Some Methodological Challenges in Studying Resilience

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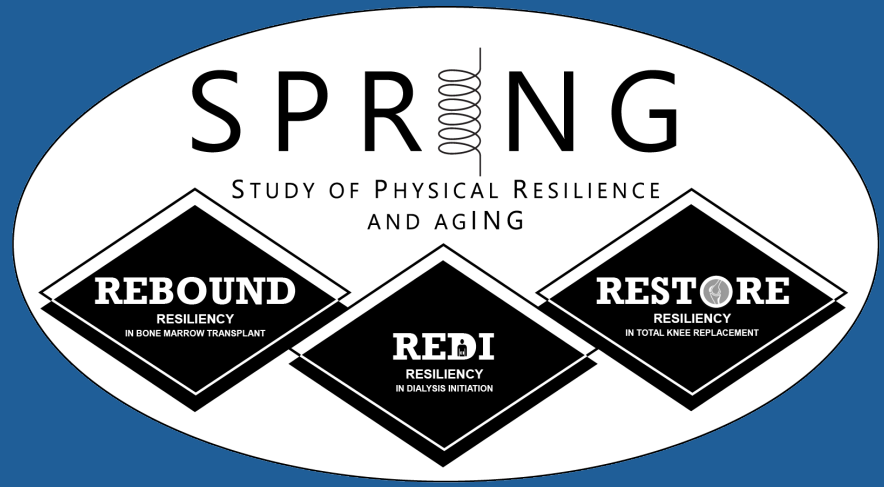
Gratitude

- Drs. Bandeen-Roche, Walston, Buta, Xue
- NIA UH2/UH3
- The organizers of RCCN

Characterizing Resiliencies to Physical Stressors in Older Adults: A Dynamical Physiological Systems Approach

