



The Dutch National Structured Care Pathway for post-COVID

*Systematic Integration of Off-Label Pharmacological
Interventions for Dominant Symptoms*

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No conflicting interests

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Health care in the Netherlands



Dutch Post-COVID
Academic Centers of Expertise

- **The Netherlands - 18 million inhabitants**

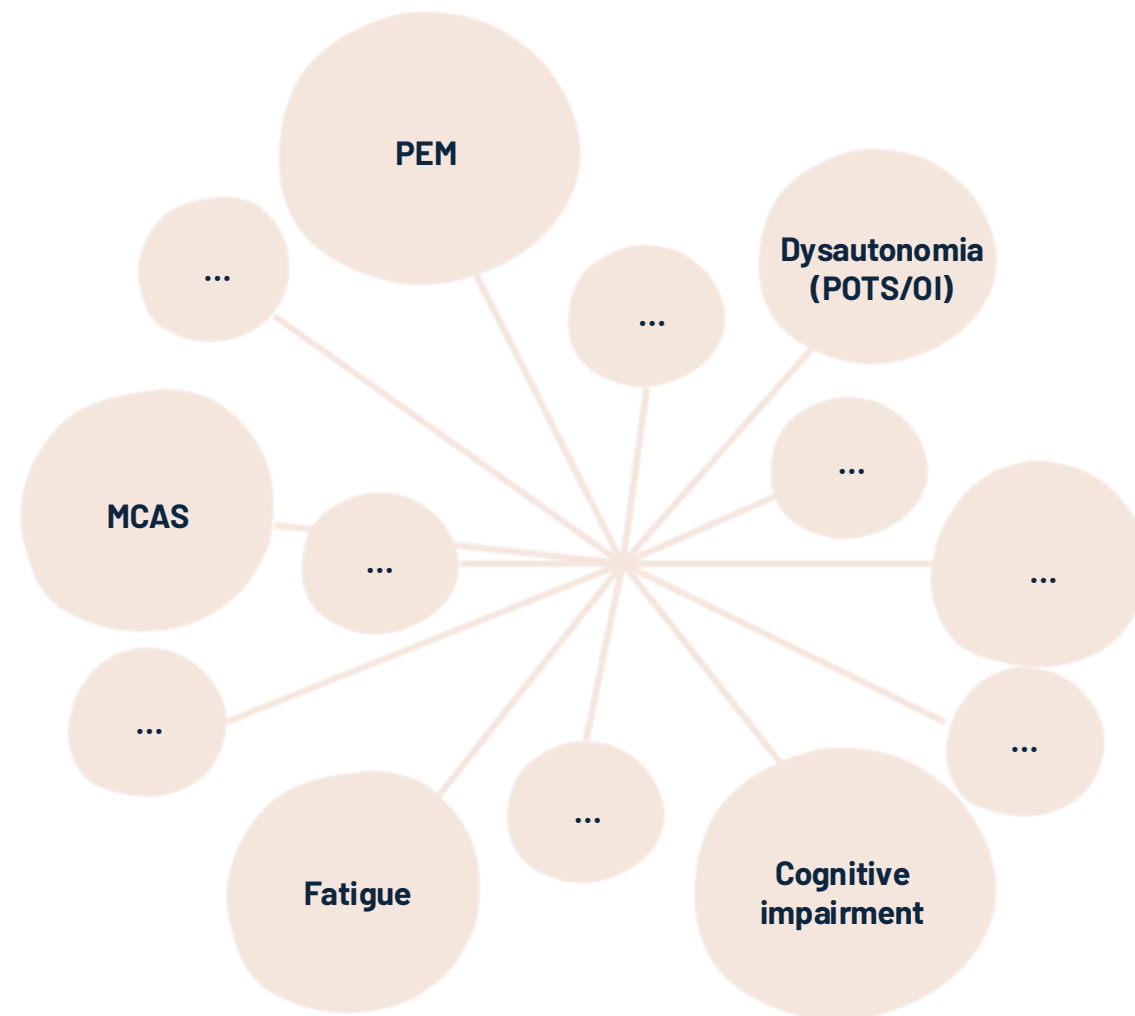
- 7 Academic Medical Centers
- 113 Hospital locations
- 12,000 General Practitioners

