

Immune-metabolic Recovery and Post-exertional Malaise (Bio-SIG PEM study)

Identification of molecular and clinical phenotypes in ME/CFS · PEM Recovery model · Predictive PEM-Models wearables

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on behalf of the Bio-SIG PEM working group

Thank you!



Federal Ministry
of Research, Technology
and Space

LONG COVID
DEUTSCHLAND

ME/CFS
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FÜR ME/CFS E.V.

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Bundesverband ME/CFS

Post-COVID-Zentrum
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**Center for Sepsis
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BIO-SIG PEM
Understanding biology signature of
Post-Exertional Malaise in ME/CFS

Bio-Sig PEM Study Group

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Bio-SIG of Post-Exertional Malaise

Six parallel subprojects converging on a shared PEM bio-signature · radial view

COHORT
40 ME/CFS · 40 KK · 40 IBD

COORDINATION
Prof. C. Puta · UKJ

NETWORK
6 partner institutions



INPUTS

- Cohort triad · 40 ME/CFS · 40 KK · 40 IBD
- PEM challenge · repeated anaerobic exercise · 1-min STS
- Sample capture · serum · vesicles · cells · wearables · imaging

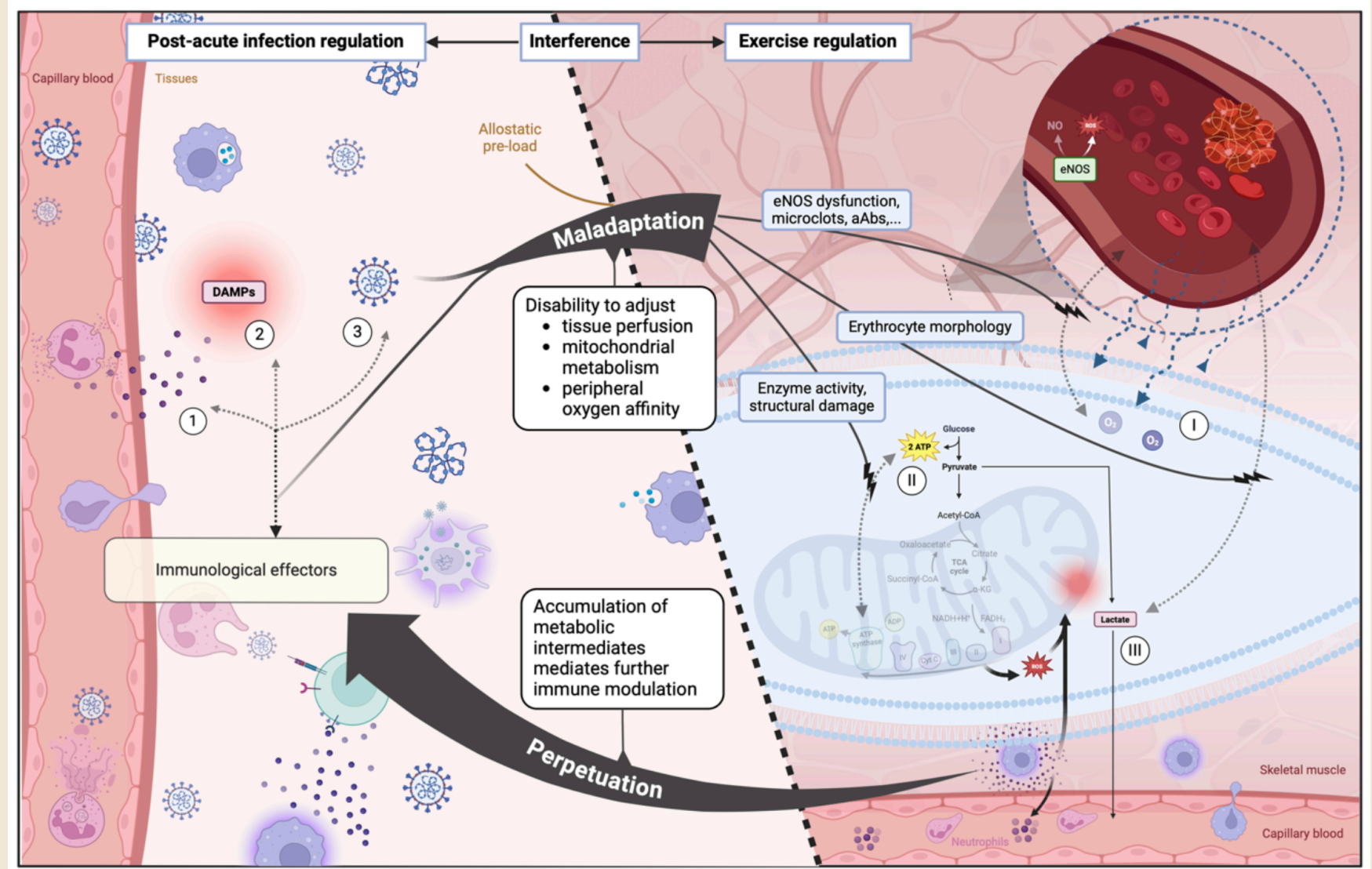
OUTPUTS

- Composite PEM panel discriminating ME/CFS from KK & IBD
- Predictive wearable digital phenotype of PEM susceptibility
- Translation → IC-PAIS day-clinic pathway (Slide 1)

Immunomodulatory mediators (1)
 tissue damage (2)
 viral antigen (3)
 autoimmune responses (AAB,
 molecular mimicry)
 can be considered key triggers
 that maintain infection regulation.

Their multisystemic adverse
 effects on metabolic
 pathways and vascular functions
 contribute to maladaptation to
 physical activity.

Upon physical activities, the
 organism is thus confronted with
 hypoxia (I),
 energy deprivation (II) and tissue
 acidosis (III) that can further
 modulate immune activation



Haunhorst S, Dudziak D, Scheibenbogen C, Seifert M, Sotzny F, Finke C, Behrends U, Aden K, Schreiber S, Brockmann D, Burggraf P, Bloch W, Ellert C, Ramoji A, Popp J, Reuken P, Walter M, Stallmach A, Puta C. Towards an understanding of physical activity-induced post-exertional malaise: Insights into microvascular alterations and immunometabolic interactions in post-COVID condition and myalgic encephalomyelitis/chronic fatigue syndrome. *Infection*. 2025 Feb;53(1):1-13. doi: 10.1007/s15010-024-02386-8. Epub 2024 Sep 6. PMID: 39240417; PMCID: PMC11825644.

Three stages phenotype procedure - Bio-SIG PEM

#1 Outpatient phenotype screening: IC-PAIS day clinic (three days)

N = 251 (1/2025-12/2025) > 27/125 ME/CFS eligibility for #2 Inpatient

#2 Inpatient phenotype: four days and nights

May 2026: 11/27 | 40 IBD, 40 Controls, 40 ME/CFS 05/2027

#3 Follow up (after 12 weeks) > IC PAIS ambulance

N = 8

1: outpatient phenotype screening (3 days)

The intersection of the metabolic and recovery phenotypes determines the outpatient individual PEM signature —and, consequently, the precision of pacing recommendations, pharmacological target values, and rehabilitation protocols within the framework of the IC-PAIS model.

2: inpatient phenotype (4 nights and days)

Inpatient phenotype involves the crucial expansion of the *immunometabolic* biomarker panel (red blood cell changes, deep immune profile, endothelial markers, microbiome and brain analysis).

Outpatient phenotype screening: The IC-PAIS Patient Pathway

COHORT
Suspected PCS · ME/CFS

SETTING
Tertiary day clinic

DURATION
~9 months end-to-end

1

Intake
≈ 6 MONTHS · PRE-CLINIC

●

Online registration 01
Self-referral via portal · prior records submitted.

○

Record review 02
Internal medicine & neurology screen documentation.

○

First assessment 03
Video / phone · SARS-CoV-2 link · differential diagnostics.

○

Alternative diagnosis excluded?
Psychiatric · endocrine · malignant · autoimmune

NO → Refer to alternative specialty

○

Invitation to day clinic 04
Or: single outpatient appointment if criteria not met.

2

IC-PAIS Day Clinic
3 DAYS · MULTIDISCIPLINARY

DAY 1

Internal medicine · baseline workup

● **Consultation**
Physical exam · blood draw · ECG · autoimmune panel

● **Functional tests**
NASA lean test · STS + HKT · lactate · glucose · CBC

● **Diagnostics**
Exclude PoTS / OH · pre & post-exercise dysregulation

DAY 2

Physical medicine & sports · function & pacing

● **Physical rehab**
Musculoskeletal causes · pain syndromes · structural exclusion

● **Sports medicine**
Exercise plan · yoga · PMR · relaxation · pacing strategies

DAY 3

Psychology · neurology · social · cognition & reintegration

● **Psychology**
Neuropsych testing · cognitive deficits · alertness

● **Neurology**
Physical exam · exclusion of neurological conditions

● **Social medicine**
Rehab · pension · DoD · care level · reintegration

3

Outcomes & Follow-up
DISCHARGE → 12 WK → 9 MO

A

Multidisciplinary team meeting
Synthesise Day 1–3 findings · classify **PCS / ME/CFS** yes or no.

B

Discharge consultation
20 min · diagnosis communication · treatment plan · Bio-SIG PEM screen.

— NO PEM

Standard follow-up

Re-assessment at 6–9 months for confirmed patients.

— BIO-SIG PEM

Inpatient phenotyping

4 nights · structured PEM protocol · 12-week reassessment.

Inpatient phenotyping

A positive Bio-SIG PEM screen bifurcates the pathway — questionnaire screen *and* clinical assessment, per ICC / CCC

TRIGGER
Positive Bio-SIG PEM screen

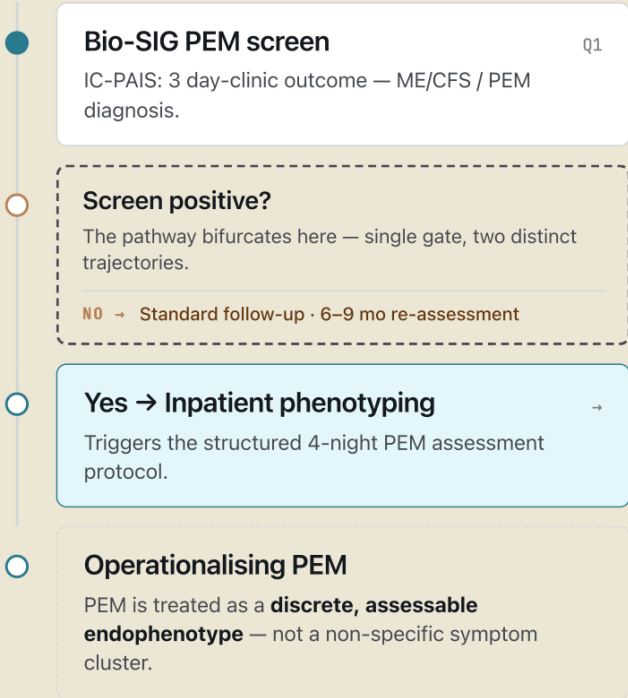
PROTOCOL
4 nights · inpatient phenotyping

REASSESSMENT
12 weeks post-discharge

1

Decision gate

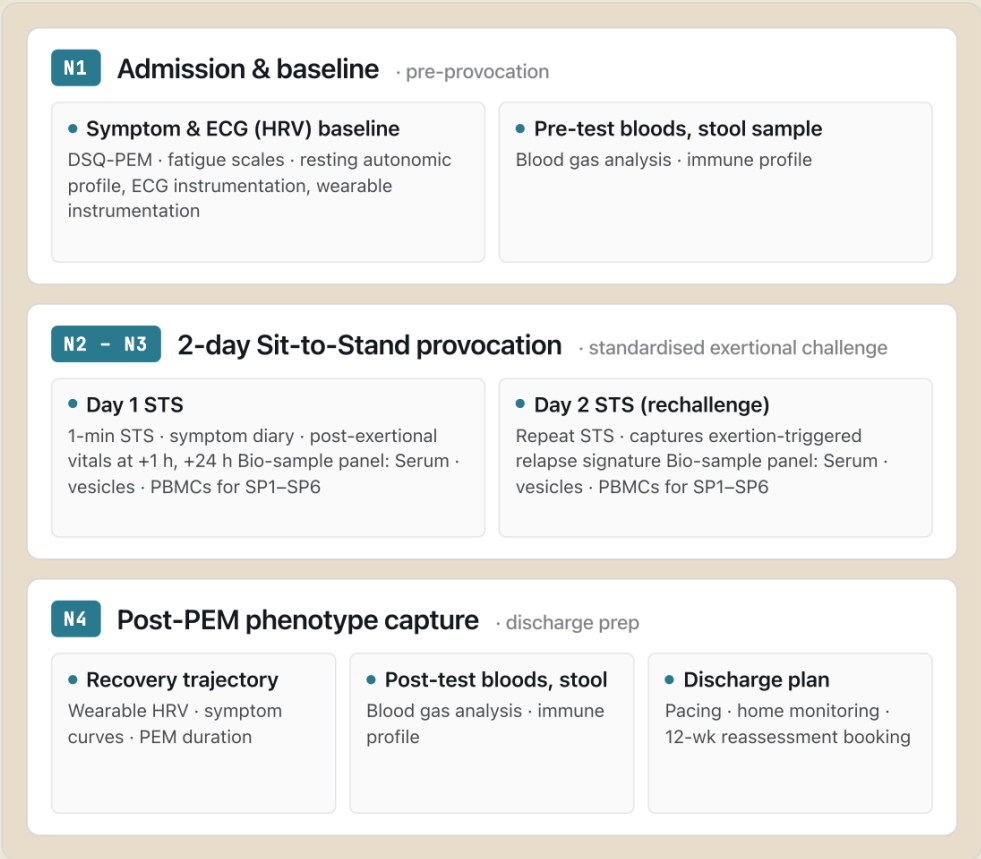
DISCHARGE CONSULTATION · SLIDE 1, STEP B