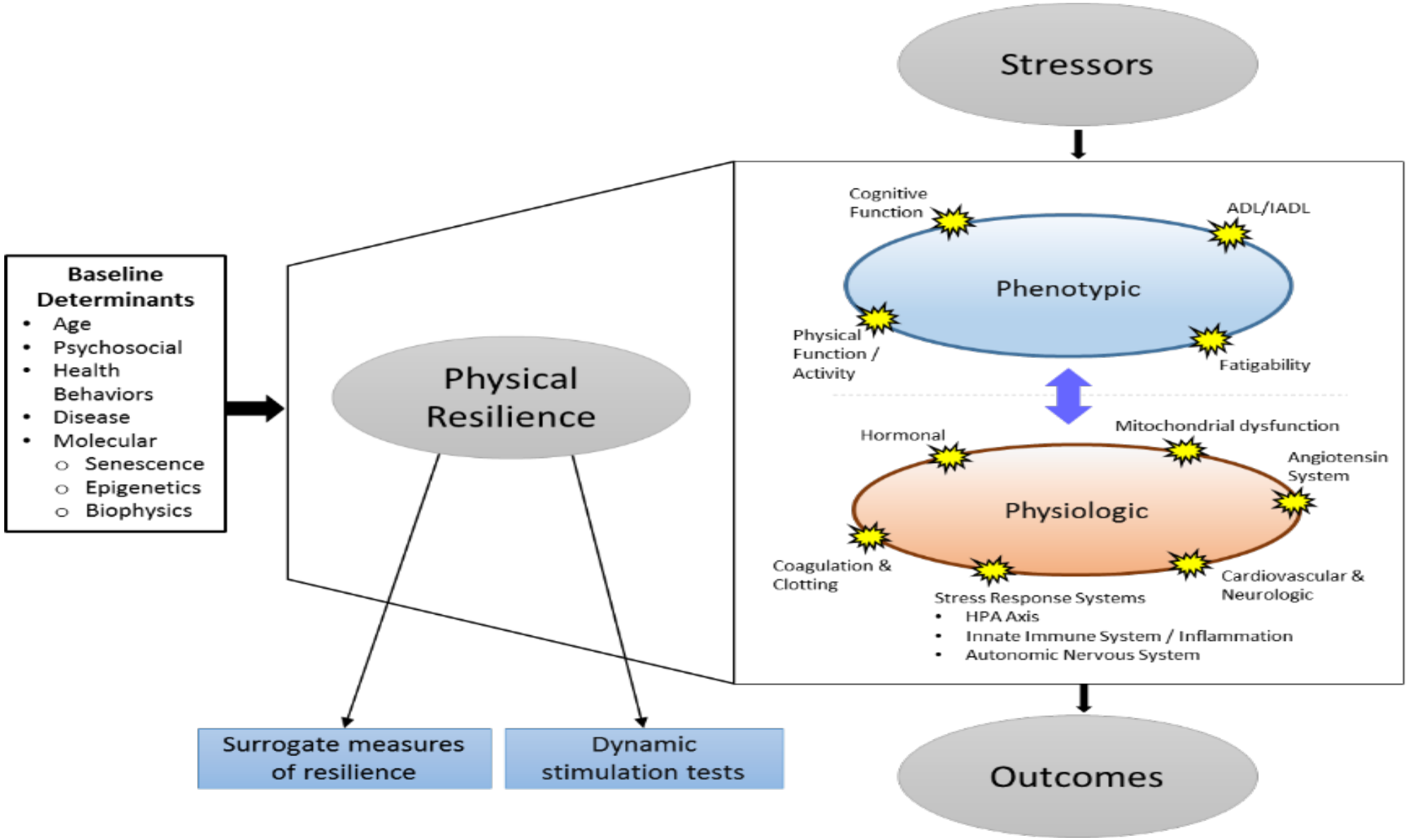
Johns Hopkins University

NIA Grant # UH2AG056933



PIs: Jeremy Walston, MD, Karen Bandeen-Roche, PhD, Ravi Varadhan, PhD, PhD

Conceptual Framework for Physical Resiliency



Key Methodological Challenges

- Recruitment of representative participants
- Ability to probe physiology of resilience with stimulus-response tests
- Ability to collect exquisite post-stressor longitudinal data
- Modeling and characterization of phenotypic trajectories
- Handling death

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Selection Bias in Recruitment

- This is a very difficult problem
- People are undergoing serious clinical stressors such as BMT and TKR
  - Our recruitment yields are around 50%
- Selection bias is inevitable and affects generalizability
- Through secondary data sources, we may be able to assess the impact of selection bias

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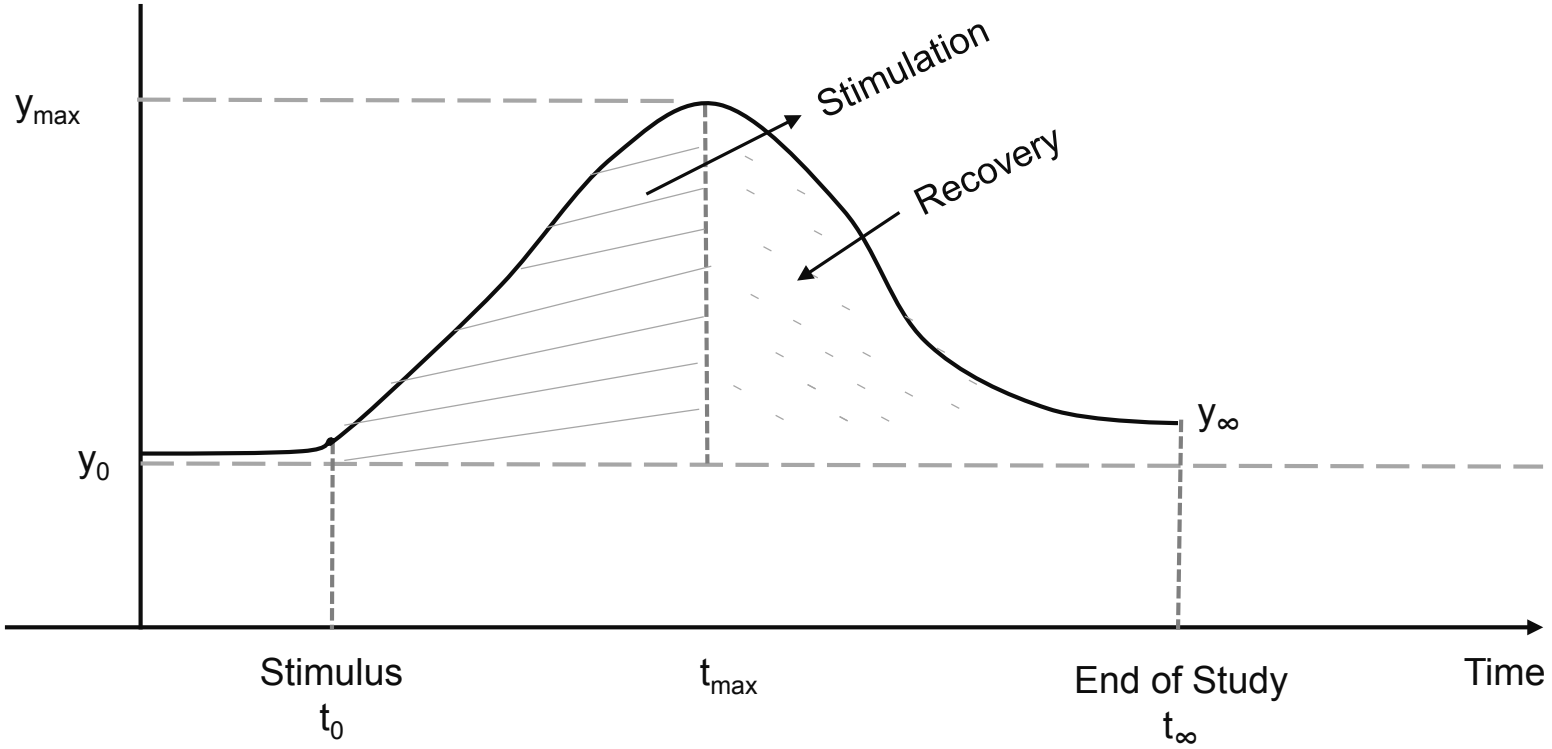
Stimulus-Response Testing Paradigm