- **Patients with post-COVID**

- Mild symptoms: up to 500,000 patients
- Severe symptoms: 100,000 patients
- Multisystem condition, over 200 reported symptoms

- **Lack of care**

- Fragmented, variable care between providers
- Urgent need for adequate care



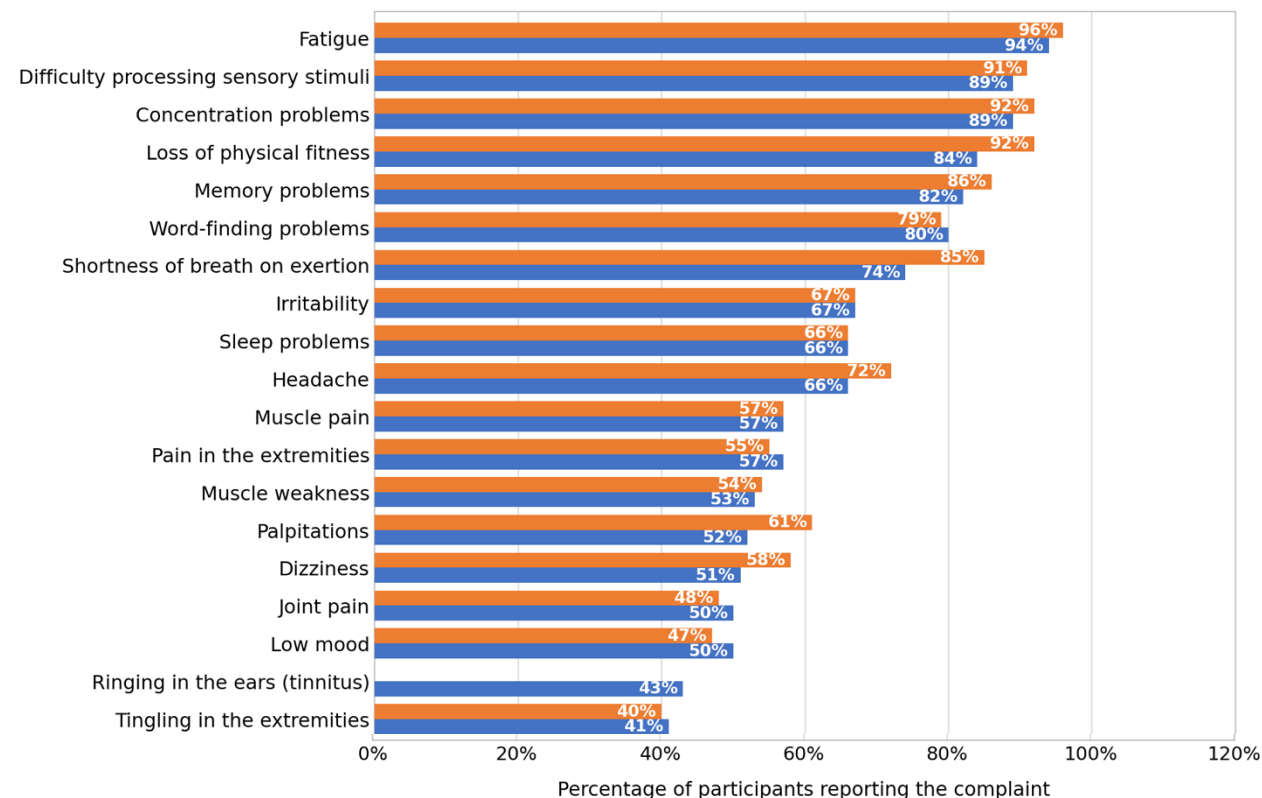
MCAS: mast cell activation syndrome, OI: orthostatic intolerance
PEM: post-exertional malaise, POTS: postural orthostatic tachycardia syndrome,

Evaluation of complaints (>200)