2

Inpatient phenotyping

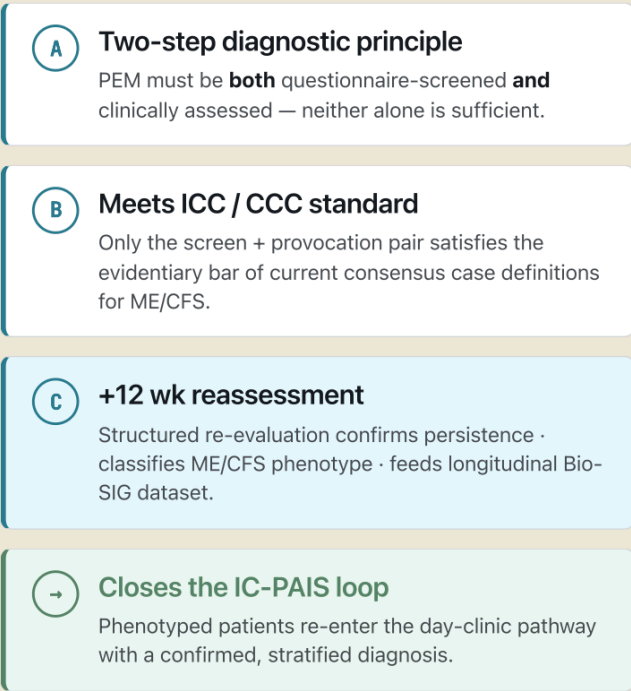
4 NIGHTS · STRUCTURED PEM PROTOCOL



3

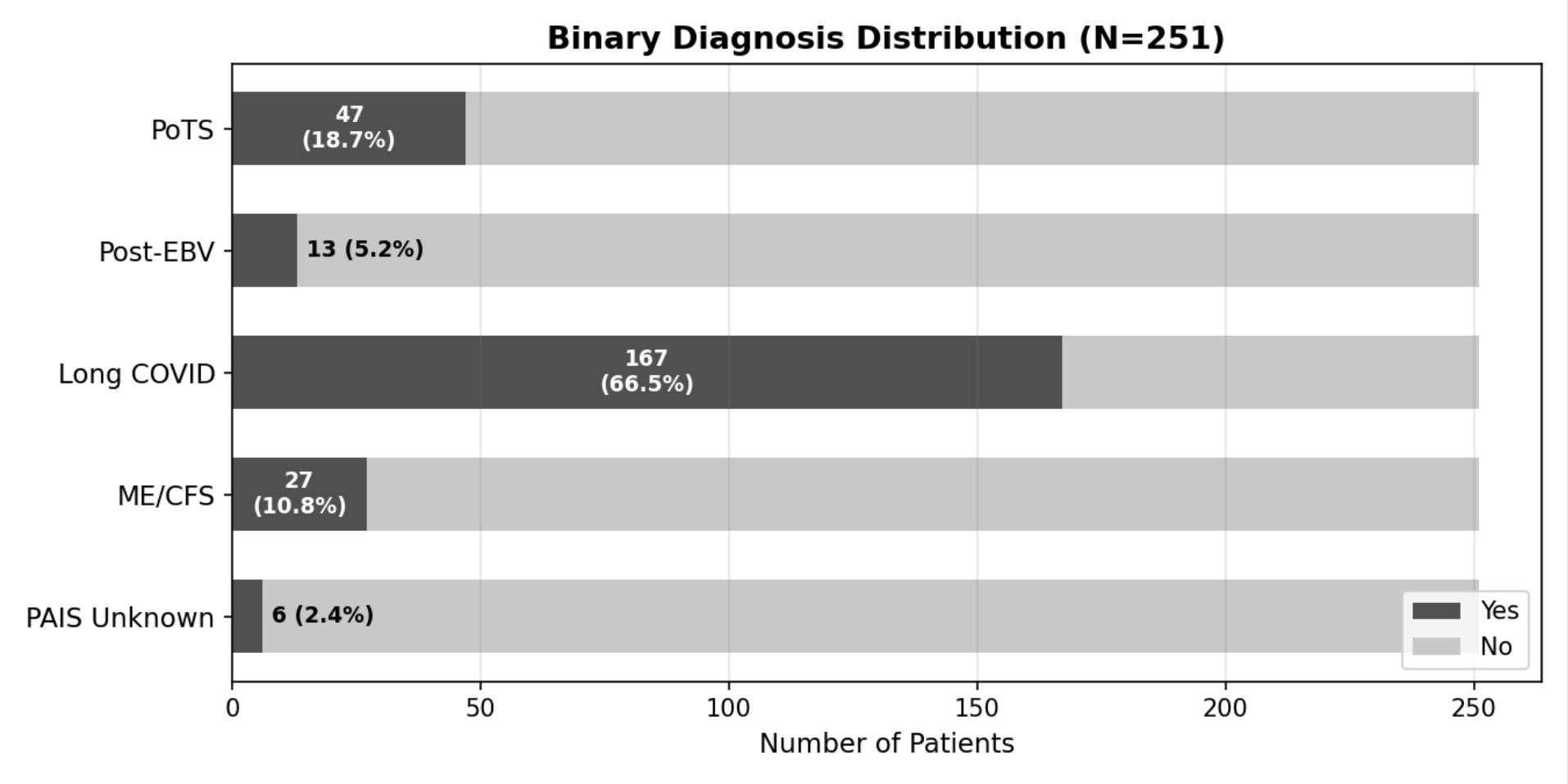
Rationale & reassessment

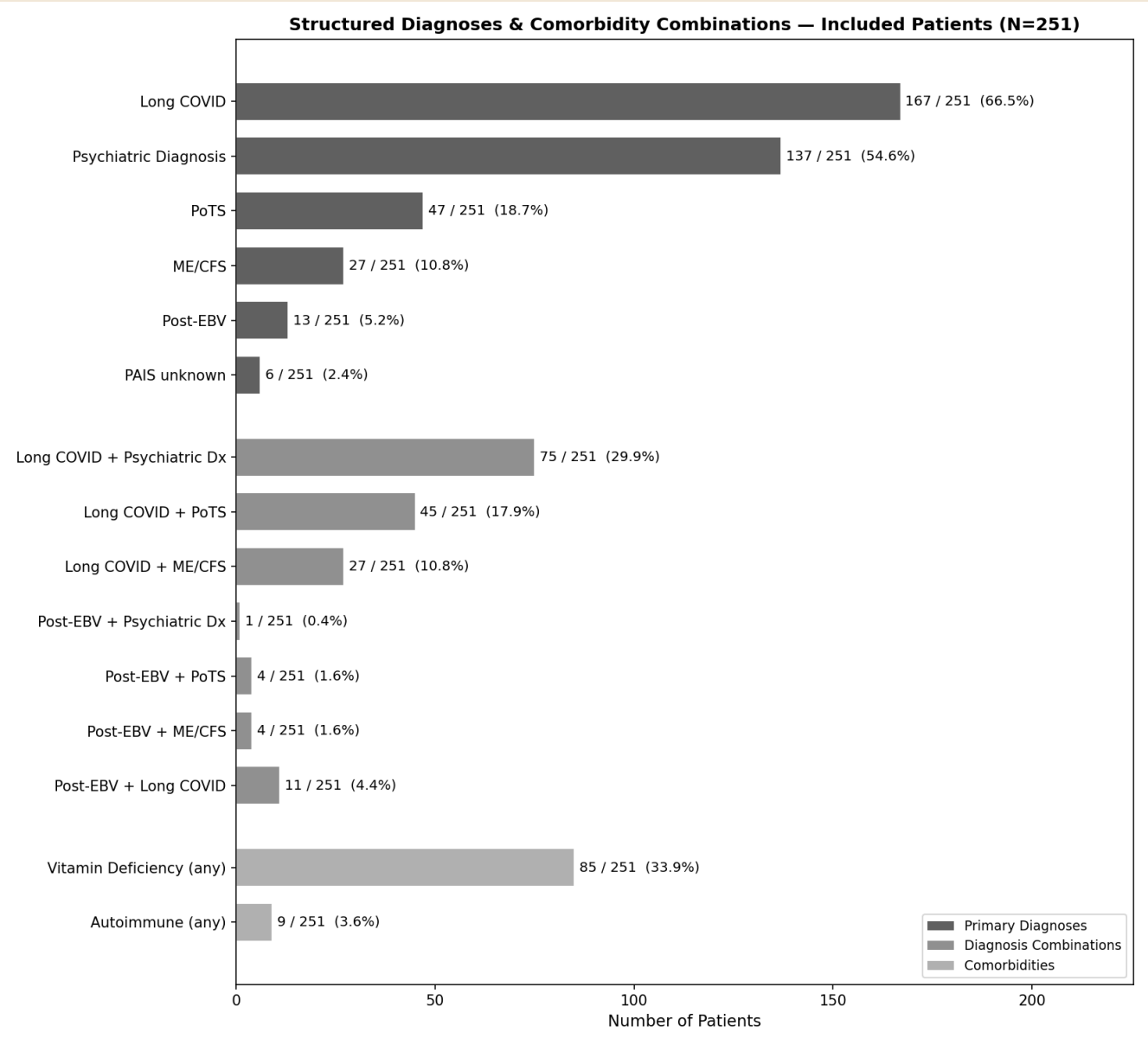
WHY TWO STEPS · 12-WEEK FOLLOW-UP



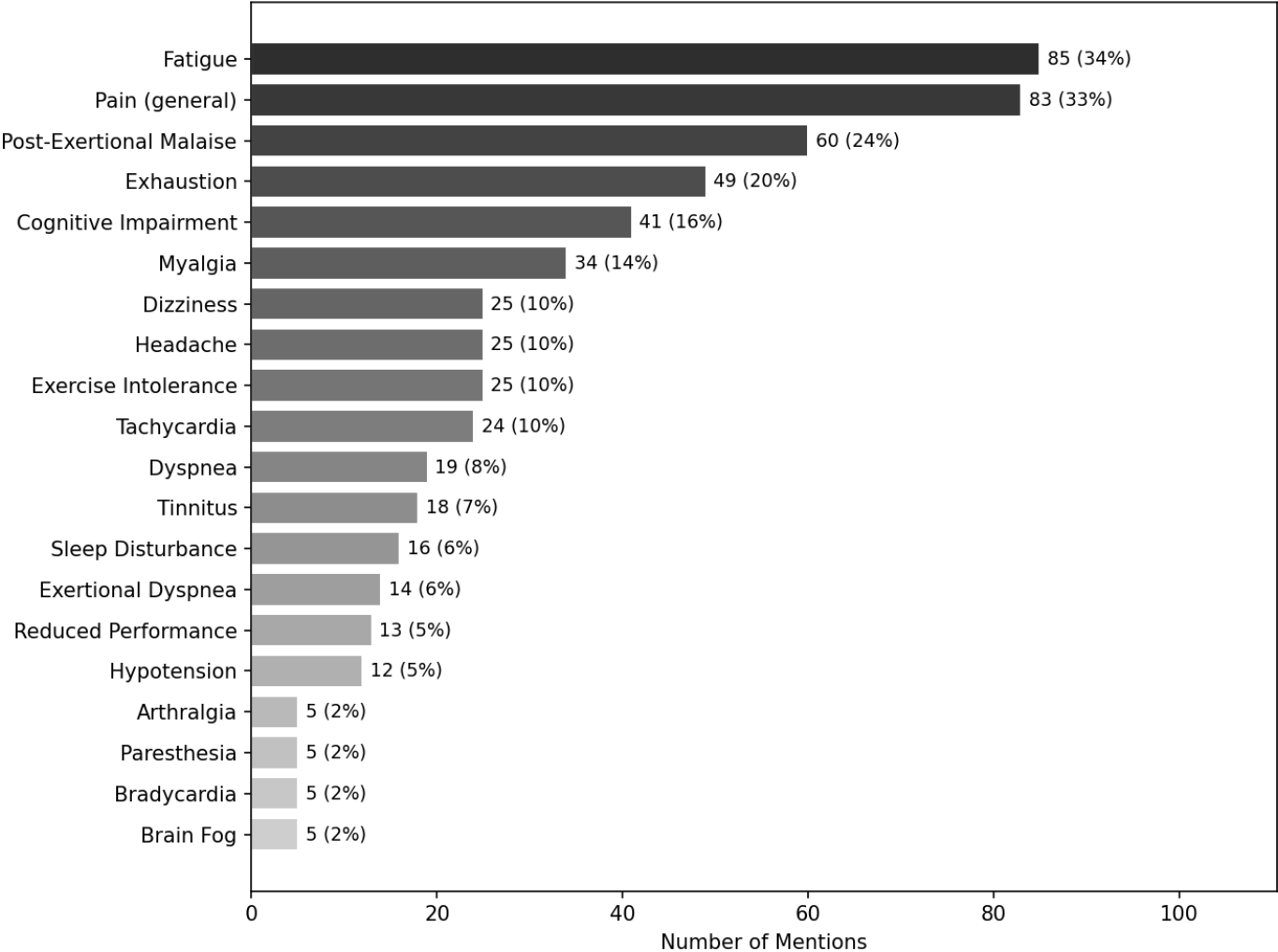
Outpatient IC-PAIS day clinic: Binary Diagnosis

01/2025-12/2025



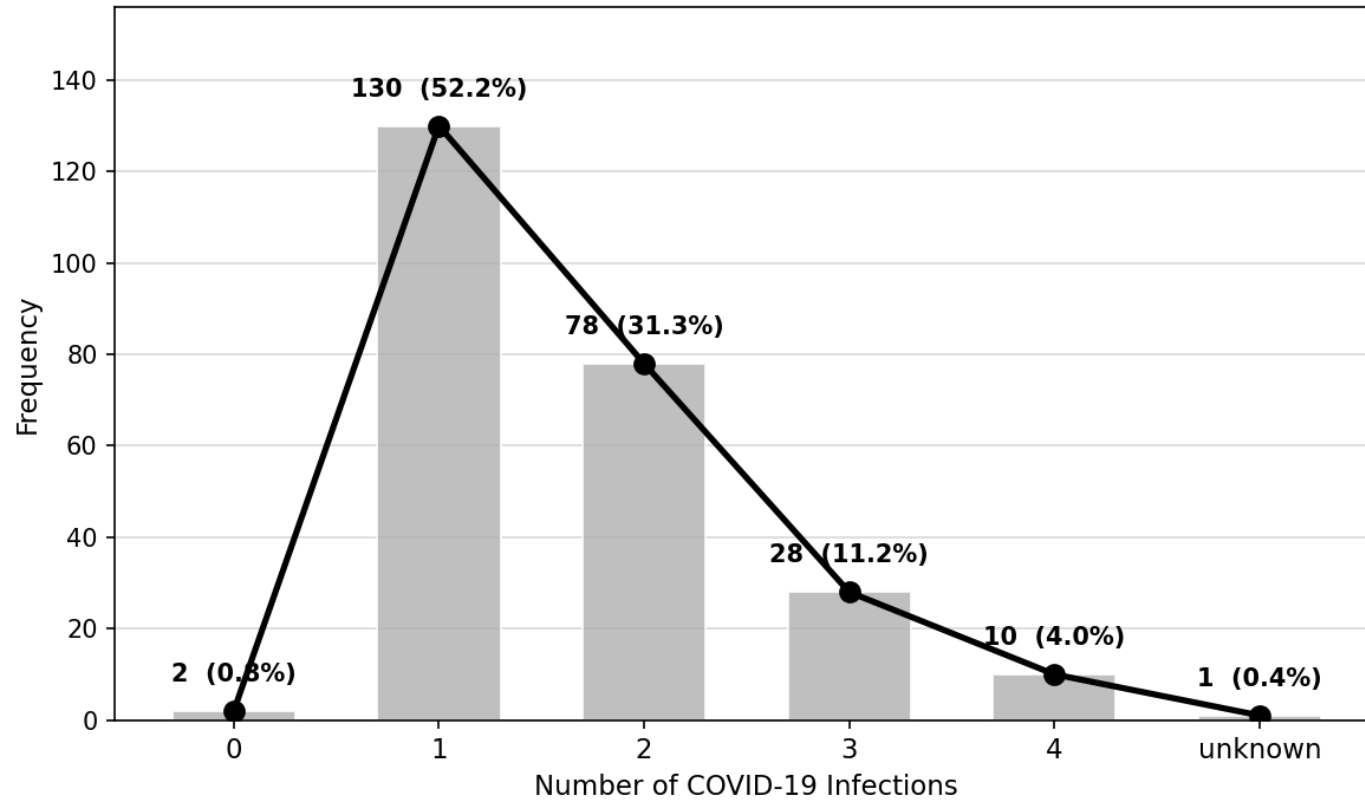


**Outpatient IC-PAIS day
clinic: diagnoses and
comorbidity
combinations**
01/2025-12/2025



Outpatient IC-PAIS day clinic: symptom report

01/2025-12/2025



Outpatient IC-PAIS day clinic: Infections

01/2025-12/2025

Three Metabolic Phenotypes and Three Recovery Phenotypes

Bio-SIG PEM — study flow (CONSORT-style)

Bio-SIG PEM cohort · 01/2025 - 12/2025
n = 251

Excluded / drop-out

Complete lactate profile
(pre · 1 · 5 · 10 min post STST)
n = 188

Excluded: n = 63
(incomplete lactate values)

Metabolic phenotyping (K-Means, k = 3)
n = 188

*Phenotype 1
Low-lactate /
efficient (n=82)*

*Phenotype 2
Moderate /
plateau (n=82)*

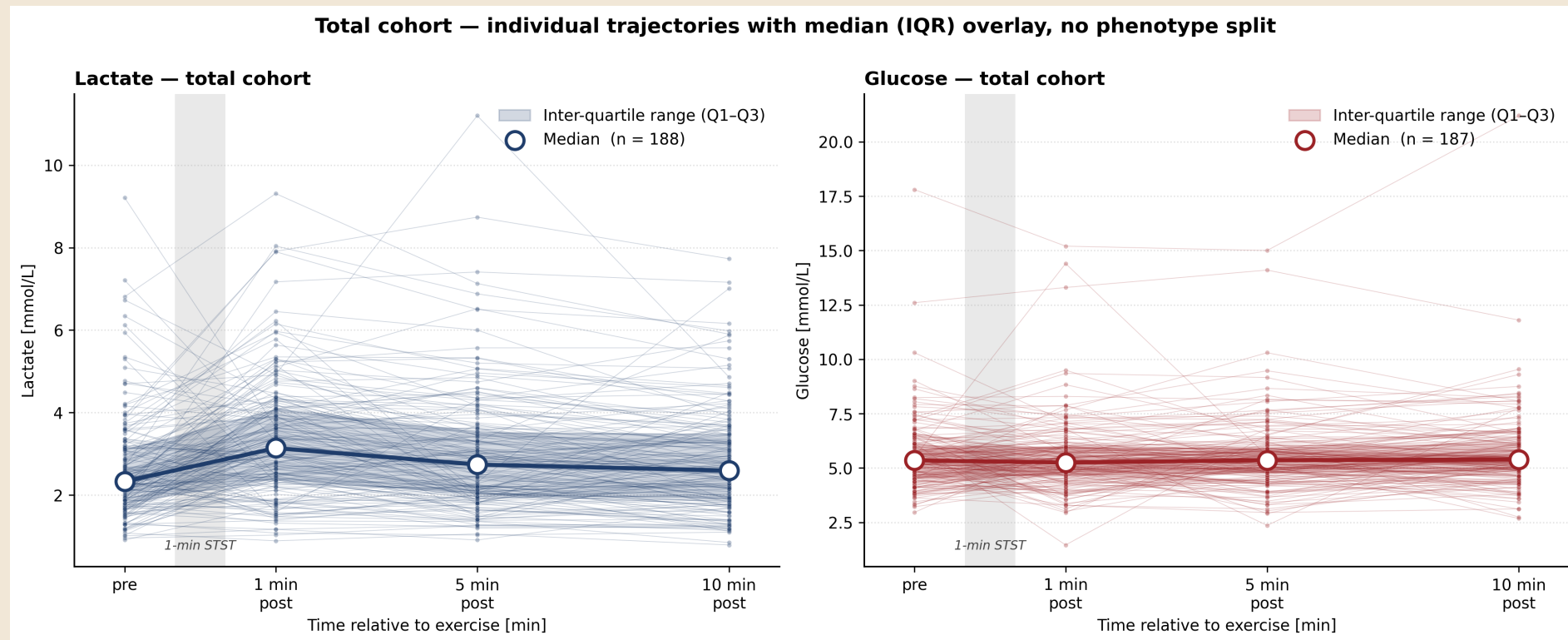
*Phenotype 3
High-peak /
impaired (n=24)*

Recovery phenotyping (K-Means, k = 3)
n = 170 (complete sub-domains)

*R-A: globally impaired (n=54)
R-B: metabolically slow (n=57)
R-C: PRO-burdened (n=59)*

Cohort-level lactate and glucose response.

