

Cognitive, psychological, and physical functioning in patients with post-COVID-19 syndrome: a study protocol for data-driven phenotyping

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Background

Definition: Post-COVID-19 syndrome (PCS) is defined by the World Health Organisation (WHO) as symptoms that continue or newly emerge 3 months after a probable or confirmed SARS-CoV-2 infection, last for at least 2 months, and cannot be explained by another diagnosis. (Davis et al., 2023; Soriano et al., 2021) PCS is described as a heterogeneous condition, with common symptoms including fatigue, cognitive difficulties, and psychological distress, all of which may affect daily functioning. (Sykes et al., 2021; Malik et al., 2021)

Current knowledge gaps: Current research often relies on retrospective self-report and tends to study isolated symptom domains. This limits insight into how physical, cognitive, psychological, and sociodemographic factors jointly shape symptom persistence.

Aim: To identify clinically meaningful PCS subgroups using data-driven phenotyping based on comprehensive physical, cognitive, psychological, and symptom-related assessment.

Methodology

Participants: 69 Dutch-speaking adults meeting the WHO criteria of PCS, fatigued, and experiencing functional limitations

Design: Cross-sectional study with 2 in-person sessions and ambulatory actigraphy between sessions.

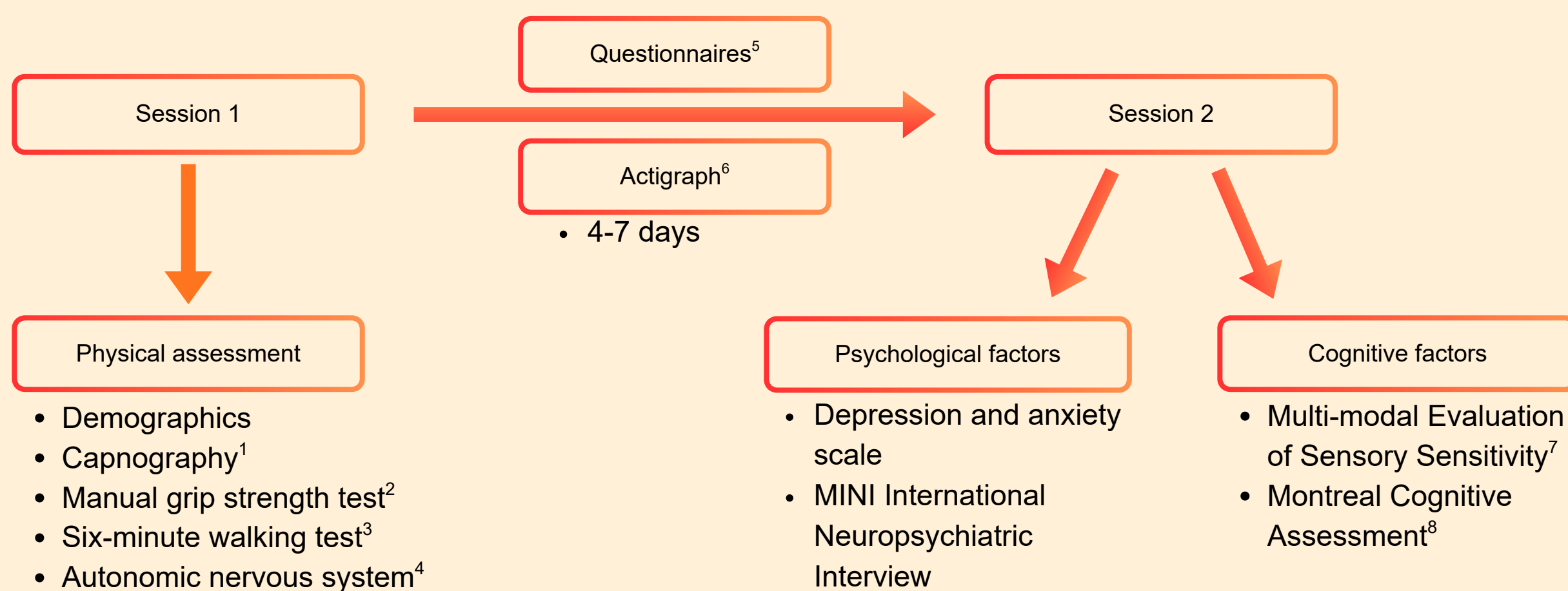


Figure 1. General procedure of the experiment. 1: measure of end-tidal CO₂ during rest and two respiratory challenges; 2: indicator of maximal muscle strength; 3: measure of functional exercise capacity; 4: standardized psychosocial stress test (Smets et al., 2018) to examine physiological stress reactivity; 5: fatigue, dyspnea, hyperventilation-related symptoms, quality of life, work productivity, stress, and burnout; 6: assessment of active and sedentary behavior; 7: awareness/ responsiveness to stimuli across multiple senses; 8: general cognitive functioning.

Analysis: Statistical analyses will include normality testing and descriptive statistics of baseline characteristics, followed by cluster analysis with dimensionality reduction, cluster identification, and outcome evaluation. Factor analysis of mixed data and unsupervised clustering will be used to identify the best-fitting and most reliable PCS subgroups, with between-cluster differences tested using ANOVA or Kruskal-Wallis tests.

Clinical relevance

PCS presents with highly variable symptom profiles, meaning diagnosis-based care alone may not be sufficient. A data-driven subgrouping approach may help clinicians move toward symptom-based and individualized treatment pathways. By combining self-report with in-person assessments of physical, cognitive, and psychophysiological functioning, the study may yield more meaningful patient profiles for clinical practice.

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