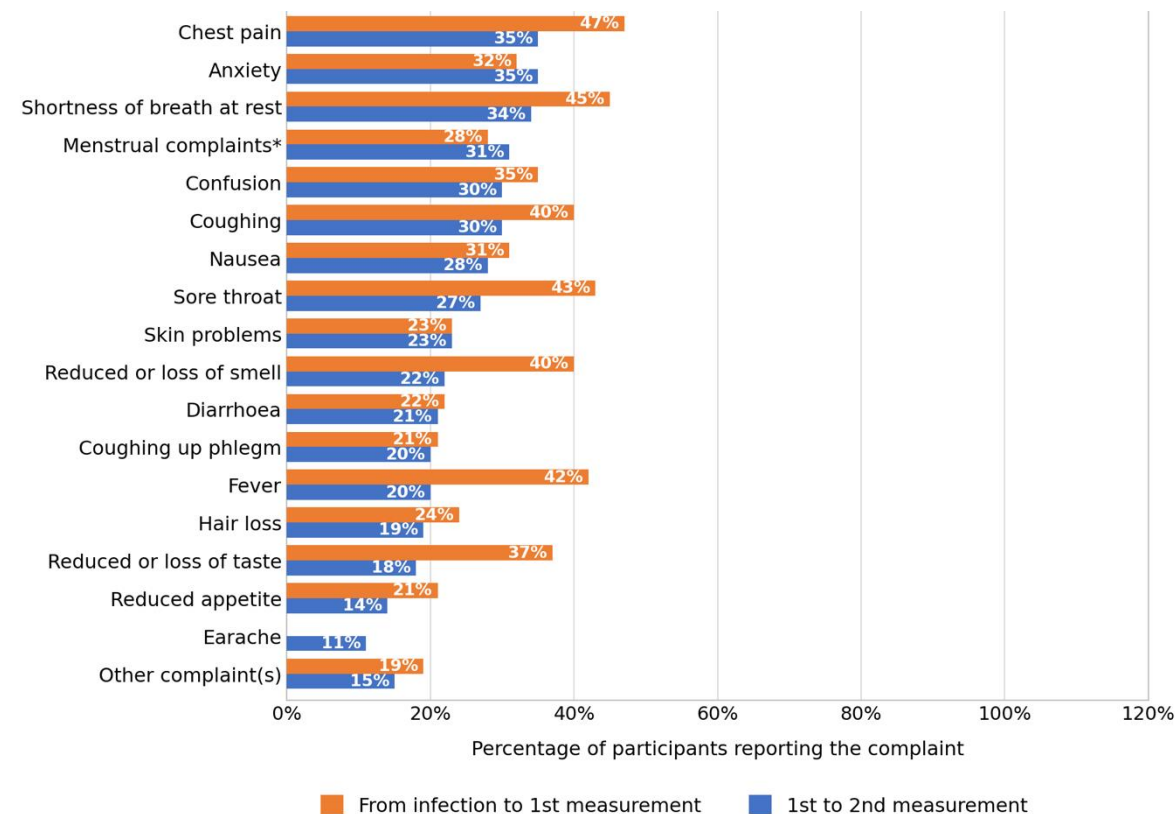
Occurrence of health complaints (n=7,750)

This figure shows the occurrence of health complaints from the COVID-19 infection up to the 1st measurement (orange) and between the 1st and 2nd measurement (blue). Complaints are sorted by occurrence at the 2nd measurement.