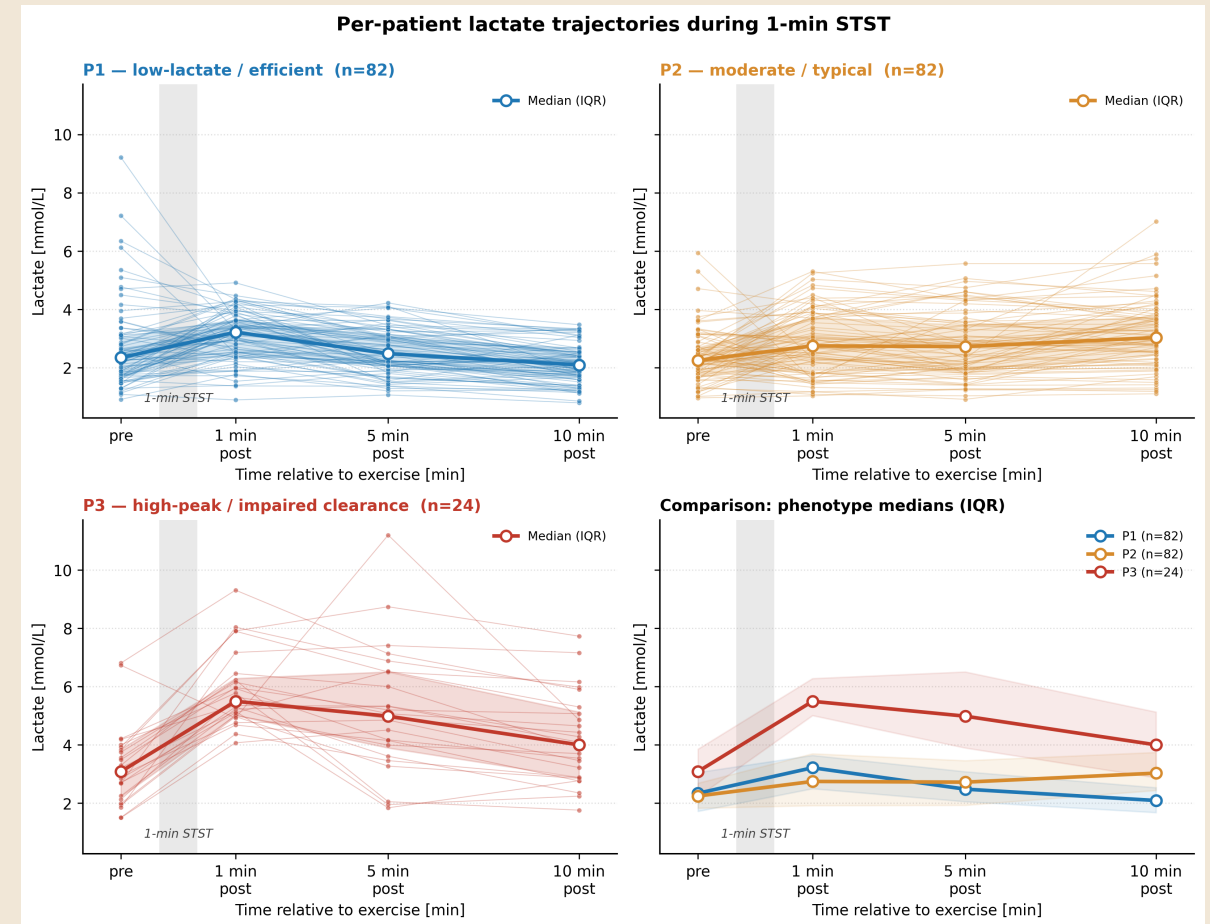
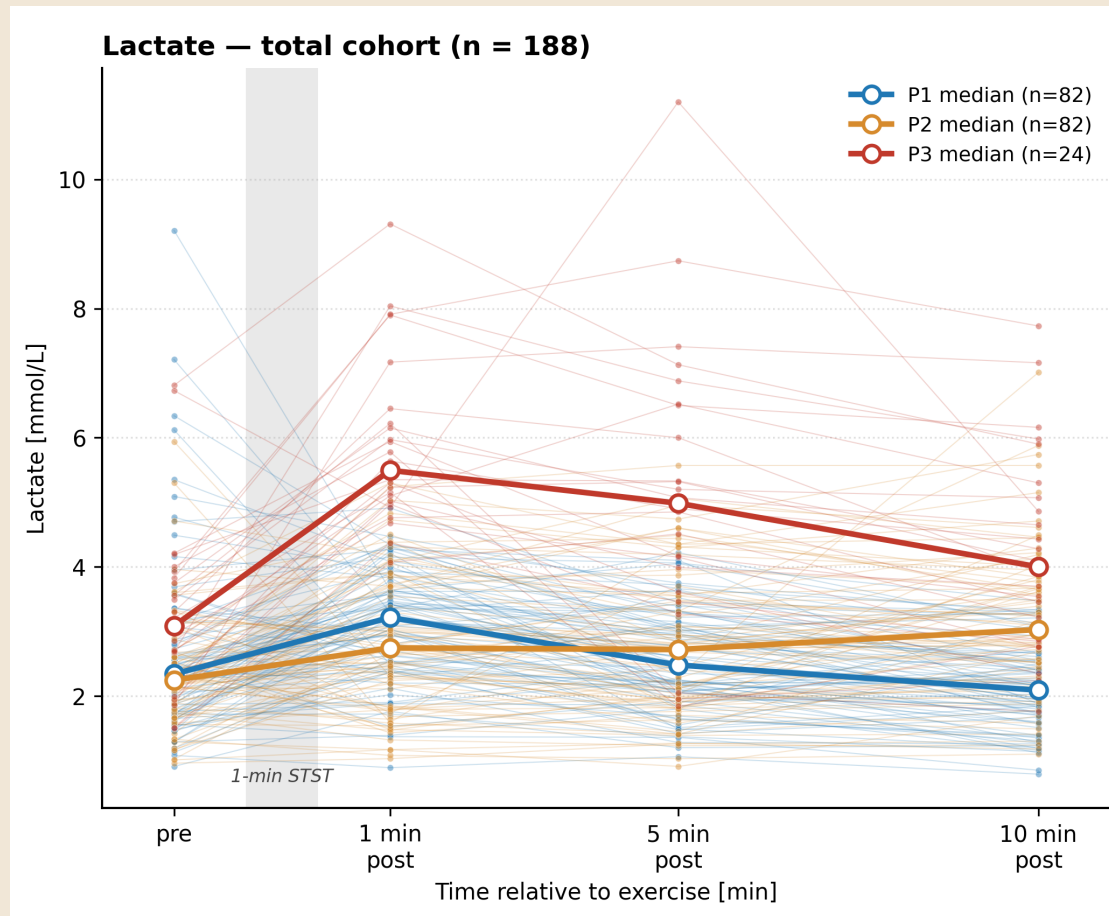
Each thin line = one patient's individual trajectory. Overlaid: cohort median (white circles + connecting line) with inter-quartile range (Q1–Q3) shaded. No phenotype differentiation yet — the next slide decomposes the cohort into the three lactate phenotypes.



Take-home • the cohort median peaks at 1 min post and clears slowly back toward baseline at 10 min — clean signal at the population level, but it hides three distinct sub-trajectories.

Metabolic Phenotypes

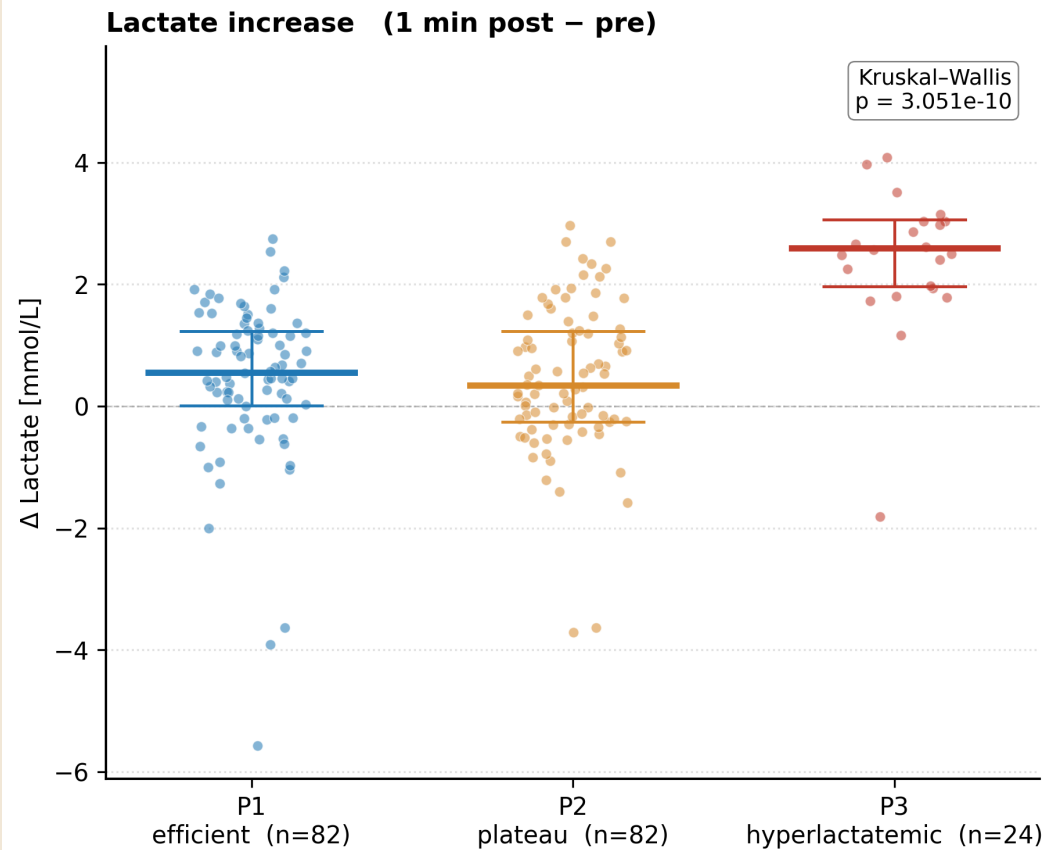
Three trajectories emerge after a 1-minute exercise test.



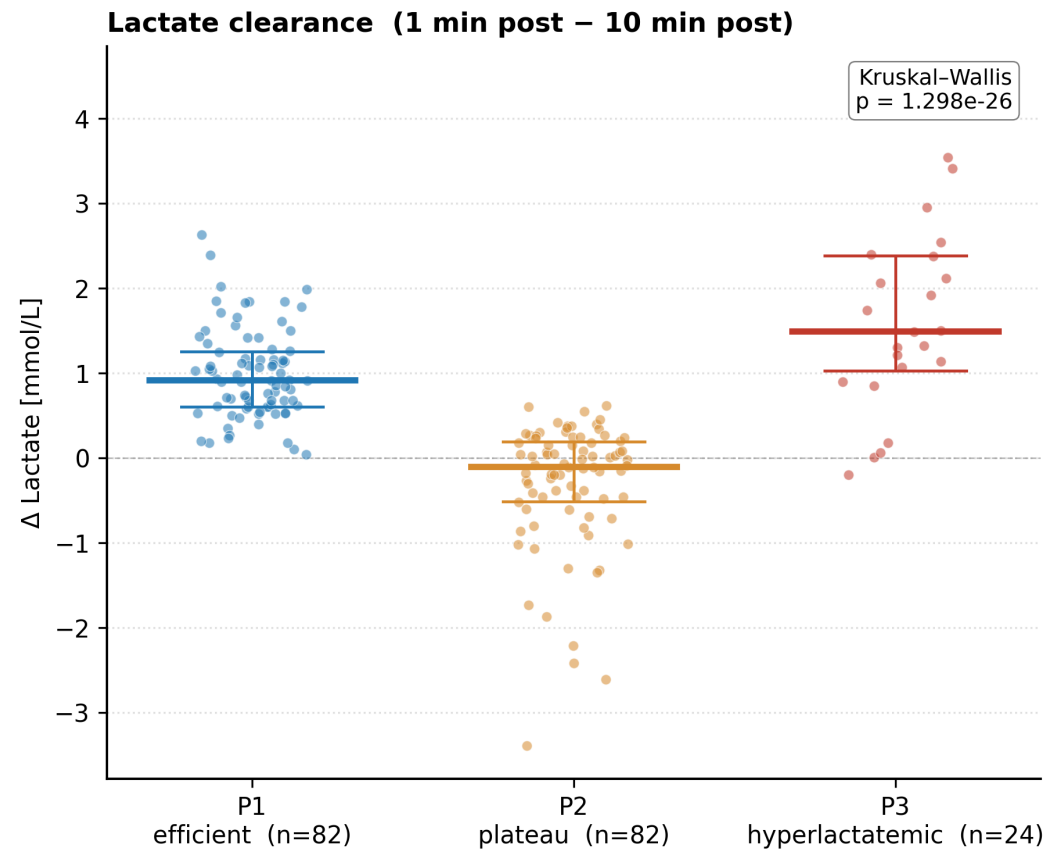
Take-home · P1 clears efficiently · P2 plateaus (no clearance) · P3 hyperlactatemic peak — all lactate parameters $p < 10^{-4}$ (Kruskal-Wallis).

P3 produces the largest spike; P2 fails to clear it.

Δ Lactate: exercise increase & 10-min clearance

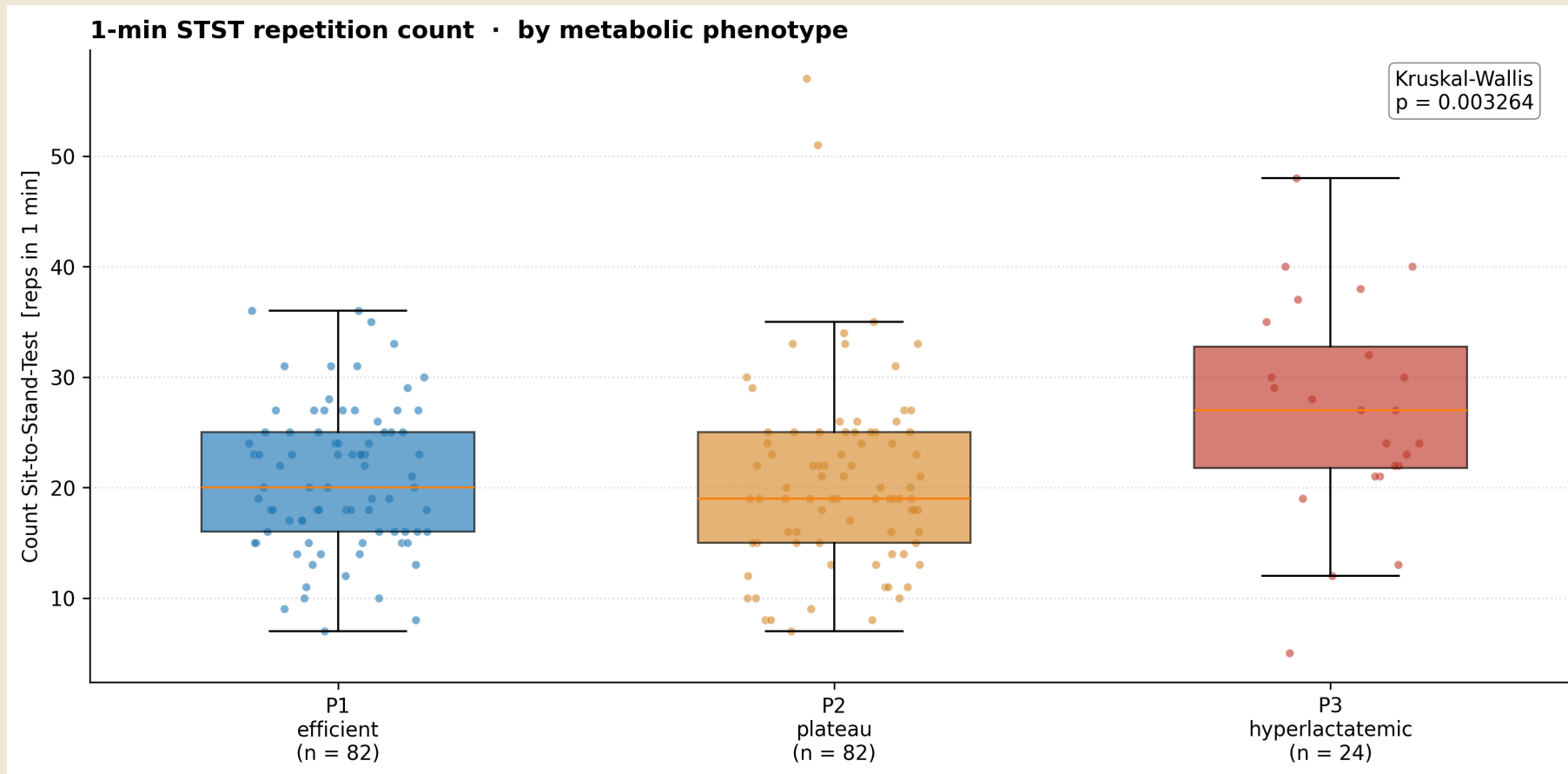


INCREASE
(1 min post – pre)



CLEARANCE
(1 min post – 10 min post)

P3 carries the highest STST count — and the highest lactate.



Medians • P1 20 • P2 19 • P3 27 reps • Kruskal-Wallis $p = 0.003$

Take-home • P3's hyperlactatemic peak is therefore a mechanical-output effect — these patients simply do more reps and produce more lactate; it is not a dominant metabolic-clearance failure as in P2.

FROM METABOLIC PHENOTYPE to RECOVERY- SCORE ARCHITECTURE

FROM METABOLIC PHENOTYPE to RECOVERY- SCORE ARCHITECTURE

Four orthogonal domains, each scaled 0–100 · higher = better recovery.

