS and Hypermobility**
   - 2017 criteria
   - Hypermobility via Beighton score also recorded separately
1. **Mast Cell Activation Syndrome**
   - MCAS questionnaire
1. **Endometriosis**
   - ENDOPAIN-4D
1. **Other**
   - Additionally, **document all pre-existing diagnoses** of the above.
   - All projects required patient engagement, funding for this was provided.

PATIENT-LED RESEARCH COLLABORATIVE

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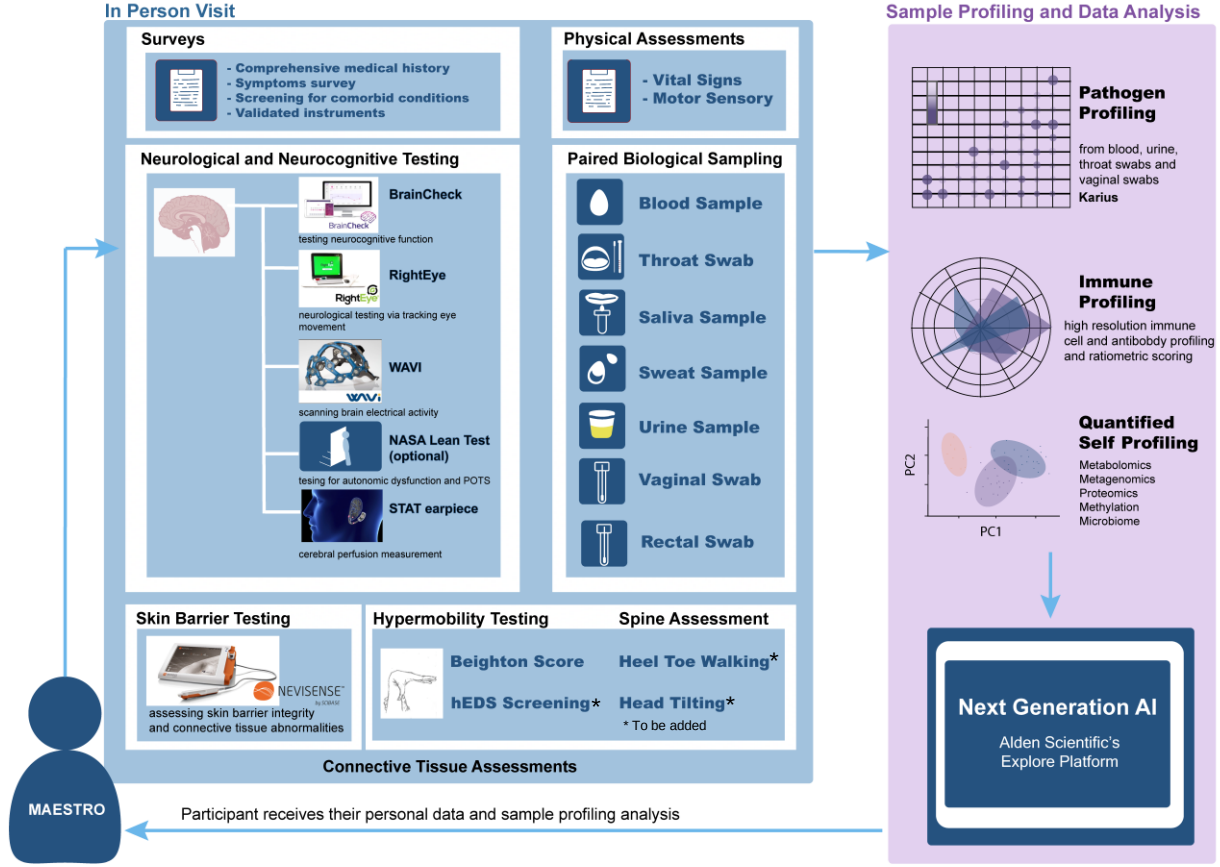
Cross-Illness Research: MIT MAESTRO Clinical Study



Largest clinical study study in MIT history

Comprehensive longitudinal clinical study:

- Multiple types of neurological and neurocognitive testing
- Deep immune and pathogen profiling
- Orthostatic testing while measuring cerebral blood flow
- Hypermobility and skin integrity assessment
- Symptom and medical history surveys
- Multiple types of biological sample collection

Current cohorts:

- 60 Long COVID
- 60 Acute Lyme
- 60 Chronic Lyme
- 60 Suspected Chronic Lyme
- 60 Healthy Controls
- Cohorts we aim to add: in-person ME/CFS, environmental sensitivities (across illnesses), a severely ill homebound ME/CFS cohort.

MAESTRO-To-Go: Study is transportable for home visits for severely ill patients.

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MIT MAESTRO Clinical Study Aims

MAESTRO Aims

- Identify new mechanistic biomarkers of illness.
- Identify phenotypes both *within* individual illnesses and *across* infection-associated chronic illnesses to help inform future clinical studies/trials.
- Predict who develops chronic illness after infection and how/why.
- Advance a deeper understanding of illness trajectories and mechanisms driving disease pathologies, including pathologies shared across illnesses.
- Identify therapeutic targets. Inform the development of therapeutics and future clinical trials.

WAVi - EEG measurements


Multiple types of biological sample collection


Orthostatic testing


RightEye - eye movement tracking (neurological assessment)

How We Incorporate Comorbidities & Less Studied Pathologies into Our Research

1 Comorbidities

Screen for all common comorbidities and less studied pathologies discussed in the webinar via:

- Medical history
- Validated surveys
- Diagnostic criteria
- In-person assessments

2 Connective Tissue Disorders

- Nevisense for assessing skin integrity
- Screen for relevant symptoms and diagnoses
- Beighton score (in person)
- hEDS assessment (part in person part questionnaire)
- Mouse research (e.g. impacts of infection, immune responses, and disease on joints)

3 Spinal Conditions

- Heel - toe walking
- Neck movements (up/down/left/right)
- Screen for relevant symptoms and medical history (injuries and diagnoses)
- Mouse research, spine

Future Research

- Neurosurgical tissue analysis
- Screen for comorbidities in neurosurgical patients
- MRIs (add in screen for spinal conditions)

4 Reproductive Health

Screening via symptoms, medical history, validated surveys (eg Endopain-4D for endometriosis)

- Vaginal swab
- Future? Menstrual effluence, “Smart tampon” (eg. NextGen Jane)
- Multi-omics profiling
- Mouse models of endometriosis and reproductive tract pathologies in infection-associated chronic illnesses

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- We are based in the MIT Center for Gynepathology Research.
- We study infection-associated chronic illnesses (IACI) including acute and chronic Lyme, Long COVID, ME/CFS and their associated pathologies and co-occurring conditions.
- Focus on translational science.
- Research areas of focus in IACI
    - Our clinical study
    - Antibody research and immune biomarkers
    - Sex differences
    - Mouse models
    - Shared pathobiology and pathophysiology
    - Reproductive health conditions
    - Expanding into connective tissue and spinal issues

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