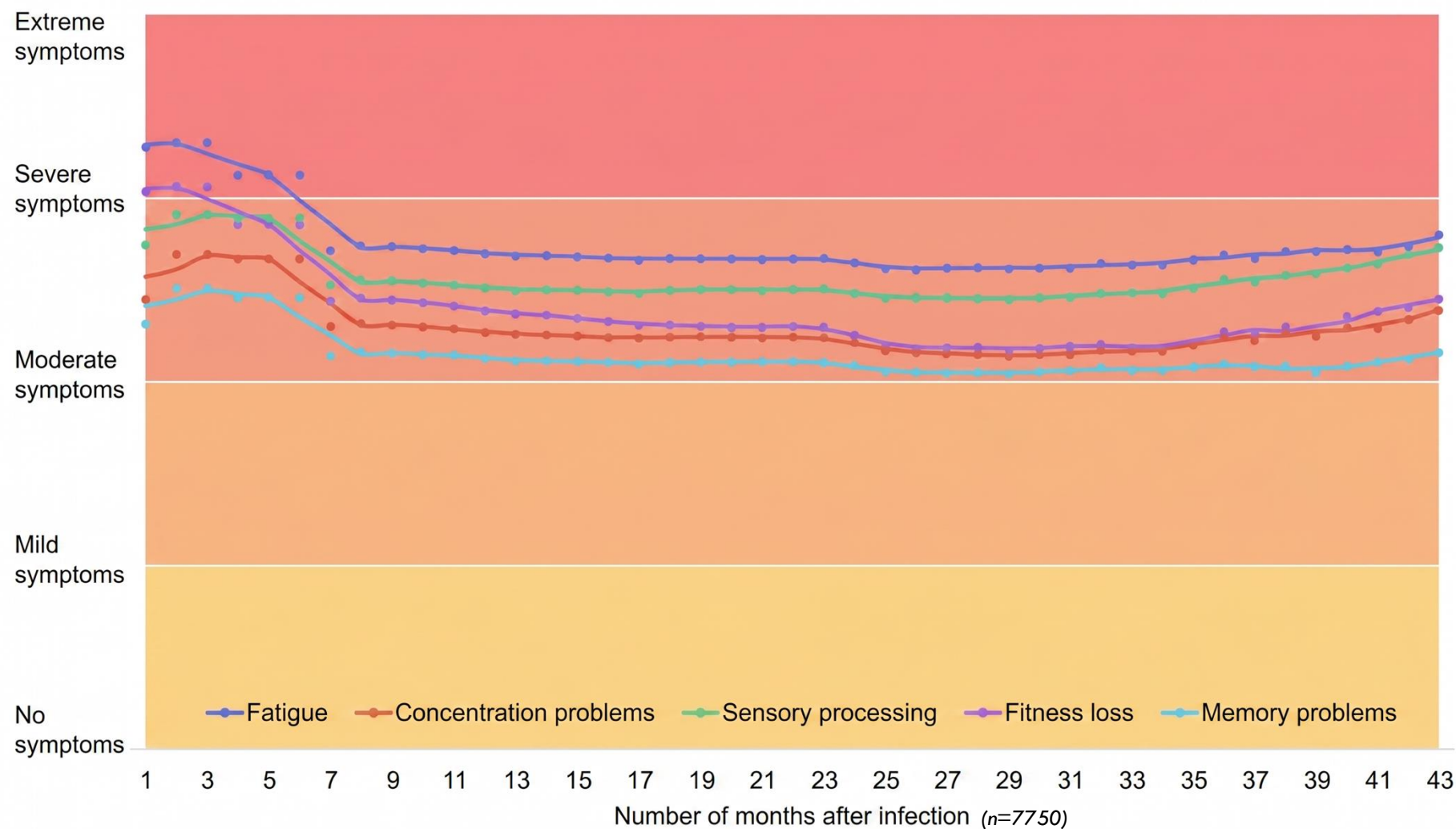
1st measurement feb 2022 – feb 2024 (orange)

2nd measurement 12 months later (blue)



Ref: C-support report: Post-COVID: impact on health, daily life and health care utilisation, 2024

Severity of top 5 complaints



Ref: C-support report: Post-COVID: impact on health, daily life and health care utilisation, 2024

Mission for the Centers of Expertise



Dutch Post-COVID
Academic Centers of Expertise

- **Assignment by the government in 2024**

- 27 million made available up to 2027
- Combine patient care with real-world data

- **Dutch POST-COVID Academic Centers of Expertise (D-PACE)**

- Initial collaboration between Dutch academic centers
- Uniform, data-driven approach to post-COVID care for diagnosis and therapy
- Dynamic if new evidence emerges
- Creation of a scalable structured health care pathway