LR

Metabolic recovery

% lactate clearance peak → 10 min (50 % → 100)
Slope 1 → 10 min (–0.30 → 100)
Δ peak – pre (0 → 100)

CR

Cardiac / effort recovery

HRR_exercise (heart-rate drop) (40 bpm → 100)
Borg RPE post (perceived exertion) (6 → 100)
Borg dyspnoea post (0 → 100)

SQR

Patient-reported outcomes

PCS (post-COVID symptom score) (10 → 100; 60 → 0)
BFI · FAS · BDI-II · PSQI · PEM inversely scaled
mean of available questionnaires

SB

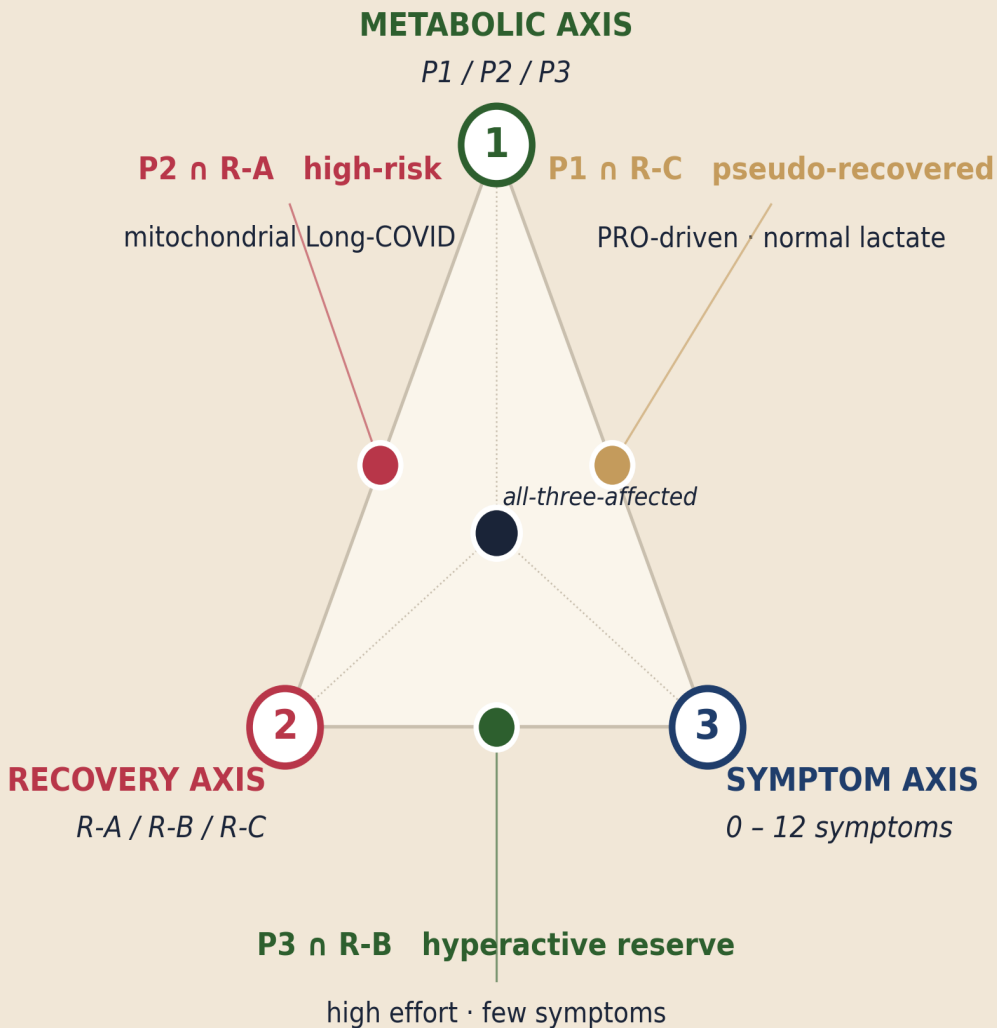
Symptom burden (clinical assessment)

12 cardinal symptoms from deskriptive_analyse_2
PEM · fatigue · exhaustion · exertion intolerance · brain fog
cognitive impairment · exertion dyspnoea · ↓ performance
tachycardia · PoTS · myalgia · pain · SB = 100 · (1 – count/12)

RS = mean of available sub-domains · missing items within a domain are dropped; a missing whole domain is omitted from the composite mean.

THREE ORTHOGONAL AXES

One axis is not enough. Three orthogonal axes localize the patient.



Source: lactate kinetics in 1-min STST
P1 clears efficiently
P2 plateaus (no clearance)
P3 hyperlactatemic peak

Source: composite RS = LR + CR + SQR + SB
R-A: globally impaired
R-B: metabolically slow / cardio-preserved
R-C: physiologically recovered / PRO-burdened

Source: diagnosis,
anamnesis, clinical documentation

RECOVERY PHENOTYPES

Three recovery phenotypes · not just ‘bad → mid → good’.

All sub-score comparisons $p < 10^{-14}$ (Kruskal-Wallis, $n = 170$ with complete sub-domain coverage).

Variable	R-A: globally impaired (n = 54)	R-B: metabolically slow / cardio-preserved (n = 57)	R-C: physiologically recovered / PRO-burdened (n = 59)
LR — Metabolic recovery	45.2	38.9 ◀ worst	69.0 ◀ best
CR — Cardiac / effort recovery	38.0 ◀ worst	60.2 ◀ best	52.6
SQR — Patient-reported outcomes	42.7	43.4	33.2 ◀ worst PROs
SB — Symptom burden	75.0 ◀ most symptoms	91.7 ◀ fewest	83.3
Recovery score (RS)	49	58	61
HRR exercise [bpm]	10	29	25
Long-COVID	85 % (46/54)	49 % (28/57)	63 % (37/59)
ME/CFS [diagnosis]	19 % (10/54)	2 % (1/57)	8 % (5/59)
PEM	48 % (26/54)	7 % (4/57)	12 % (7/59)
BDI-II (median, depression)	16	14.5	22.5 ◀ highest depression

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PEM challenge · repeated anaerobic exercise · 1-min STS

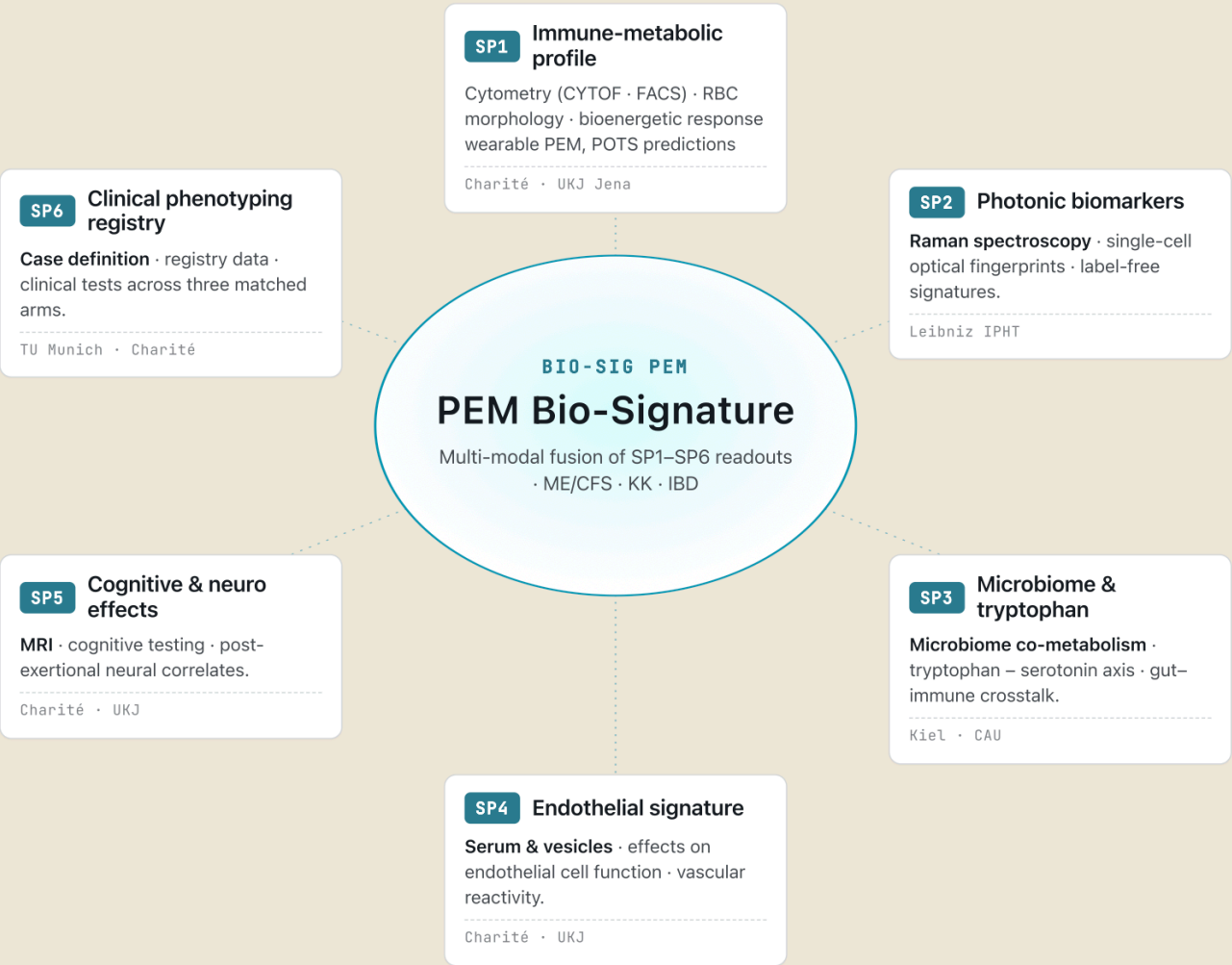
Sample capture · serum · vesicles · cells · wearables · imaging

OUTPUTS

Composite PEM panel discriminating ME/CFS from KK & IBD

Predictive wearable digital phenotype of PEM susceptibility

Translation → IC-PAIS day-clinic pathway (Slide 1)



Poster presentation by Klaudziya Kamiak

Immune-metabolic profile changes (outpatient) after exertion (1-minute sit to stand test) in Post- COVID ME-CFS patients

Poster: Ramoji A, Kamiak K, Yeo TC, Stallmach A, Puta C, Popp J, Reuken P (2026)
Heterogeneous Biochemical Responses to Exertion in Post-COVID ME/CFS Revealed by
Raman Spectroscopy

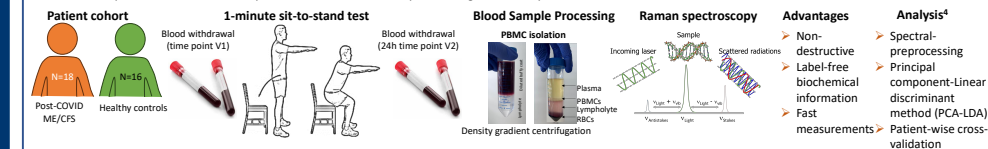
Heterogeneous Biochemical Responses to Exertion in Post-COVID ME/CFS Revealed by Raman Spectroscopy

Anuradha Ramoji^{1,2,3}, Klaudziya Kamiak², Tze-Ching Yeo², Andreas Stallmach^{3,4}, Christian Puta^{3,4,5}, Juergen Popp^{1,2}, Philipp Reuken^{3,4}

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2. Leibniz Institute of Photonic Technology - Member of the research alliance "Leibniz Health Technologies", member of the Leibniz Centre for Photonics in Infection Research (LPI), Albert-Einstein-Straße 9, 07745 Jena, Germany;
3. Jena University Hospital, Center for Sepsis Control and Care, Friedrich-Schiller-University Jena, Am Klinikum 1, 07747 Jena, Germany;
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5. Friedrich-Schiller-University Jena, Department of Sports Medicine and Health Promotion, Wollnitzer Straße 42, 07749 Jena, Germany

BACKGROUND and METHODS

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with post-exertional malaise following SARS-CoV-2 infection (post-COVID ME/CFS) is a complex condition associated with persistent immune and metabolic dysfunction¹. However, the underlying biochemical variations lead to immune and metabolic dysfunction. remain unclear, and no routinely used diagnostic biomarkers are currently available. In this pilot study, Raman spectroscopy was applied for the investigation of peripheral blood mononuclear cells (PBMCs) before (V1) and 24 hours after (V2) STS-test (one minute sit-to-stand test) in individuals with post-COVID-19 ME/CFS (n = 18) and healthy controls (n = 16). Raman spectroscopy is a non-destructive method that can profile cellular biochemistry and detect subtle immune system changes in these syndromes^{2,3}.



RESULTS

Immune cell chemical profile changes after exertion in Post-COVID ME-CFS patients

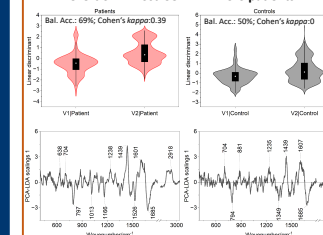


Fig 1: PCA-LDA Raman model for differentiation of PBMCs before (V1) and 24h after (V2) exertion and the loadings.

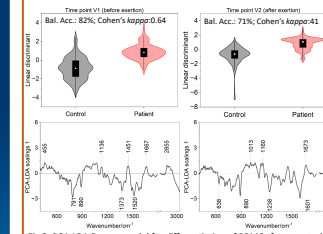


Fig 2: PCA-LDA Raman model for differentiation of PBMCs from control and patients for before (V1) and 24h after (V2) exertion and the loadings.

Raman difference spectra of PBMCs reveals metabolically distinct subgroups in Post-COVID ME/CFS

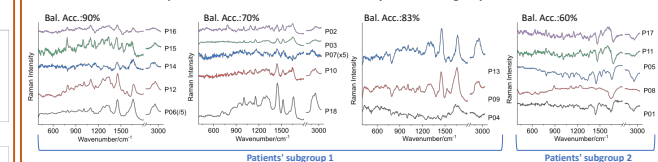


Fig 3: Raman difference spectra of PBMCs, obtained by subtracting the mean spectrum at 24 h post-exertion (V2) from the pre-exertion mean spectrum (V1) for each patient. Difference spectra are grouped according to their spectral profiles. The balanced accuracy and Cohen's kappa were obtained after re-evaluation from the PCA-LDA model shown in Fig. 1.

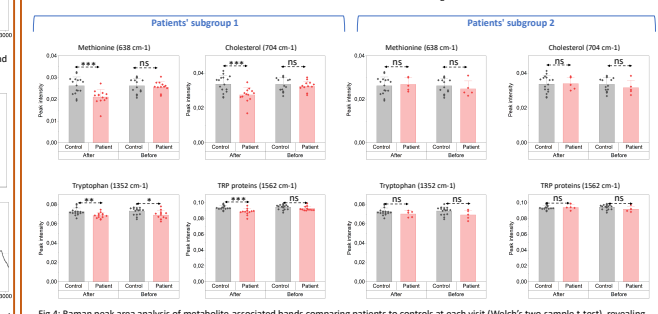


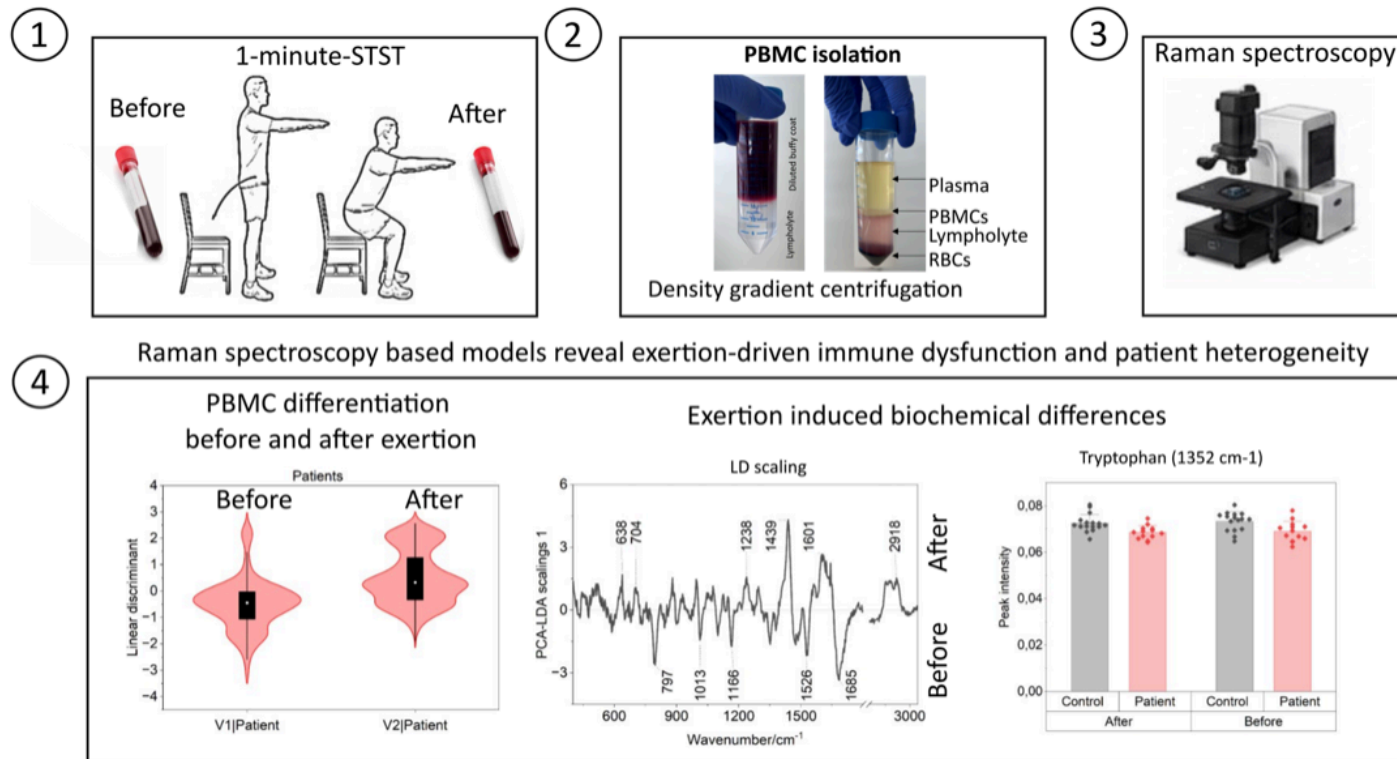
Fig 4: Raman peak area analysis of metabolite-associated bands comparing patients to controls at each visit (Welch's two-sample t-test), revealing differences in Group 1 but not in Group 2. Welch's two-sample t-test for unequal variance (ns: not significant (*p < 0.05; **p < 0.01; ***p < 0.001).