- Resilience is a property of a complex, dynamical system
- Perturb the system with a finite stimulus and study its response (Varadhan 2008)
- Response is typically biphasic, i.e. stimulation and recovery phases
- Estimate magnitude and kinetics of response (e.g. characteristic time constants)

SRT Paradigm



Stimulation phase = $t_0 < t \leq t_{max}$
Recovery phase = $t_{max} < t \leq t_\infty$
Peaks response = y_{max}
Stimulation = y_{max} / y_0
Recovery = y_∞ / y_0

Stimulus-Response Tests (SRT)

- SRTs potentially useful for probing resilience
- Unfortunately, we don't know the optimal SRTs
- We need novel SRTs that are safe and yet probe the stress-response physiology
- Non-linear random effects models or non-parametric approaches may be used for analysis

SRTs in SPRING

- ACTH Stimulation
- Diurnal Salivary Cortisol Profile
- Oral Glucose Tolerance Test
- Treadmill fatigability assessment
- Holter Monitoring
- Dynamic ex-vivo response of immune cells to LPS stim
- Orthostatic Blood Pressure

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Longitudinal Sampling

- To study resilience, we need pre-, peri- and post-stressor measures
- Pre-stressor performance measures not possible for unplanned stressors (e.g., hip fracture)
  - is it possible to impute this?
  - self or proxy report measures may be useful
- Utility of peri-stressor measures needs to be examined
  - Changes in physiology during and 24-48 hours after stressor
- Post-stressor measures:
  - sampling time frame?
  - sampling frequency?

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Modeling Phenotypic Response Trajectories

- Models of longitudinal response: well-established in biostatistics

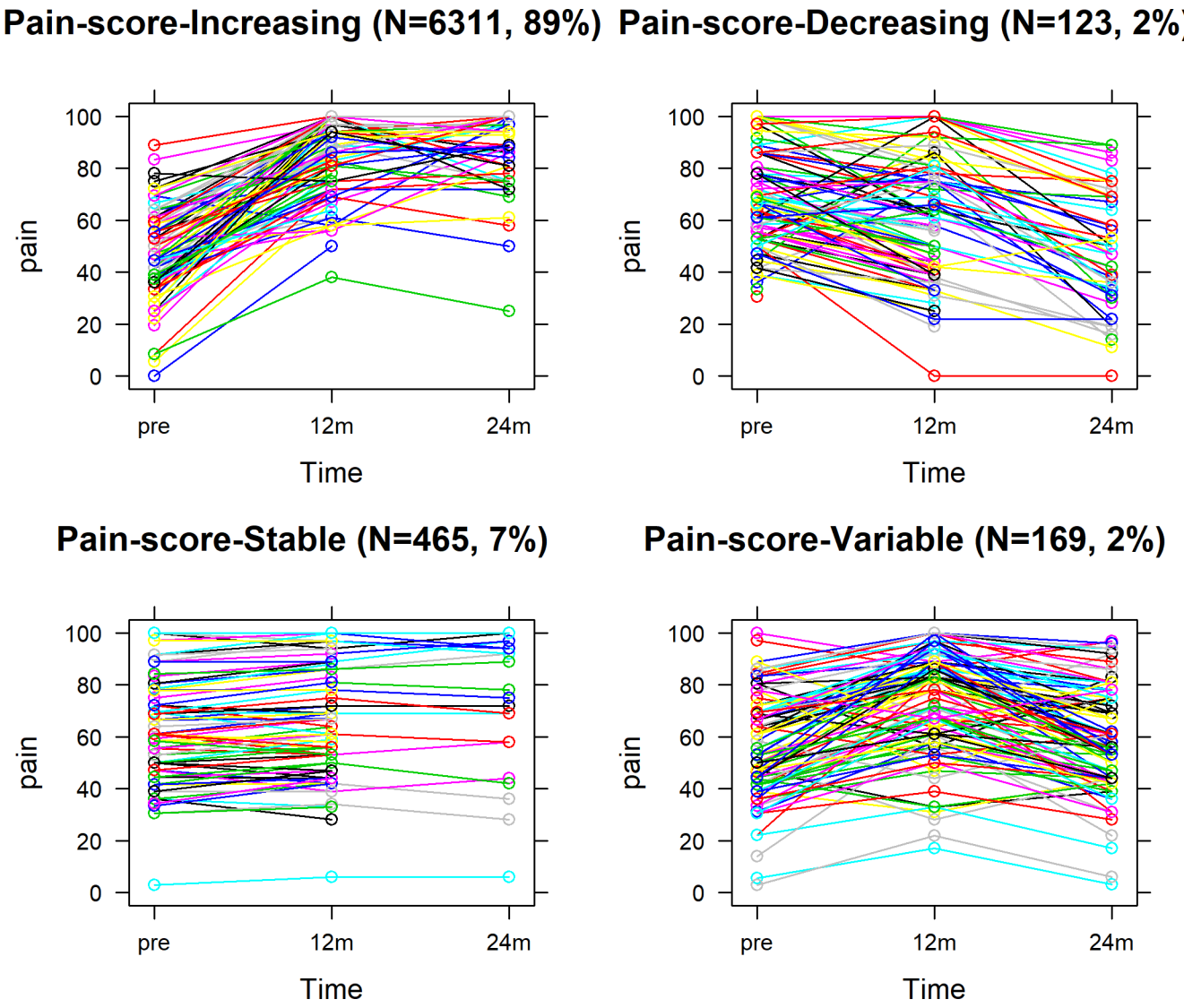
- Conditional (mixed-effects) versus marginal (GEE) models
  - Pros and cons for each
  - choose depending on the goal