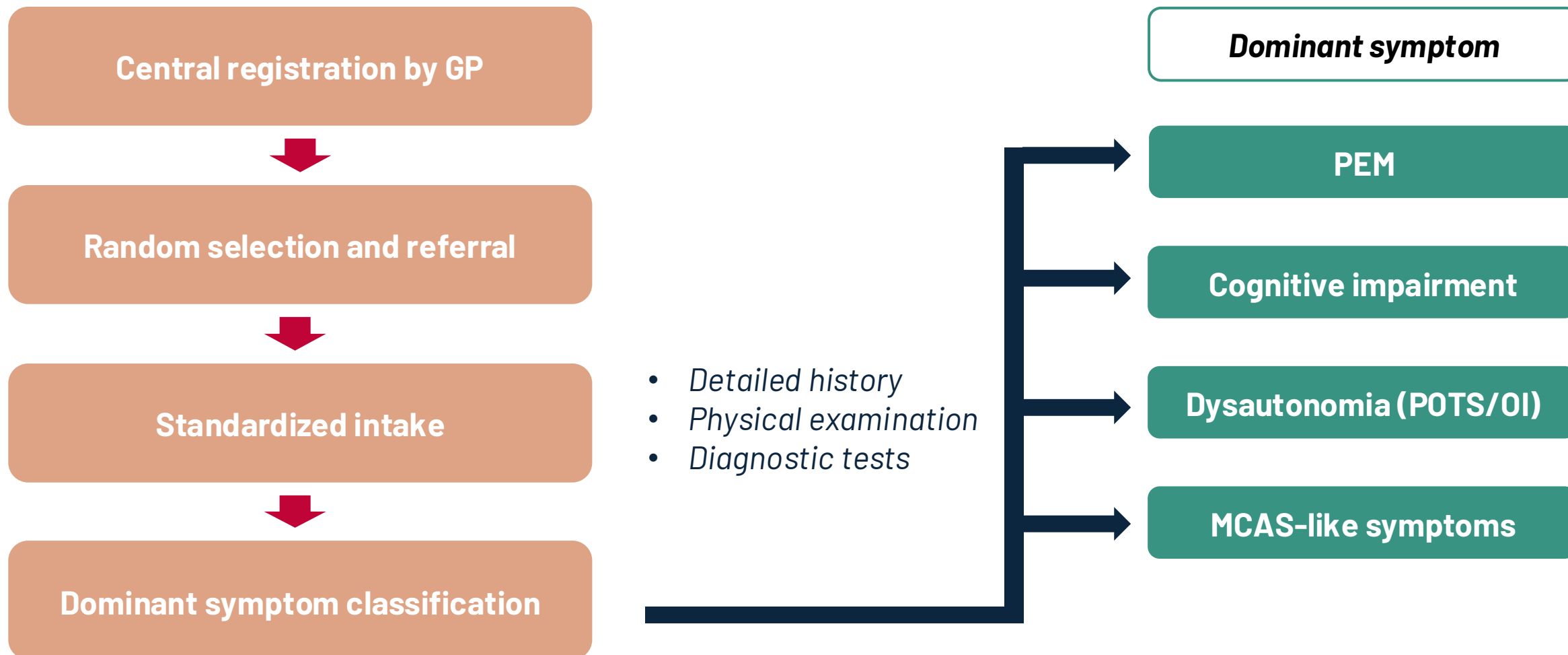
- Adult Centers of Expertise
- Children Centers of Expertise



From registration to phenotyping



Dutch Post-COVID
Academic Centers of Expertise



Referral and selection



● Registration criteria

- Complaints after a COVID-19 infection
- Bell disability scale <75 (loss of functioning of >30%)
- Complaints for at least 1 year
- No alternative diagnosis
- If possible previous paramedical care (physiotherapy or occupational therapy)

● Central random selection

- Allocation to the nearest academic center
- Request for available recent medical history
- Triage
- Approximately 16,000 adult patients on the waiting list

Bell's Functionality Score

100	Fully recovered. Normal activity level with no symptoms	☐
90	Normal activity with mild symptoms at times	☐
80	Near normal activity with some symptoms	☐
70	Able to work full time but with difficulty. Mostly mild symptoms	☐
60	Able to do about 6-7 hours of work a day. Mostly mild to moderate symptoms	☐
50	Able to do about 4-5 hours of work or similar activity at home. Symptoms mostly moderate. Daily rests required	☐
40	Able to leave house every day. Moderate symptoms on average. Able to do about 3-4 hours a day of work or activity like housework, shopping, using computer	☐
30	Able to leave the house several times a week. Moderate to severe symptoms much of the time. Able to do about 2 hours a day of work at home or activity like housework, shopping, using computer	☐
20	Able to leave house once or twice a week. Moderate to severe symptoms. Able to concentrate for one hour or less per day	☐
10	Mostly bedridden. Severe symptoms	☐
0	Bedridden constantly. Unable to care for self	☐