CONCLUSION: The study illustrates the role of the immune system in the pathophysiology of chronic fatigue syndrome. The Raman spectral based predictive model indicated immunological changes in post-COVID ME/CFS patients. The ability to discriminate between CFS patients before and after physical exertion (Fig. 1) shows the influence of minimal physical activity on their immune system. Furthermore, the immune cells differ in their baseline chemical profile compared to healthy controls (Fig. 2). Following the STS test, ME/CFS patients showed disrupted lipid metabolism (reduced phosphatidylinositol and cholesterol) indicating impaired energy distribution. Amino acids, especially tryptophan, were decreased, while disordered proteins increased and TRP proteins declined, suggesting issues with ion balance. Reduced nucleic acid signals point to altered gene expression and immune function. Two patient subgroups emerged—one with significant biochemical changes and one without—highlighting heterogeneity (Fig. 3 and 4). Overall, Raman spectroscopy captured exertion-related metabolic and molecular changes, supporting its potential for precision diagnostics, though larger studies are needed. As a result, Raman spectroscopy could open new opportunities for research into the pathophysiology of CFS and long-term COVID.

REFERENCE: 1) Haunhorst et al., Infection, 2024, 53, 1; 2) Ramoji et al., 2021, Crit Care Explor., 2021, 3(5), e0394; 3) Ramoji et al., 2025, Biotechnology Journal, 2025, 20, e70105; 4) <https://ramanmetrix.eu/>

ACKNOWLEDGEMENTS: This research was supported by funding from the Deutsche Gesellschaft ME/CFS (Number #007622). Federal Ministry of Research, Technology and Research (BMFT) funded project BioSig-PEM (Number FKZ: 01E124088) and 'SARS-CoV-2DX' (Number FKZ: 13N15745).

- Distinct immune-metabolic signature in patients (N=18) vs. controls (N=16)
- Exertion amplifies differences, enabling clear pre/post discrimination
- Two patient subgroups identified (Methionine, Cholesterol, Tryptophan, TRP proteins)



Key Findings

- **Lipid metabolism disrupted** — reduced phosphatidylinositol and cholesterol, indicating impaired cellular energy distribution
- **Amino acid depletion** — particularly tryptophan, suggesting compromised metabolic and neuroimmune signalling
- **Increased disordered proteins** — alongside declining TRP proteins, pointing to disturbed ion homeostasis
- **Reduced nucleic acid signals** — reflecting altered gene expression and impaired immune function

Poster: Ramoji A, Kamiak K, Yeo TC, Stallmach A, Puta C, Popp J, Reuken P (2026) Heterogeneous Biochemical Responses to Exertion in Post-COVID ME/CFS Revealed by Raman Spectroscopy

Lessen learned from highly trained athletes

Is symptom persistence following SARS-CoV-2 infection associated with altered peripheral immune cell proportions and impaired immunological recovery **in highly trained athletes** across a four-month post-infection observation period?

Ringleb M, et al. (2026) J Clin Immunol. 27;46(1):44.

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Immune Dysregulation and Persistent Symptoms: Insights into T Cell Dynamics in Post-COVID among Athletes from the CoSmo-S Study

Research | [Open access](#) | Published: 27 April 2026

Volume 46, article number 44, (2026) [Cite this article](#)

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CoSmo-S sub-study: T-cell dynamics after SARS-CoV-2 in athletes

Three-timepoint flow-cytometry follow-up across persistent-symptom and symptom-free arms

DESIGN

Prospective · 3 timepoints

ASSAY

Flow cytometry · PBMC

FOLLOW-UP

3 months post-infection

1 Timeline

PRE-INFECTION → +3 MONTHS

- T -1 · Pre-infection** 01
Reference baseline · prior to SARS-CoV-2 infection.
- SARS-CoV-2 infection**
Index event · acute viral exposure across cohort.
- T 0 · 2–4 weeks post-infection** 02
First post-infection assessment · early convalescence window.
- T 1 · +3 months after T 0** 03
Follow-up assessment · symptom persistence vs. resolution.

2 Cohort & Arms

PERSISTENT SYMPTOMS VS. SYMPTOM-FREE

PS Persistent symptoms (n = 19)
≥ 1 persistent symptom at T₁ · age 24.9±6.3, sex (f12/m7), VO_{2peak} 43.1±8.0 ml/kg/min, training load 9.5 (5–18) hrs/week.

Most frequent symptoms · fatigue (45%) · reduced performance (45%) · muscle/joint pain (27%) · headache (27%)

SF Symptom-free (n = 17)
Asymptomatic post-infection · age 21.1±4.2, sex (f10/m7), VO_{2peak} 43.0±6.9 ml/kg/min, training load 10.2 (2–14) hrs/week.

Reference arm for resolved post-acute trajectory · matched to PS on key covariates.

MATCH Group comparability (Table 1)

Groups **comparable on age, sex, BMI, VO_{2peak} and training load** — supporting attribution of T-cell differences to symptom trajectory rather than baseline fitness or demographics.

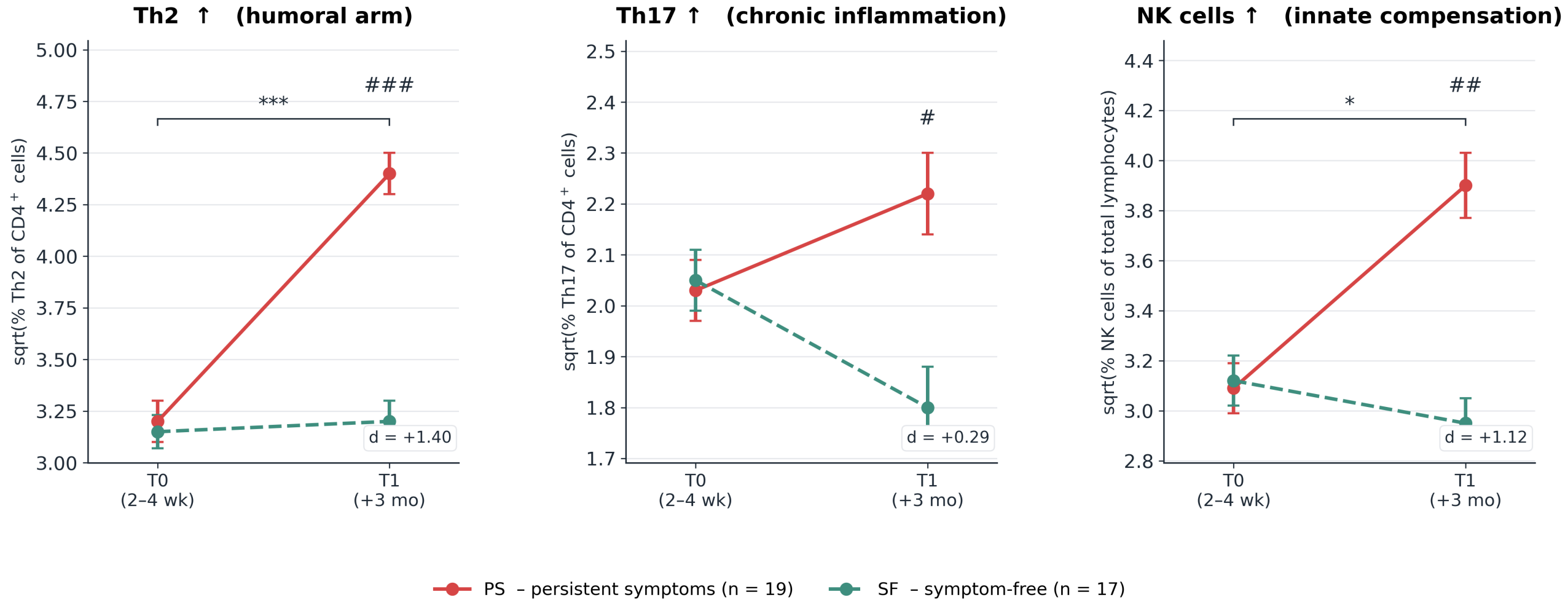
Covariate balance verified prior to immune-phenotype comparison · CoSmo-S sub-study, Ringleb et al. 2026

3 Assay & Readouts

FLOW CYTOMETRY · PBMC

- A** **PBMC isolation**
Peripheral blood mononuclear cells harvested at each timepoint · standardized cryopreservation.
- B** **Flow-cytometry panel**
T-cell subsets · Th1 / Th2 / Th17 · NK cells · regulatory T cells · activation markers.
- C** **Longitudinal contrast**
Within-subject change T₋₁ → T₀ → T₁ · between-arm comparison PS vs. SF.
- **Feeds Bio-SIG PEM**
Athlete cohort signal anchors the broader Th1 → Th2 / Th17 shift seen across post-infectious populations (Slide 3).

Three immune populations rise in PS athletes from T0 to T1



Immune rewiring towards humoral immunity in athletes with persistent symptoms

Highly trained athletes, 3 months after SARS-CoV-2 — PS vs SF arm comparison (T₀ → T₁)

COHORT
Highly
trained
athletes

WINDOW
T0 (2–4 wk) →
T1 (+3 mo)

CONTRAST
PS (n=19) vs
SF (n=17)

PS group · persistent symptoms

T₀ → T₁ · immune rewiring toward humoral / inflammatory dominance

TRIGGER SARS-CoV-2

SAMPLE n = 19 (16 at T0 · 8 at T1)

SYMPTOMS fatigue · reduced performance · pain · headache

Th1	↓	anti-viral arm weakens
Th2	↑	humoral / antibody arm rises
Th17	↑	chronic inflammation
NK cells	↑	innate compensation
Naive T	↑	immature compartment expands
Tregs	↔	no regulatory rebalancing

SF group · symptom-free

T₀ → T₁ · resolution of post-acute immune perturbation

TRIGGER SARS-CoV-2

SAMPLE n = 17 (14 at T0 · 10 at T1)

STATUS asymptomatic post-infection · matched on age, sex, BMI, VO₂peak

Th1	↔	stable / mild decline
Th2	↔	stable
Th17	↓	inflammation resolves
NK cells	↓	innate response normalises
Naive T	↔	stable
Tregs	↔	stable

TAKE-HOME FOR PEM RESEARCH

Th1 ↓ Th2 ↑ Th17 ↑

Even highly trained athletes show a Th1 → Th2 / Th17 shift with persistent symptoms — a humoral / inflammatory imprint reminiscent of post-infectious ME/CFS, with no compensatory Treg response.

Is the immunological shift (Th1 → Th2 / Th17) a shared signature of post-infection associated chronic illness?

Ringleb M, et al. (2026) J Clin Immunol. 27;46(1):44.

A Th1 → Th2 / Th17 shift is a shared signature of infection associated chronic illness

Convergent immune phenotype across four post-infectious populations — two SARS-CoV-2 cohorts, one EBV cohort, and chronic ME/CFS

COHORTS	MARKERS	CONVERGENCE
4 populations	Th1 · Th2 · Th17 · NK · Tregs	Th1↓ · Th2↑ · ratio↓

Highly trained athletes with persistent symptoms	Long COVID, general population	Post-EBV / mononucleosis fatigue	ME / CFS
<i>Ringleb et al. 2026, J Clin Immunol · CoSmo-S sub-study</i>	<i>Kratzer 2024 Allergy · Klein 2023 Nature · Yin 2024 Nat Immunol</i>	<i>Broderick & Katz 2012 J Transl Med · Katz 2009 Pediatrics · Sepulveda 2022</i>	<i>Broderick 2010 Brain Behav Immun · Hornig 2015 Sci Adv · Vu 2024 Front Immunol</i>
TRIGGER SARS-CoV-2	TRIGGER SARS-CoV-2	TRIGGER Epstein-Barr virus (EBV)	TRIGGER Heterogeneous (post-viral, idiopathic)
SAMPLE n = 36 (PS = 19 vs SF = 17)	SAMPLE n = 106 (Kratzer); n = 99 (Klein)	SAMPLE n = 301 adolescents (prospective)	SAMPLE n = 40–298 across studies
WINDOW T0 (2–4 wk) → T1 (+3 mo)	WINDOW 10 weeks → 10 months post-infection	WINDOW 6, 12, 24 months post-mononucleosis	WINDOW Established / chronic disease (≥ 6 mo)
Th1 ↓ anti-viral arm; d = −0.92	Th1 ↓ Th1 cytokines decline (IFN-γ, TNF-α)	Th1 ↓ attenuated IFN-γ network signalling	Th1 ↓ attenuated Th1 cytokine network
Th2 ↑ humoral arm; d = +1.40	Th2 ↑ Th2 serum cytokines dominate	Th2 ↑ augmented Th2 response (EBNA1-driven)	Th2 ↑ established Th2 inflammatory milieu
Th17 ↑ inflammation; d = +0.29	Th17 ↑ elevated; gut / endothelial inflammation	Th17 ↑ dysregulated IL-23 / Th17 priming	Th17 ↓ attenuated in network analysis
NK cells ↑ innate; d = +1.12	NK cells ↓ reduced cytotoxic NK phenotypes	NK cells ↓ reduced cytotoxicity post-EBV	NK cells ↓ reduced NK cytotoxicity (consistent)
Tregs ↔ no rebalancing	Tregs ? heterogeneous (Haunhorst 2022)	Tregs ? EBV-driven Treg recruitment to B cells	Tregs ? FoxP3+ Tregs altered, direction varies
Th1 / Th2 ↓ ratio collapses; d = −1.36	Th1 / Th2 ↓ reversal of Th1-dominated pattern	Th1 / Th2 ↓ altered cellular immunity, Th2 skew	Th1 / Th2 ↓ Th2-skewed cytokine ratio

COMMON DENOMINATOR · ALL FOUR POPULATIONS

Th1 ↓ Th2 ↑ Th1 / Th2 ↓

Two SARS-CoV-2 cohorts, one EBV cohort and chronic ME/CFS converge on the same phenotype: cellular antiviral control gives way to humoral / inflammatory dominance — regardless of training status, infection severity, or trigger pathogen.

A Th1 → Th2 / Th17 shift is a shared signature of infection associated chronic illness

Convergent immune phenotype across four post-infectious populations — two SARS-CoV-2 cohorts, one EBV cohort, and chronic ME/CFS

COHORTS		MARKERS	CONVERGENCE
4 populations		Th1 · Th2 · Th17 · NK · Tregs	Th1↓ · Th2↑ · ratio↓
Highly trained athletes with persistent symptoms			
Ringleb et al. 2026, J Clin Immunol · CoSmo-S sub-study			
TRIGGER SARS-CoV-2			
SAMPLE n = 36 (PS = 19 vs SF = 17)			
WINDOW T0 (2–4 wk) → T1 (+3 mo)			
Th1	↓	anti-viral arm; d = −0.92	
Th2	↑	humoral arm; d = +1.40	
Th17	↑	inflammation; d = +0.29	
NK cells	↑	innate; d = +1.12	
Tregs	↔	no rebalancing	
Th1 / Th2	↓	ratio collapses; d = −1.36	
Long COVID, general population			
Kratzer 2024 Allergy · Klein 2023 Nature · Yin 2024 Nat Immunol			
TRIGGER SARS-CoV-2			
SAMPLE n = 106 (Kratzer); n = 99 (Klein)			
WINDOW 10 weeks → 10 months post-infection			
Th1	↓	Th1 cytokines decline (IFN-γ, TNF-α)	
Th2	↑	Th2 serum cytokines dominate	
Th17	↑	elevated; gut / endothelial inflammation	
NK cells	↓	reduced cytotoxic NK phenotypes	
Tregs	?	heterogeneous (Haunhorst 2022)	
Th1 / Th2	↓	reversal of Th1-dominated pattern	
Post-EBV / mononucleosis fatigue			
Broderick & Katz 2012 J Transl Med · Katz 2009 Pediatrics · Sepulveda 2022			
TRIGGER Epstein-Barr virus (EBV)			
SAMPLE n = 301 adolescents (prospective)			
WINDOW 6, 12, 24 months post-mononucleosis			
Th1	↓	attenuated IFN-γ network signalling	
Th2	↑	augmented Th2 response (EBNA1-driven)	
Th17	↑	dysregulated IL-23 / Th17 priming	
NK cells	↓	reduced cytotoxicity post-EBV	
Tregs	?	EBV-driven Treg recruitment to B cells	
Th1 / Th2	↓	altered cellular immunity, Th2 skew	
ME / CFS			
Broderick 2010 Brain Behav Immun · Hornig 2015 Sci Adv · Vu 2024 Front Immunol			
TRIGGER Heterogeneous (post-viral, idiopathic)			
SAMPLE n = 40–298 across studies			
WINDOW Established / chronic disease (≥ 6 mo)			
Th1	↓	attenuated Th1 cytokine network	
Th2	↑	established Th2 inflammatory milieu	
Th17	↓	attenuated in network analysis	
NK cells	↓	reduced NK cytotoxicity (consistent)	
Tregs	?	FoxP3+ Tregs altered, direction varies	
Th1 / Th2	↓	Th2-skewed cytokine ratio	

COMMON DENOMINATOR · ALL FOUR POPULATIONS

Th1 ↓ Th2 ↑ Th1 / Th2 ↓

Two SARS-CoV-2 cohorts, one EBV cohort and chronic ME/CFS converge on the same phenotype: cellular antiviral control gives way to humoral / inflammatory dominance — regardless of training status, infection severity, or trigger pathogen.

