# Investigating pathophysiological mechanisms underlying ME/CFS and post-COVID symptoms in a paediatric population

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Muscle disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON57253

**Source**
ToetsingOnline

**Brief title**
Pediatric cohort of ME/CFS and post-COVID patients

### Condition

- Muscle disorders
- Central nervous system infections and inflammations
- Vascular disorders NEC

**Synonym**
ME/CFS and post-COVID

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** ZonMw

## Intervention

**Keyword:** Biomaterials, Fatigue/pain, Paediatric, post-COVID

## Outcome measures

### Primary outcome

For our primary endpoint we will clinically (questionnaires and physiological tests; e.g. fatigue) and biologically characterise patients and controls. For biological characterisation we will focus on determining blood proteome (with multiplex assays we will determine ~200 proteins) and blood metabolome (untargeted direct-infusion high-resolution mass spectrometry, >1800 metabolites, on blood and isolated immune cells followed by validation through targeted LC-MS/MS based metabolomics, depending on the initial findings) to identify factors that can discriminate paediatric ME/CFS and post-COVID from healthy controls or identify subgroups within the patient group.

For clinical characterisation we will focus on:

• The ME/CFS criteria. Several criteria exist to diagnose children with ME/CFS. These criteria differ in stringency. To participate in this study, all patients must meet the CDC-94 criteria. To characterise patients further, we will check whether patients also meet the CCC and ICC criteria for ME/CFS. To see the differences between the three criteria, we refer to the table below. Doctor reports from standard care and DSQ questionnaires will be used to check whether

patients meet all criteria.

• Self-reported data at inclusion (demographic, behavioural, symptoms, clinical, and fatigue/pain) at inclusion, repeated 6 and 12 months after inclusion. For more information, see METC protocol 24/217.

**Secondary outcome**

We will determine:

• Hair cortisol

• Oral microbiota composition

• Immune cell transcriptome: RNA sequencing

• Dynamic change in metabolism (fluxomics)

• Derangements in mitochondrial functions in immune cells (e.g. mitophagy, mitochondrial membrane potential, fission and fusion, and superoxide production

• Rest material of biologicals will be stored in a biobank for 15 years. This biobank is the central biobank of the UMCU and is located in the Wilhelmina Children*s Hospital. This biobank will be created to facilitate (future) research on ME/CFS, post-COVID and other immune diseases. Biomaterials can be requested by our consortium members for research purposes if participants gave informed consent for research related to chronic fatigue and other immune or metabolic diseases.

• Other study parameters/endpoints: Researchers from the national effort (the Netherlands ME/CFS Cohort and Biobank, NMCB, consortium and Post-COVID Network Netherlands, PCNN) funded by ZonMw may request data from our cohort for their research purposes or to collaborate with us. These specific research questions remain to be determined and will also depend on the research now done in

adults.

# Study description

### Background summary

Rationale: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease that currently still lacks a universally accepted cause, diagnosis, or treatment. Manifestations of ME/CFS can develop for example after infection with Q fever, Epstein-Barr, or SARS-COV-19, where it is also called post-COVID. Often, the infectious trigger of ME/CFS remains unidentified. Recently, a large national effort has been established to build an adult cohort of patients with ME/CFS symptoms (plus healthy controls) and post-COVID. This cohort aims to unravel biomedical aspects of ME/CFS and post-COVID in order to improve our understanding and treatment of the disease. A paediatric cohort is missing in the national effort - but given that paediatric ME/CFS and post-COVID present themself differently than adult - an understanding of ME/CFS *across the lifespan* is essential to provide the best possible treatment at any age. The necessity of building and studying a paediatric cohort is underlined by studies showing that 1) ME/CFS symptoms are related to lower quality of life and decreased school attendance; 2) one out of five paediatric patients still have debilitating symptoms one year after diagnosis; and 3) longer disease duration is related to lower effectiveness of non-pharmacological treatment as usual.

### Study objective

The primary objective is to identify clinical and biological measures that discriminate paediatric ME/CFS and post-COVID patients from healthy controls based on either clinical (based on physiological tests and questionnaires) and biological (based on biomaterials) data, or a combination thereof.

Secondary objectives are to assess whether specific immunological, microbiome, cardiovascular, and/or hormonal disturbances are associated with specific symptoms and whether these measures have predictive and/or prognostic value. Additionally, a ME/CFS and post-COVID biobank will be built by storing collected biomaterials in the UMCU biobank. This biobank will facilitate paediatric ME/CFS and post-COVID research as well as research into other immune and metabolic diseases.

### Study design

Study design: Observational study collecting data from questionnaires, physical measurements, and biomaterials (blood, hair, oral swab). Follow-up visit after

6 months to collect new biomaterials, follow-up questionnaires at 6 months and 12 months.

**Study burden and risks**

Burden and benefits: Burden will be minimised by taking data from standard care questionnaires (PROactive) and combining blood drawn from standard care with research. Additional research activities (three additional questionnaires, physiological measurements, and collection of hair and oral swab) will take place during one study visit at the 030-lab (max. 1,5 hours). For participants, the collection of data from questionnaires, physiological measurements, and biomaterials (blood, hair, oral swab) will have negligible risks. Patients might experience PEM or fatigue after the physiological tests, which might in some cases cause (temporary) worsening of symptoms. To minimise the burden on patients, a separate room will be made available in the 030-lab to give patients the opportunity to rest between the tests.
Participants will have no direct benefit of participating in this cohort, but they will contribute to our understanding of ME/CFS symptoms.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

Inclusion criteria for patients: For eligibility, patients must meet the following criteria:
- Age of 8-18 years old;
- Able to speak, read, understand, and write Dutch;
- ME/CFS patients: A (suspected) diagnosis of ME/CFS according to the CCC and severely fatigued, as indicated by a fatigue severity score of >= 21 on the Checklist
Individual Strength-4 (CIS-4) questionnaire.
- Post-COVID patients: a (suspected) diagnosis of post-COVID according to the WHO definition. Patients should have positive COVID-19 serology and should express that their symptoms started after acute COVID-19 infection. CCC will be monitored.

Inclusion criteria for healthy controls: For eligibility, healthy controls must meet the
following criteria:
- Age of 8-18 years old;
- Able to speak, read, understand, and write Dutch;
- No ME/CFS diagnosis according to the CDC, CCC and ICC;
- No post-COVID condition or other manifestation of persistent fatigue and/or pain;
- Not severely fatigued, as indicated by a fatigue severity score of <21 on the CIS-4
questionnaire.

## Exclusion criteria

Exclusion criteria: Potential subjects who meet any of the following criteria will be excluded from participation in this cohort:

Having any concomitant diagnoses that may explain the fatigue (also including predominated psychiatric comorbidity such as major depression disorder, generalised anxiety disorder, presence of suicidal risk, etc.).

Being on therapeutic anticoagulant treatment (with an exception for

acetylsalicylic acid, dipyridamole) or having a high risk of bleeding due to a coagulation disorder.

Having cognitive impairment (with an estimated IQ of < 70).

Having morbid obesity.

# Study design

## Design

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| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-01-2025 |
| Enrollment: | 360 |
| Type: | Anticipated |

## Medical products/devices used

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| Registration: | No |

# Ethics review

Approved WMO

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| Date: | 16-01-2025 |
| Application type: | First submission |
| Review commission: | METC NedMec |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL86852.041.24 |