Intake and evaluation



● Standardized intake

- Detailed medical history
- (Validated) questionnaires
(e.g. *FUNCAP27*, *COMPASS-31*, *PROMIS*, *EQ5D*)
- Physical examination
- Hand grip test
- NASA lean test
- Extensive laboratory tests

● Determination of the dominant symptom

- PEM
- Cognitive impairment
- Dysautonomia (POTS/OI)
- MCAS



NASA lean test with Finapres



Treatment protocol

● Treatment of dominant symptom

- Determine adequate pacing
- Non-pharmacological vs off-label treatment
- Consecutive treatment options
 - 'Switch' if no effect, 'add' if some effect

● Evaluation

- Standardized follow-up every 4 ± 2 weeks using domain-specific outcome measures
- Propensity score matched controls
- Controls: untreated patients on the waiting list

● Children

- *N-of-1 studies with off-label medication*



Stepwise treatment protocol



	Non-pharmacological interventions	Off-label pharmacological interventions
PEM	Pacing Occupational therapy	1. Low-dose naltrexone (LDN) 2. Low-dose aripirazole (LDA)
Dysautonomia (POTS/OI)	Optimize fluid + salt intake Stockings Physiotherapy	1. Fludrocortisone 2. Ivabradine / propranolol 3. Midodrine 4. Pyridostigmine
Cognitive impairment	Sleep hygiene	1. Low-dose naltrexone 2. Low-dose aripirazole 3. Nicotine patches 4. SSRI
MCAS-like symptoms	Avoid triggers Dietician	1. H ₁ and H ₂ antagonists 2. Cromoglycic acid 3. Montelukast

Mid-term evaluation adults (June 2026)



Dutch Post-COVID
Academic Centers of Expertise

● Evaluation of patients

- Total number of 1041 patients met post-COVID criteria
 - <1% had other comorbidities relating to complaints

● General population

- Majority women at middle age
 - Age ranging from 18-80 year (1 to 100 year)
- Complaints lasting for over 3,5 years
- Canadian Consensus Meeting criteria ME/CFS in $\approx 75\%$

	Population (n=1041)
Female sex	771(74%)
Age (years)	51[42-59]
BMI (kg/m²)	26[23-31]
Overweight	521(59%)
Obesity	241(27%)
Duration of complaints (days)	1367[1112- 1686]
Bell score	30[30-40]

N(%); median[interquartile range]

Clinical phenotyping



● Evaluation of patients

- Total number of 1041 patients met post-COVID criteria

● Symptoms

- High majority of patients with PEM and cognitive impairment
 - Inadequate pacing in $\approx 33\%$ of patients
- Dysautonomia complaints in $\approx 40\%$ of patients
 - In $\approx 20\%$ of diagnosis POTS, otherwise OI
- MCAS-like symptoms in $\approx 15\%$

	Population (n=1041)
PEM	974 (96%)
Adequate pacing	677 (68%)
Cognitive impairment	835 (93%)
OI	205 (21%)
POTS	197 (20%)
MCAS-like symptoms	157 (16%)

N(%)



(Validated) questionnaires

● Evaluation of patients

- Complete questionnaires in 994 patients

● Symptoms in questionnaires

- DePaul Symptom Questionnaire-Short Form (DSQ-SF)
- Composite Autonomic Symptom Score (COMPASS)-31
- FUNCAP-27
- Patient-Reported Outcomes Measurement Information System (PROMIS)
- EuroQol 5 dimensions quality of life (EQ5D)

	Population (n=994)
DSQ-SF	66[42-87]
COMPASS-31	32[21-43]
FUNCAP-27	4.2[3.5-4.8]
PROMIS cognition	35[32-40]
PROMIS fatigue	64[61-68]
PROMIS pain	62[55-67]
PROMIS sleep	56[52-62]
EQ5D index	0.66[0.44-0.79]

Median[interquartile range]

Diagnostics



● No discriminating laboratory results

- Renal and hepatic parameters
- Deficiencies (iron, vitamin B6 and B12, folic acid)
- Endocrinology (cortisol, thyroid hormones)
 - No Addison's disease in OI or POTS
- Immunology (CRP, ESR, rheumatoid factor, anti-dsDNA)
- Cardiology (nt-proBNP)
- Hematology (bloodcells)
- Coagulation (von Willebrand factor, factor VIII, fibrinogen)