Can the signature interpreted as deconditioned or as impaired immunological recovery?

Ringleb M, et al. (2026) J Clin Immunol. 27;46(1):44.

The immunological shift (Th1 → Th2 / Th17) cannot be explained away as deconditioning, and neither can the bioenergetic deficit it accompanies. The CoSmo-S data therefore align with — and extend — the emerging picture of post-infectious illness as a disorder of integrated multi-system recovery.

1 ELITE-ATHLETE FALSIFIER

The shift is not deconditioning

PS athletes · 9 – 10 h/wk training · $\dot{V}O_{2\text{peak}} \approx 43 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Yet they show the canonical Th1↓ / Th2↑ shift at the same magnitude as much less active Long COVID and ME/CFS cohorts.

1 BIOENERGETIC FALSIFIER

Davenport 2026 (n = 238, 2-day CPET)

ME/CFS and Long COVID share the same bioenergetic decrement at VAT — hemodynamic and ventilatory measures normal — ‘specific pathological mechanisms rather than simple deconditioning.’

Davenport et al. Clin Transl Metab 2026 · Ringleb 2026

2 MECHANISTIC CASCADE

Immune → microvascular → bioenergetic

Instead of returning to a Th1-balanced state after acute infection, the immune system locks into a humoral / Th17-biased state that persists for months · coupled to TCA-flux failure, redox imbalance and autonomic decoupling.

Haunhorst et al. Infection 2025

3 AUTOIMMUNITY-PERMISSIVE

Tregs unchanged = functional impairment

Th2 / Th17 expansion without Treg compensation lowers the threshold for autoreactive B cells.

Kossack (2025) Severe-COVID Tregs fail to suppress T-cell proliferation in vitro — function impaired, not just numbers.

den Dunnen (2025) *PCS-IgG transferred to mice reproduces symptoms (causal evidence).*

Langston (2023) Treg-mediated mitochondrial protection (is one direct molecular link).

Sotzny (2025) autoantibodies vs EBV-mimicking peptides → α -AdR, SLC24A3, TSPYL5, SRRM3.

Stein (2025): 14/20 responders to immunoadsorption.

Haunhorst 2022 · Kossack 2025 · Fehrer et al. Autoimmun Rev 2026

Take-home · If the Th1 → Th2 / Th17 shift were an artefact of reduced physical activity after infection, it should be smallest in this population; instead, the polarization shift was as large as or larger than the directional changes reported in less active Long COVID and ME/CFS cohorts (Cohen's $d = -1.36$ for the Th1/Th2 ratio).

Thank you!



Bundesministerium
für Bildung
und Forschung



Bundesministerium
für Gesundheit

LONG COVID
DEUTSCHLAND

ME/CFS
DEUTSCHE GESELLSCHAFT
FÜR ME/CFS E.V.

Lost Voices Stiftung
HILFE FÜR MENSCHEN MIT ME/CFS

Fatigatio e.V.
Bundesverband ME/CFS

Post-COVID-Zentrum
Universitätsklinikum Jena

**Center for Sepsis
Control & Care**

FRIEDRICH-SCHILLER-
UNIVERSITÄT
JENA

**UNIVERSITÄTS
KLINIKUM
Jena**

BIO-SIG PEM
Understanding biology signature of
Post-Exertional Malaise in ME/CFS

Bio-Sig PEM Study Group

Putz C^{1,2,3#}, Dudziak D⁴, Walter M^{5,6}, Ramoji A⁷, Finke C⁸, Scheibenbogen C⁹, Seifert M^{9,10}, Behrends U^{11,12,13}, Schreiber S¹⁴, Aden K^{14,15}, Waschina S¹⁶, Ellert C¹⁷, Reuken PA², Stallmach A²

für die Bio-SIG PEM-Study Group

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¹⁷Long-COVID Deutschland

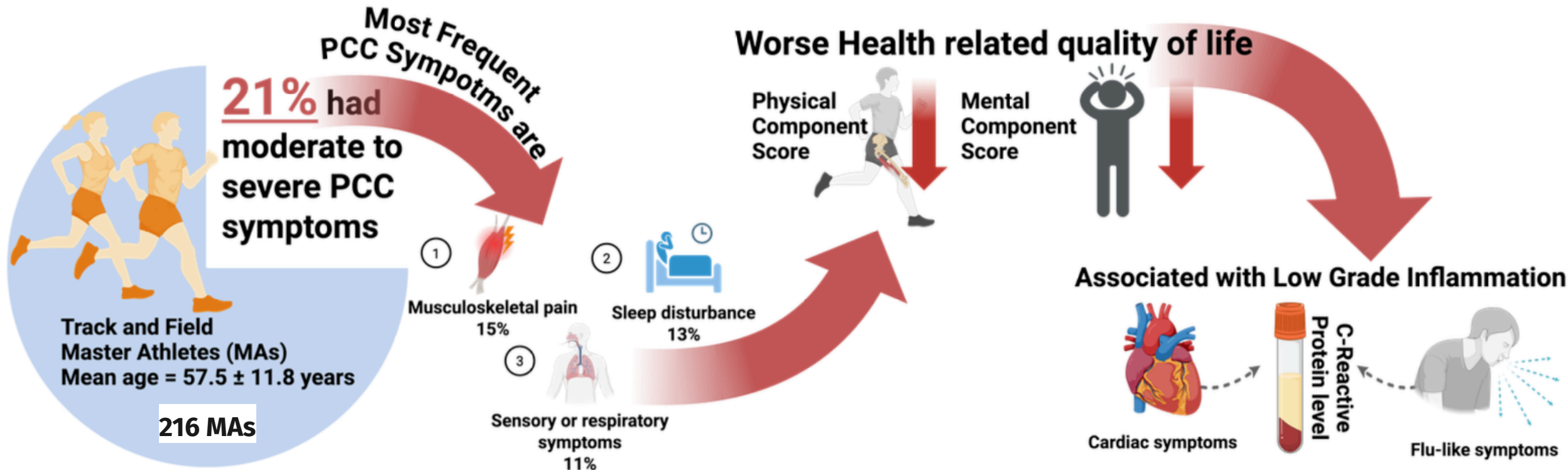
christian.putz@med.uni-jena.de

216 track and field masters athletes:

Post-COVID-19 condition is associated with reduced quality of life

(independent of sex, prior competition levels, and training characteristics)

Low- grade inflammation based on CRP levels was associated with self- reported cardiac and flu-like symptoms



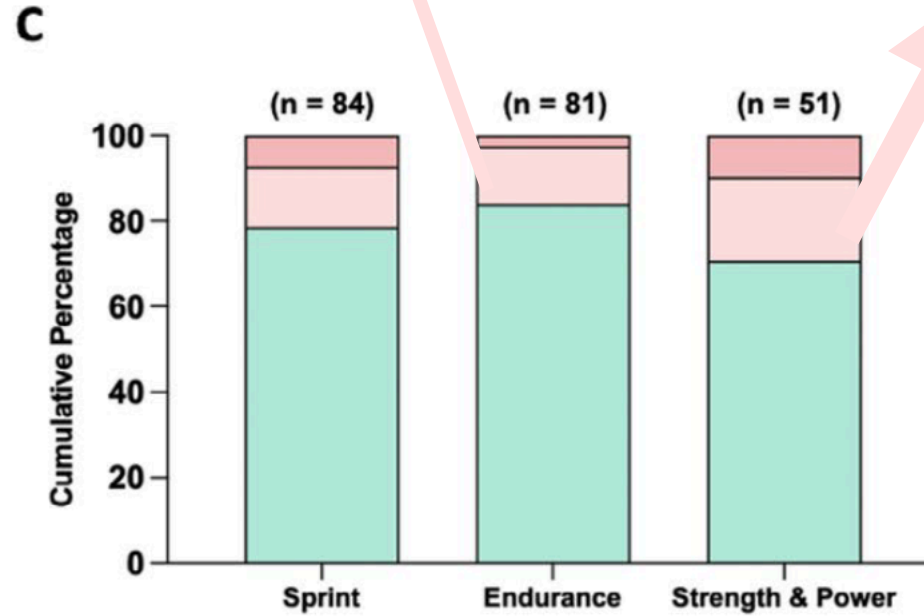
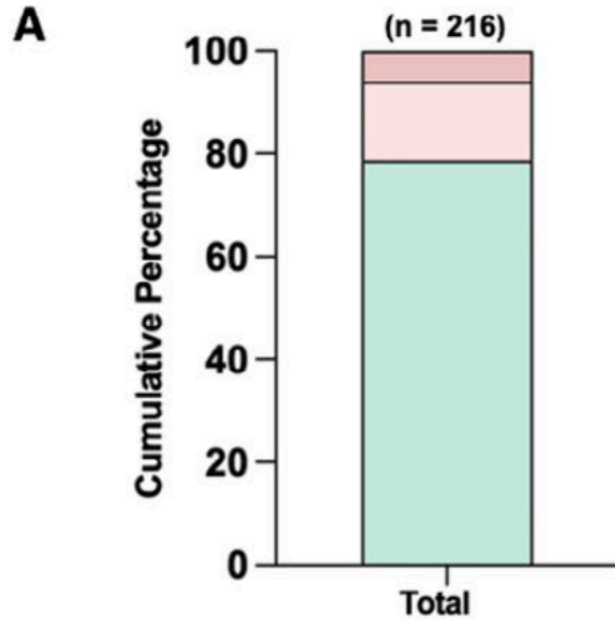
Zhang B, Grau M, Puta C, Arvidsson D, Arz M, Böcker J, Chilibeck P, Forbes SC, Kaiser-Stolz C, McLaurin N, Miyamoto-Mikami E, Pesta D, Pustowalow W, Tanaka H, Rittweger J, Bloch W.

Post-COVID-19 Condition in Track and Field Master Athletes: Severity, Symptoms, and Associations With Quality of Life and C-Reactive Protein Levels. Scand J Med Sci Sports. 2025 Jul;35(7):e70106. doi: 10.1111/sms.70106. PMID: 40650463; PMCID: PMC12254908.



Endurance:
 exhibit greater antioxidant capacity and superior cardiopulmonary adaptation

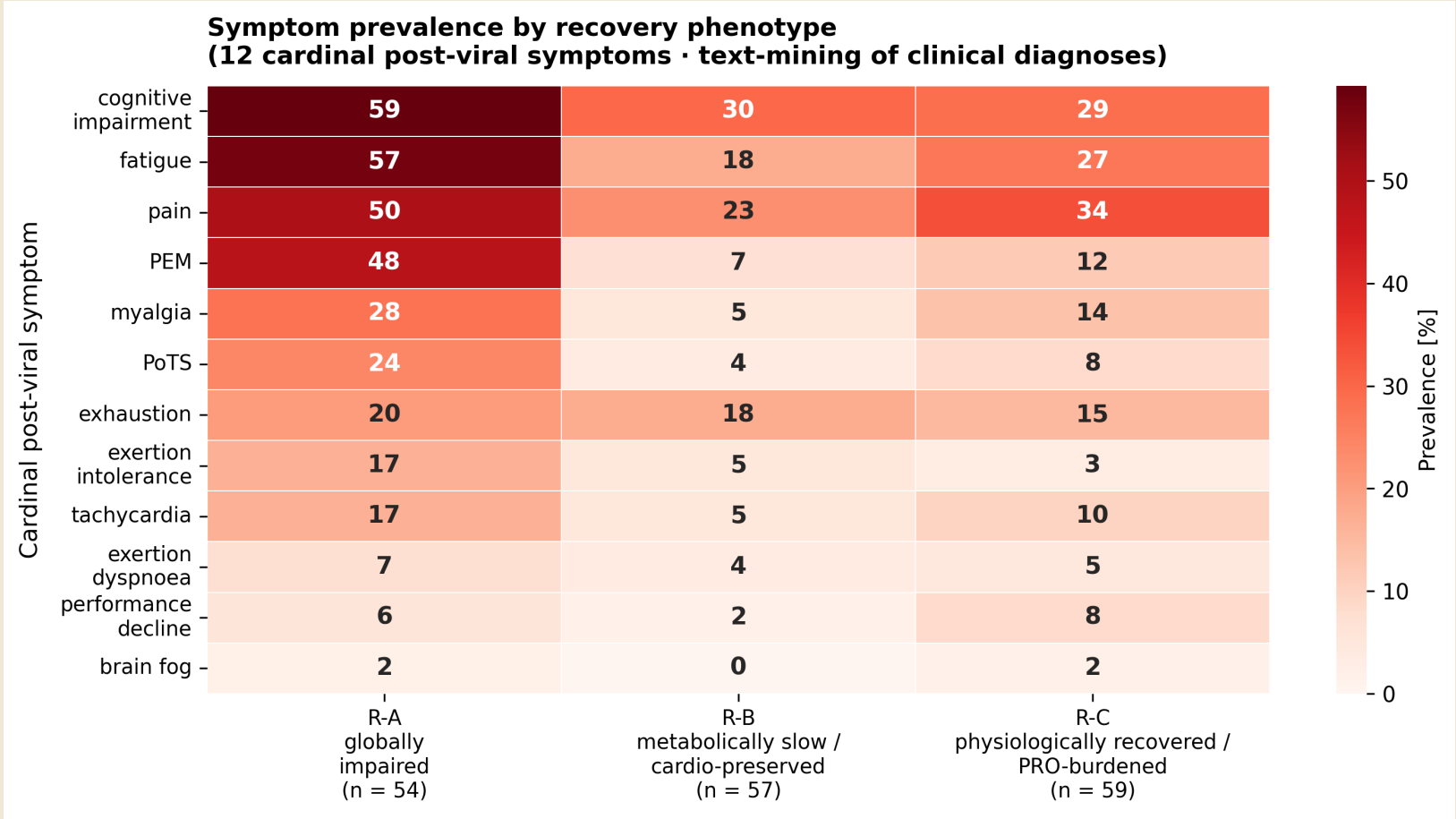
Strength/Power
 intermittent efforts that may trigger increased oxidative stress and chronic inflammation



Zhang B, Grau M, Puta C, Arvidsson D, Arz M, Böcker J, Chilibeck P, Forbes SC, Kaiser-Stolz C, McLaurin N, Miyamoto-Mikami E, Pesta D, Pustowalow W, Tanaka H, Rittweger J, Bloch W. Post-COVID-19 Condition in Track and Field Master Athletes: Severity, Symptoms, and Associations With Quality of Life and C-Reactive Protein Levels. Scand J Med Sci Sports. 2025 Jul;35(7):e70106. doi: 10.1111/sms.70106. PMID: 40650463; PMCID: PMC12254908.

SYMPTOM × RECOVERY HEATMAP

R-A concentrates almost all post-viral symptoms.



Source · 12 cardinal symptoms extracted from the clinical anamnestic protocol.

Three recovery phenotypes

R-A — most symptomatic group

- Almost one in five (10/54) carries a formal ME/CFS diagnosis.
- Half (26/54) have PEM documented; 31/54 (57 %) have fatigue.
- 85 % Long-COVID; worst HRR (10 bpm) — multisystem exhaustion.

R-B — least symptomatic despite worst metabolic recovery

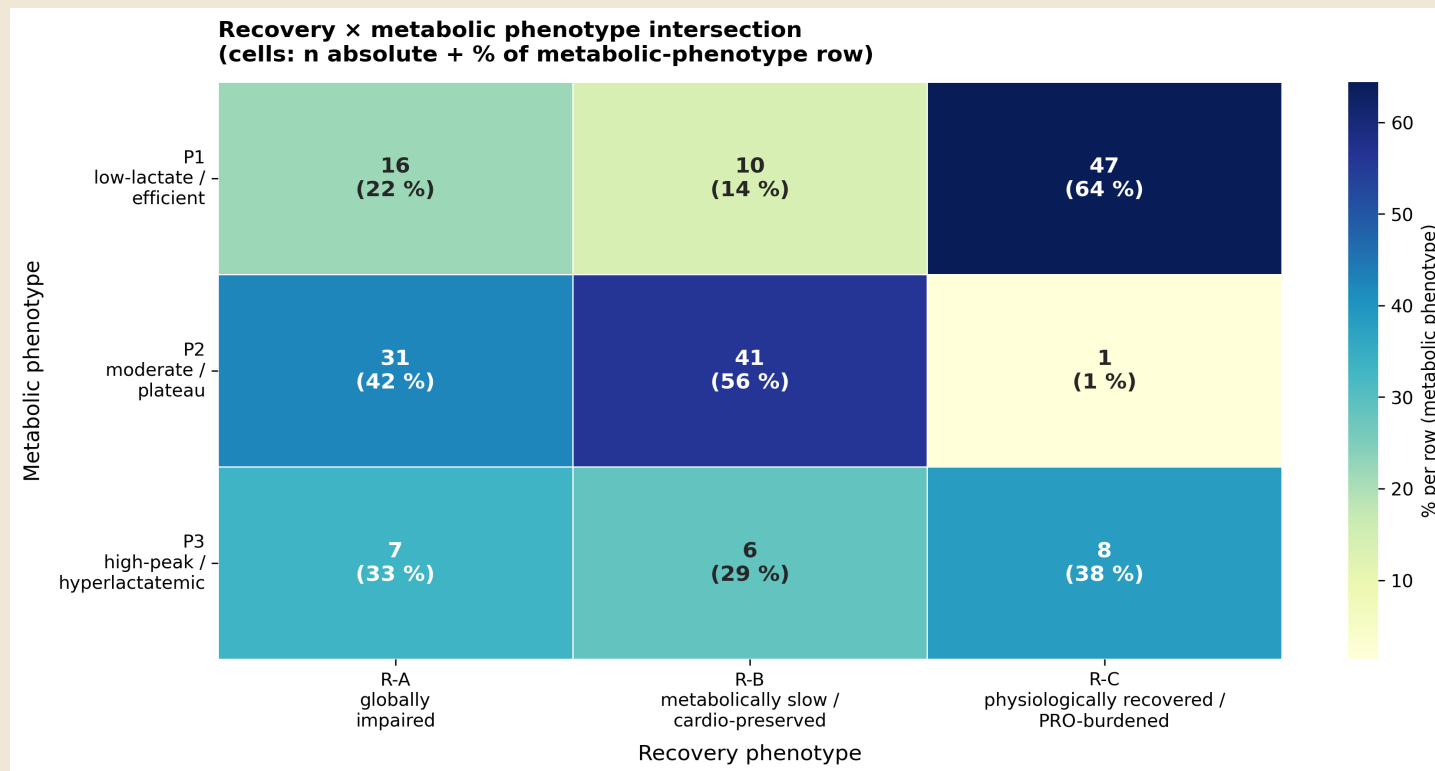
- Only 1/57 ME/CFS, 4/57 PEM, 10/57 fatigue — minimal documented symptoms.
- Best cardiac recovery (HRR 29 bpm) — autonomic reserve preserved.
- Possible early / compensated stage — close longitudinal follow-up indicated.