● Non-clinical laboratory results

- Auto antibodies G-protein coupled receptor (anti- α 1-adrenergic receptor, anti-Muscarinic Cholinergic Receptor 2 (M2))



Therapies

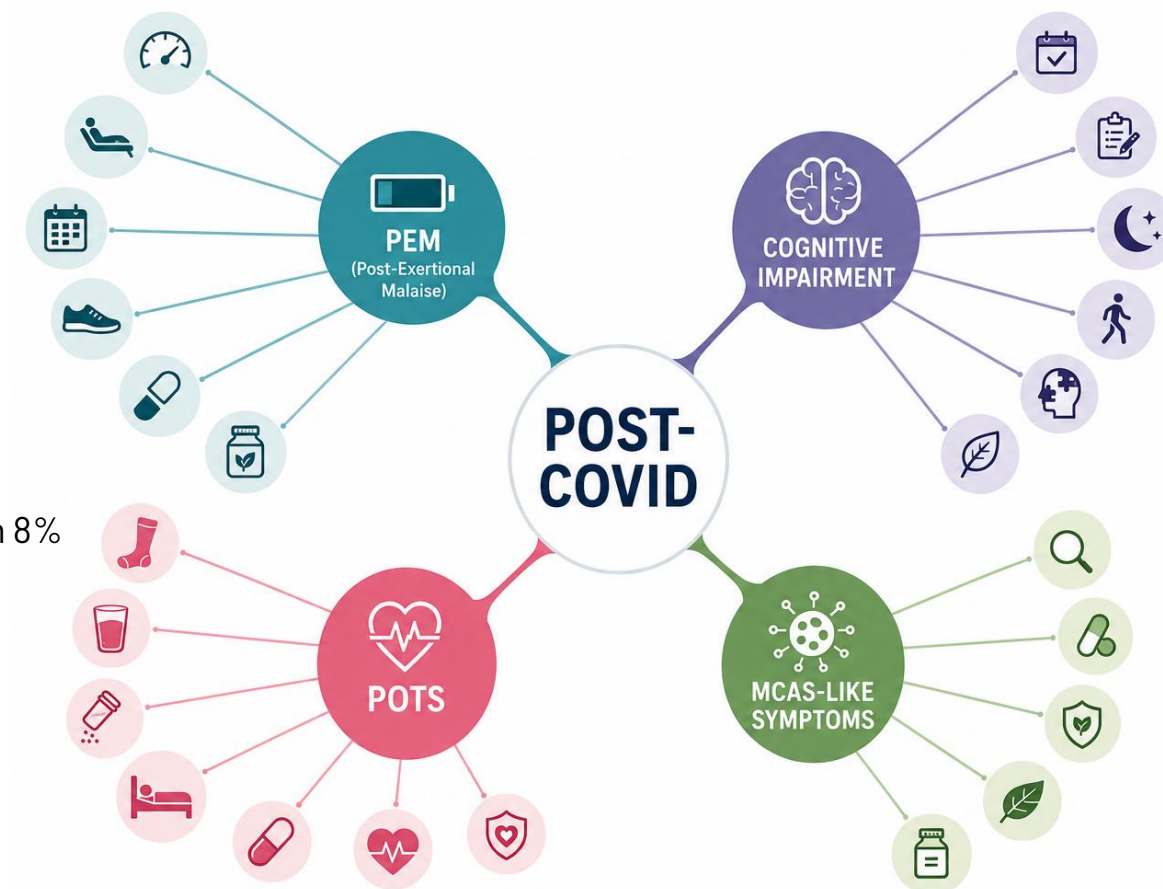


- **Evaluation of patients**

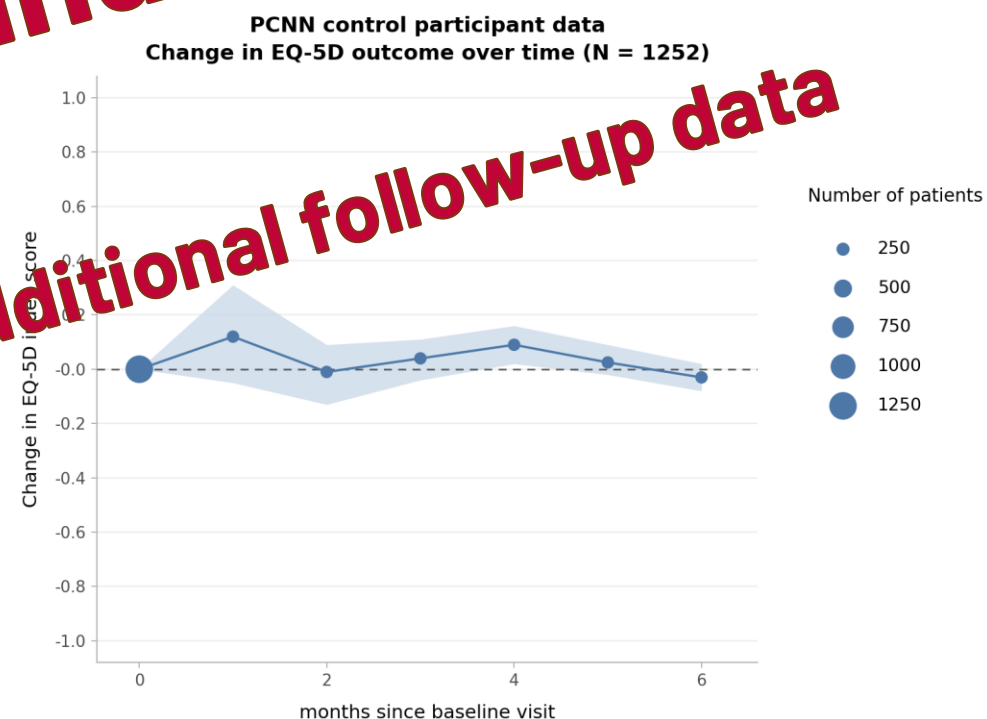
- Data on therapy in 476 patients (2 centres)

- **Dominant symptom and first step therapy**

- PEM (68%)
 - Treated with pacing in 30%, LDN in 35%
- Cognitive impairment (6%)
 - Treated with LDN in 4%
- POTS (22%)
 - Treated non-pharmacologically in 20%, fludrocortisone in 8%
- MCAS-like symptoms (<1%)



Effect of the care



To be continued

Propensity matching with additional follow-up data

Timelines



**Dutch Post-COVID
Academic Centers of Expertise**

● Goals

- New patient referrals up to December 2027
- Maximum of 6 months follow-up afterwards
- April 2027: Treatment evaluation of first years

● Interim evaluation inclusions

- August 2026: 1200 patients included



Opening visit by Queen Máxima, Princess of Oranje Nassau November 2025



Concluding remarks

● **Conclusion**

- By aligning triage, phenotyping, and evaluation with real-world data capture, the Dutch approach facilitates both individual patient care and collective knowledge generation

● **Future directions**

- Long term funding at risk
- Expand care to other post-acute infection syndromes (PAIS)



Dutch Post-COVID Academic Centers of Expertise



Special acknowledgements

Amsterdam UMC

Dr. B. Appelman
Dr. S. Biere-Rafi
Dr. R. van Hooijdonk
B. Hogewoning
B. D. Jonghe
Dr. M. Kallen
D. Schouten
Dr. M. Visser
Prof. Dr. M. van Vugt
Dr. T. Sieswerda
Dr. H. van Straaten

Leids UMC

Dr. L. Kuijpers

Maastricht UMC

Dr. H. Borggreve
Dr. Oude Lashof
J. Schippers
Dr. S. Schuurmans

UMC Groningen

Dr. R. Stienstra

UMC Utrecht

Dr. M. Janssen
Dr. J. Houtveen
Dr. A. van der Gugten
K. Spekking
Prof. Dr. S. Nijhof

Erasmus MC

Dr. G. Braunstahl
L. Chang Njoek Joen
M. Drost
Dr. M. Hellemans
Dr. S. Hoeboer
Dr. M. Huson
Dr. L. Roksnoer
Dr. H. van der Sijs
Dr. L. van den Toorn

**Thank you
for the attention**

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N. Bults / E. den Teuling
E. Koster / K. Wolffenbuttel
J. Van der Zwam

Adult Centers of Expertise, Children Centers of Expertise