R-C — subjective burden in objectively recovered patients

- ME/CFS 5/59, PEM 7/59, fatigue 16/59 — moderate symptom load.
- Highest depression (BDI-II 22.5 = moderate); worst PROs.
- Mind–body disconnect — central sensitisation pattern.

TWO-AXIS CROSS-TABULATION

The two phenotype systems are not redundant.

**P1 ∩ R-C****64 %**

Aerobic-efficient patients are metabolically recovered, yet have the worst PROs → symptoms appear immune-/central-/depression-driven, not metabolic.

P2 ∩ R-A + R-B**98 %**

Delayed lactate clearance almost never reaches a fully-recovered profile (P2 ∩ R-C = 1 %) → classic mitochondrial Long-COVID.

P3

→ all three R-clusters

The hyperlactatemic exercise response alone does not determine recovery outcome — qualitatively heterogeneous.

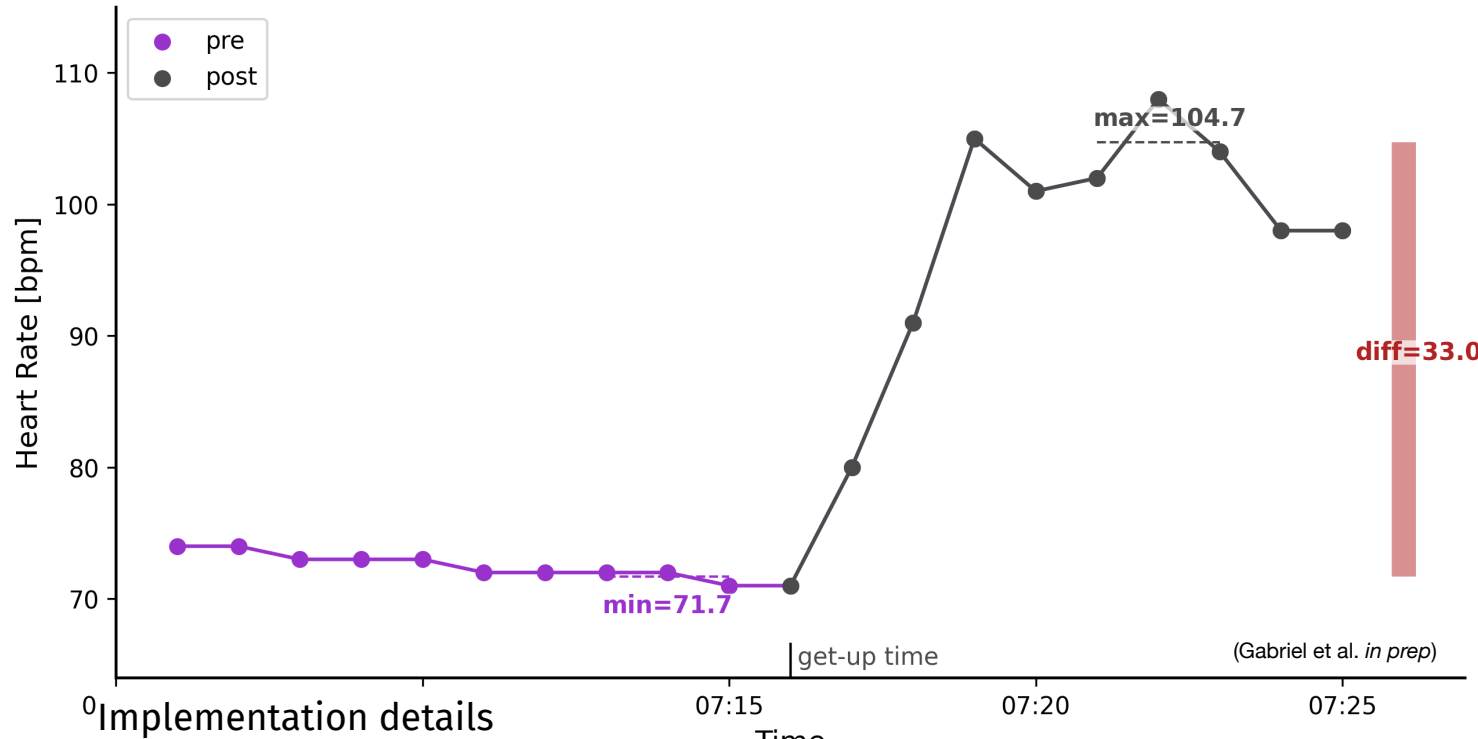
— Data-driven POTS-detection?



Marc Gabriel

Data-driven Active Standing Test

Participant: KdZ0mzwiedbLxCgd, Source: Garmin, Date: 2025-02-01



Implementation details

- The get-up time is calculated based on the first significant heart rate increase around the sleep offset
- For robustness, sustained minimum/maximum get calculated as the highest mean of three consecutive values

Table 1. Criteria for the Postural Tachycardia Syndrome

Heart rate increases ≥ 30 bpm from supine to standing (10 min)

Symptoms worsen with standing and improved with recumbence

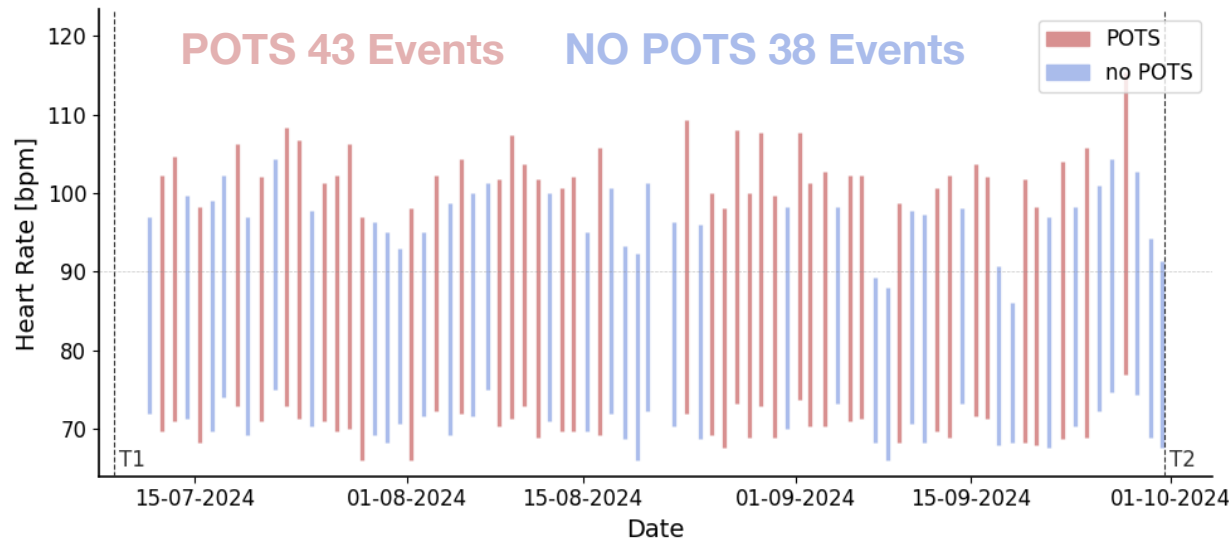
Symptoms last ≥ 6 mo

Absence of other overt cause of orthostatic symptoms or tachycardia (eg, active bleeding, acute dehydration, medications)

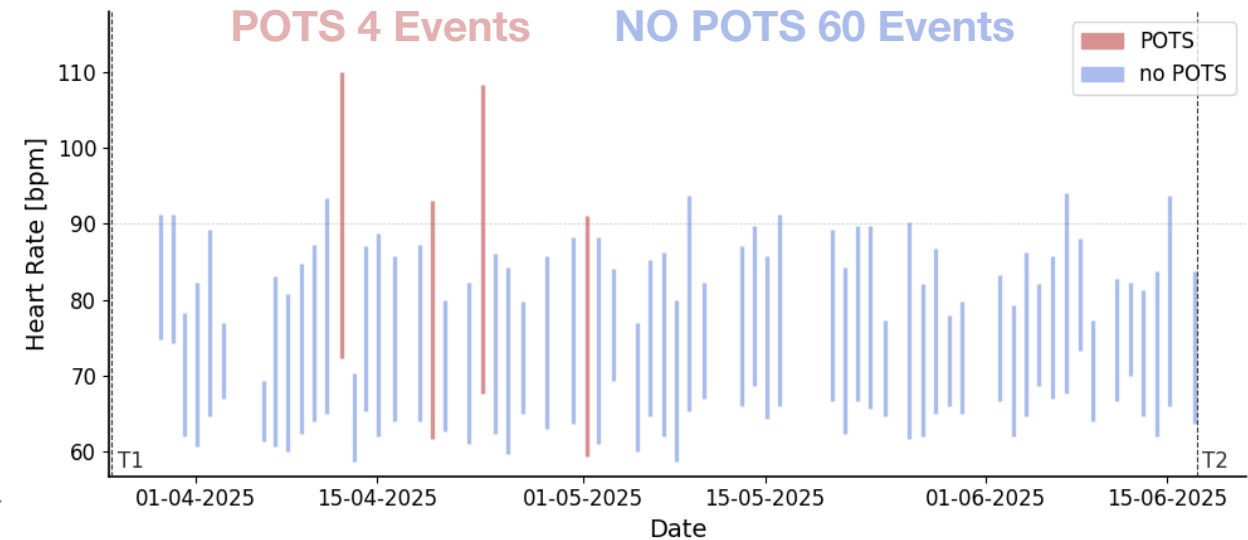
Raj, S. R. Postural Tachycardia Syndrome (POTS). Circulation 127, 2336–2342 (2013).

— Post-COVID condition: Observation phase of 12 weeks, POTS is detected, if criteria are met (at least 10 get-up times)

Heart Rate Differences of the Observation Phase



Heart Rate Differences of the Observation Phase

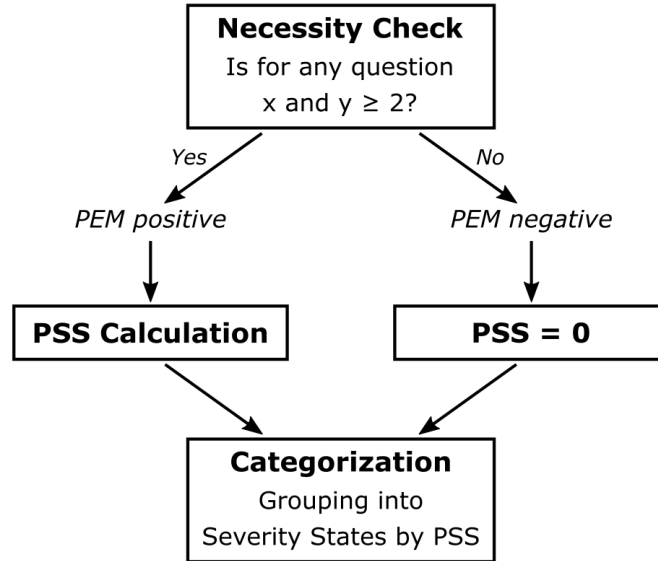


(Gabriel et al. *in prep*)

— PEM-Severity Score



Marc Gabriel



PSS	Severity State
= 0	Not affected
< 0.25	Mildly affected
< 0.5	Moderately affected
< 0.75	Severely affected
≤ 1.0	Very severely affected

Symptoms

	how <u>often</u> have you had this symptom? For each symptom listed below, circle a number from: 0 = none of the time 1 = a little of the time 2 = about half the time 3 = most of the time 4 = all of the time					how <u>much</u> has this symptom bothered you? For each symptom listed below, circle a number from: 0 = symptom not present 1 = mild 2 = moderate 3 = severe 4 = very severe				
1. Dead, heavy feeling after starting to exercise	0	1	2	3	4	0	1	2	3	4
2. Next day soreness or fatigue after	0	1	2	3	4	0	1	2	3	4
3. Mentally tired after the slightest effort	0	1	2	3	4	0	1	2	3	4
4. Minimum exercise makes you physically tired	0	1	2	3	4	0	1	2	3	4
5. Physically drained or sick after mild activity	0	1	2	3	4	0	1	2	3	4

For the purpose of the study, the questionnaire was modified to be answered in a weekly rhythm.

PEM Severity Score (PSS) calculation

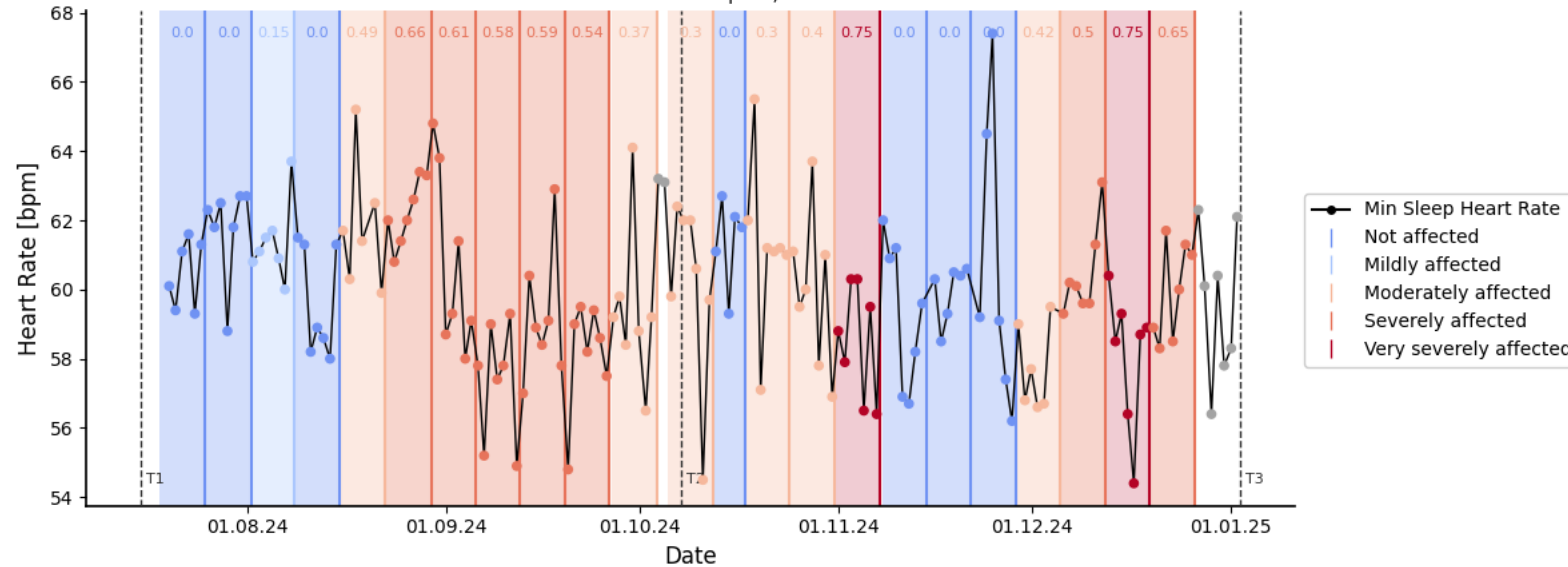
- For each question: Normalized harmonic mean
- PSS = Average of all harmonic means
- Reminder: PSS gets only calculated, if at least one pair is (2,2)

$$PSS = \frac{1}{N} \sum_{i=1}^N \begin{cases} \frac{x_i y_i}{2(x_i + y_i)}, & \text{if } x_i > 0 \text{ and } y_i > 0, \\ 0, & \text{else} \end{cases}, \text{ with } N = \text{number of answered questions, } (x_i, y_i) \in \{0,1,2,3,4\}^2.$$

— Min Sleep Heart Rate *and* PEM-Severity

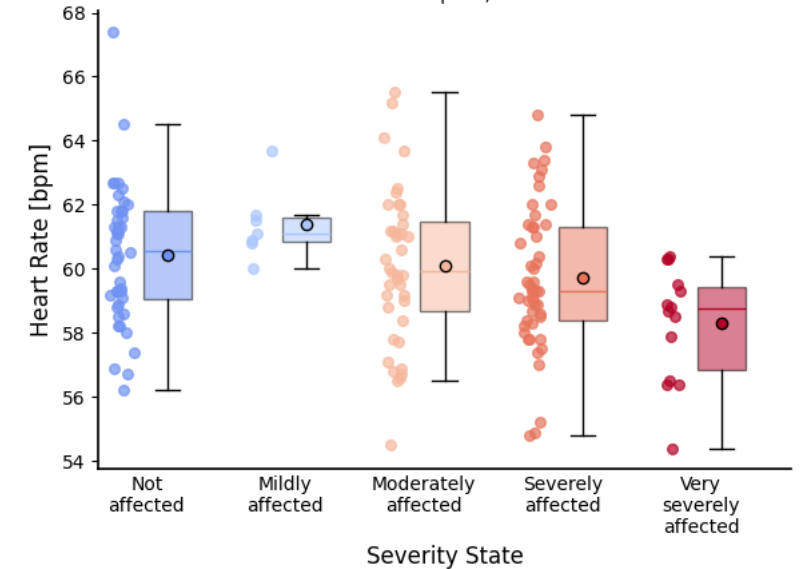
Min Sleep Heart Rate and Severity State Zones

Customer: 3mmWnH6GhV31qMe6; Source: Garmin



Min Sleep Heart Rate by Severity State

Customer: 3mmWnH6GhV31qMe6; Source: Garmin

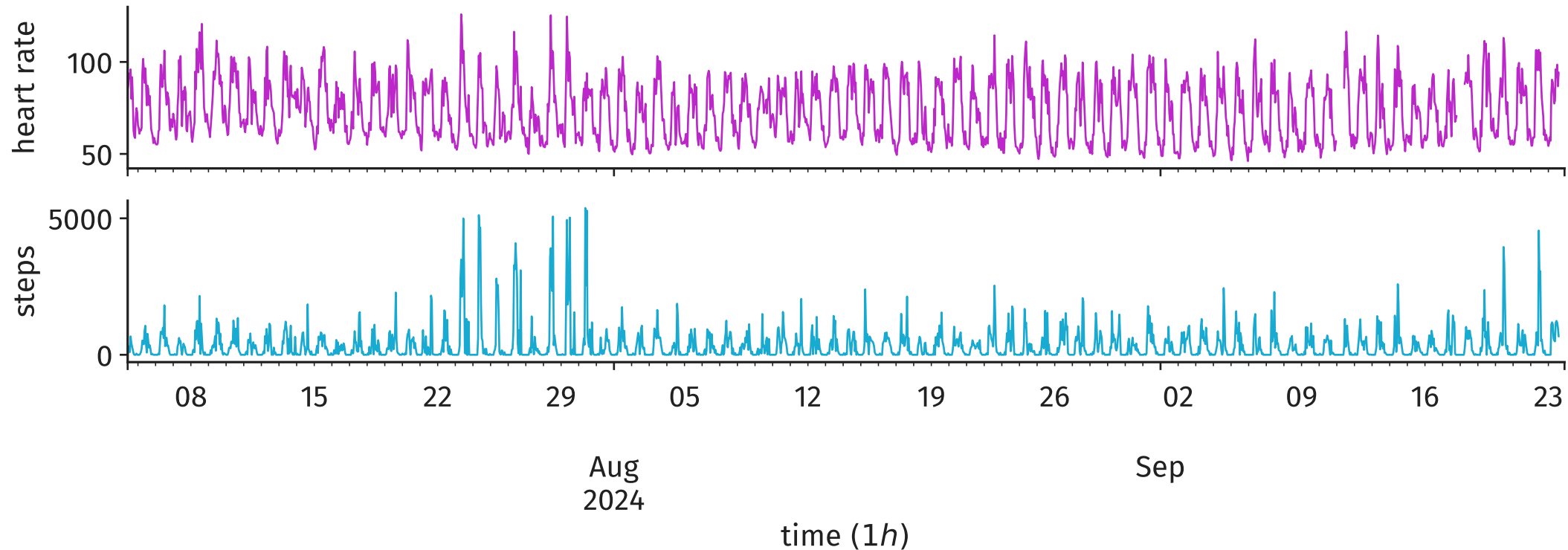


Human rhythms from time series

hours during the days in the life of...



Adrian Pelcaru

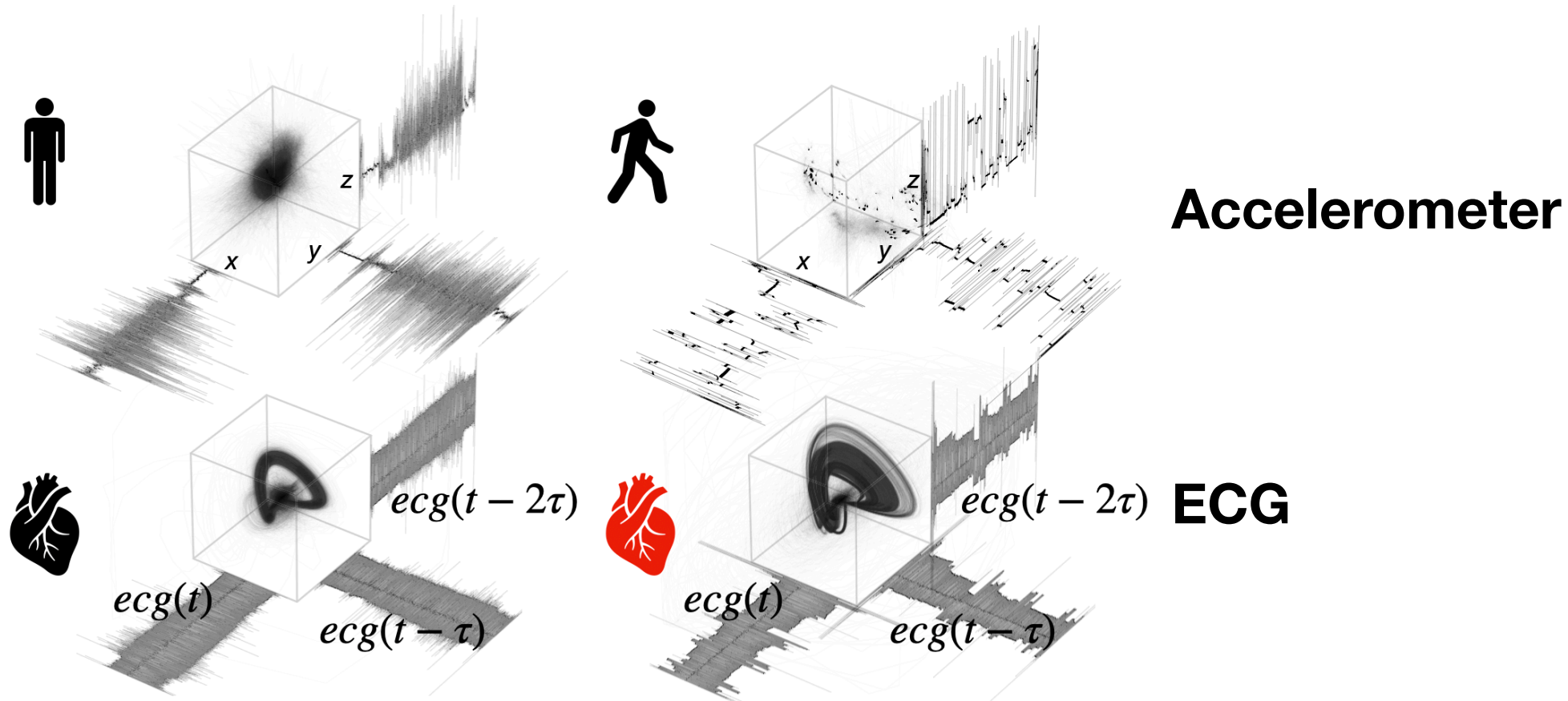


Human rhythms from time series

... a dynamic system



Adrian Pelcaru



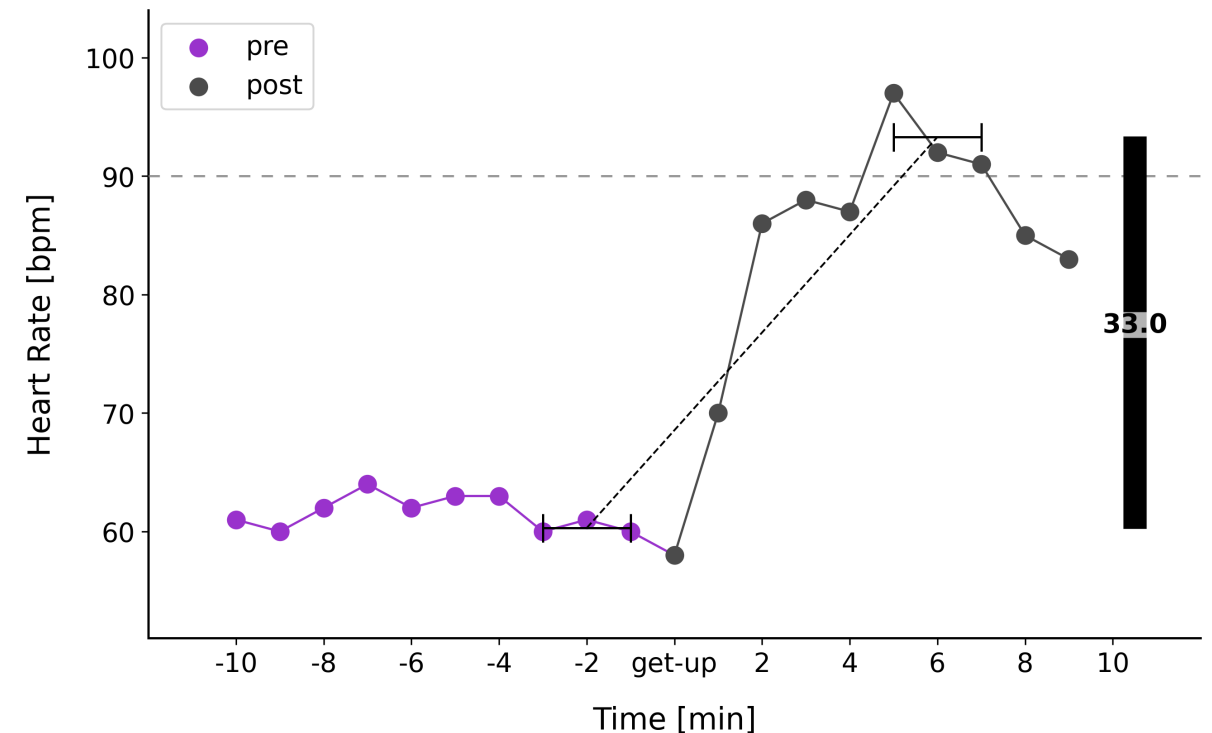
POTS detection at a single get-up time

POTS criteria²

- Increase in heart rate ≥ 30 bpm within 10 minutes of standing
- Heart rate increase must be sustained (at least 2 measurements at least 1 minute apart)
- Supine resting heart rates of < 60 bpm get set to 60 bpm
- Absence of sustained orthostatic hypotension is necessary
- Above criteria do not need to be met at every visit

Implementation details

- The get-up time is calculated based on the first significant heart rate increase around the sleep offset
- For robustness, sustained minimum/maximum get calculated as the highest mean of three consecutive values

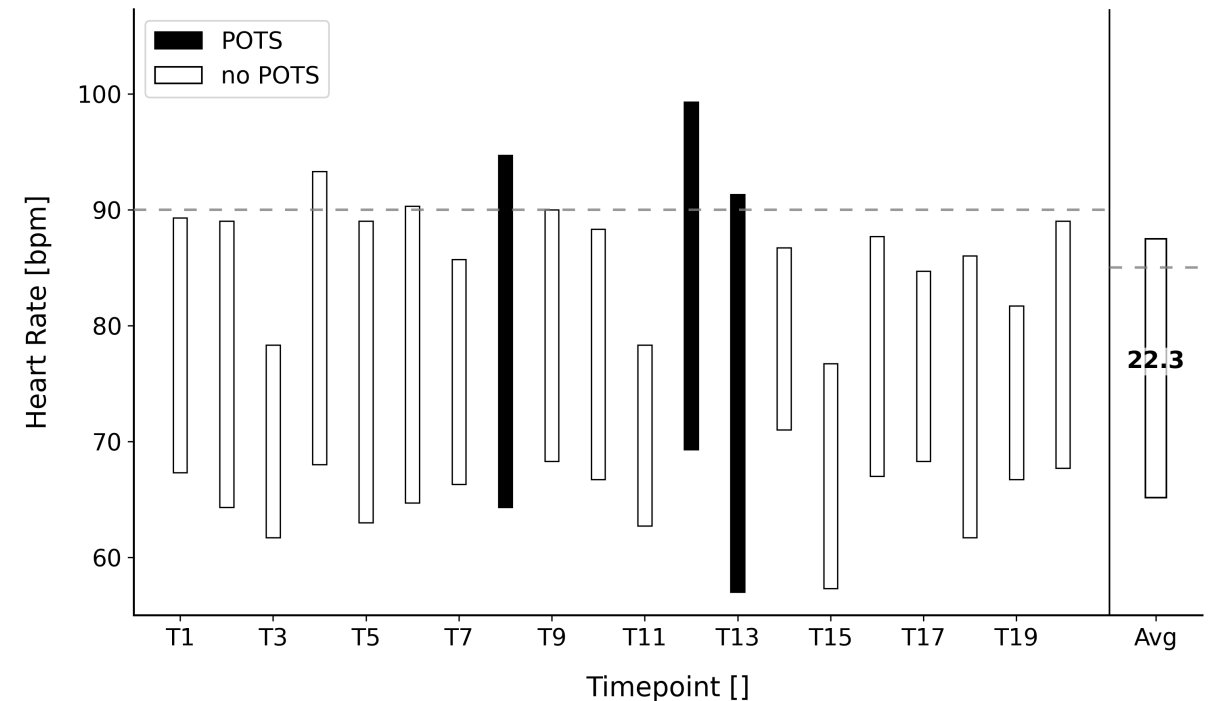
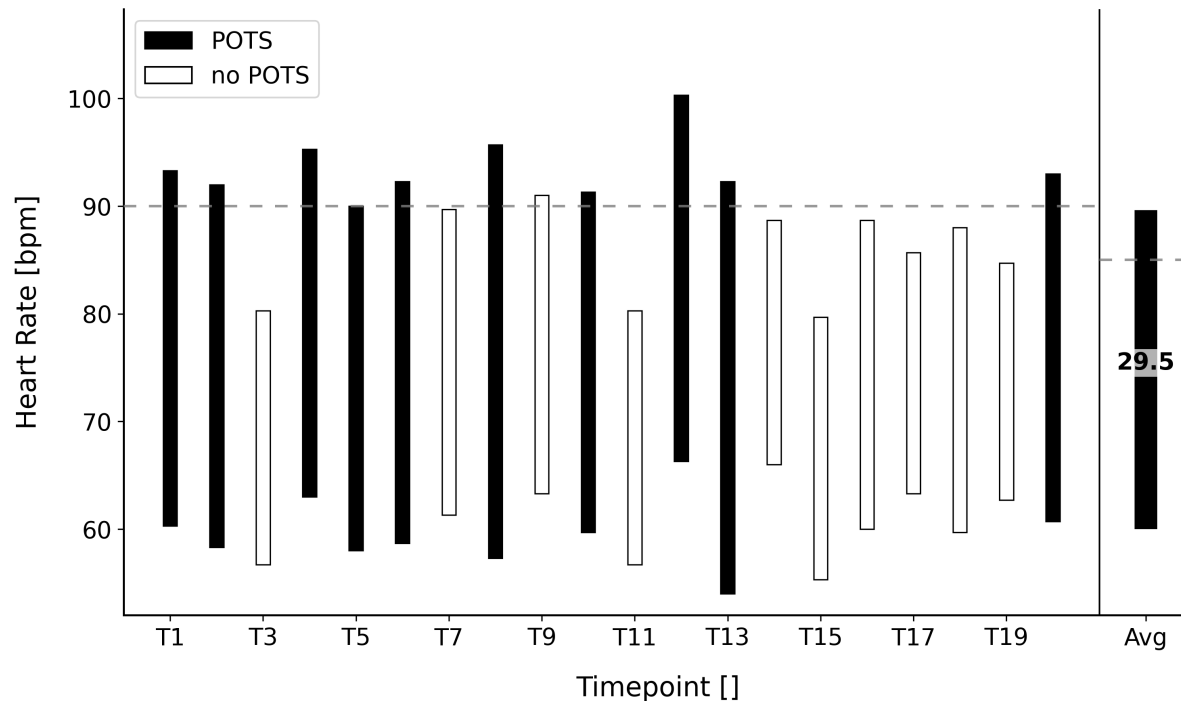


POTS detection based on a single get-up time

POTS detection over a time period

Expanded POTS criteria

- Mean sustained increase in heart rates ≥ 25 bpm within 10 minutes of standing
- Mean sustained orthostatic heart rates ≥ 85 bpm
- Mean values are calculated from a minimum of 10 get-up events
- At least one individual event meets a heart rate increase ≥ 30 bpm and an orthostatic heart rate ≥ 90 bpm



While the left patient is considered to have POTS (29.5 bpm), the right patient is not (22.3 bpm)