- Latent class or latent variable models (e.g., Colon-Emeric 2019)

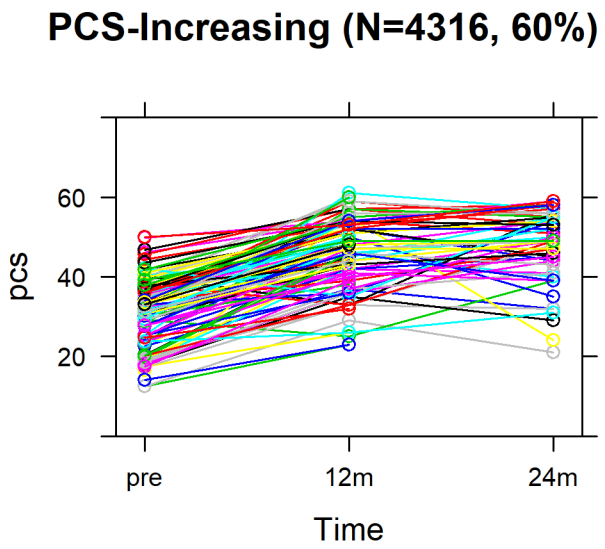
Characterizing Phenotypic Trajectories

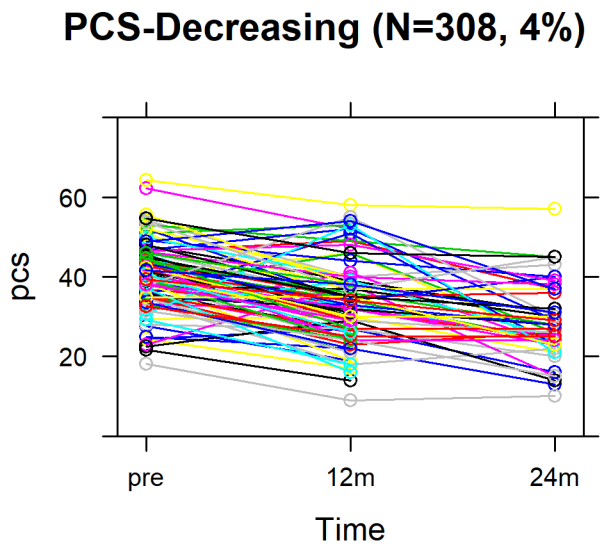
- Different forms of trajectories
- Within-person variability
- How do we utilize baseline function?
- How do we define resilience?

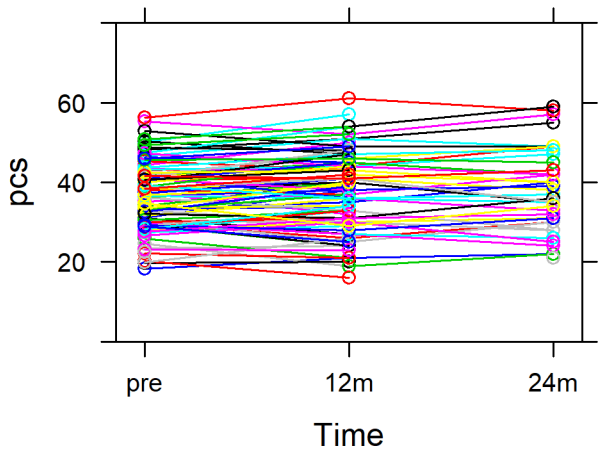
Manifest Profiles

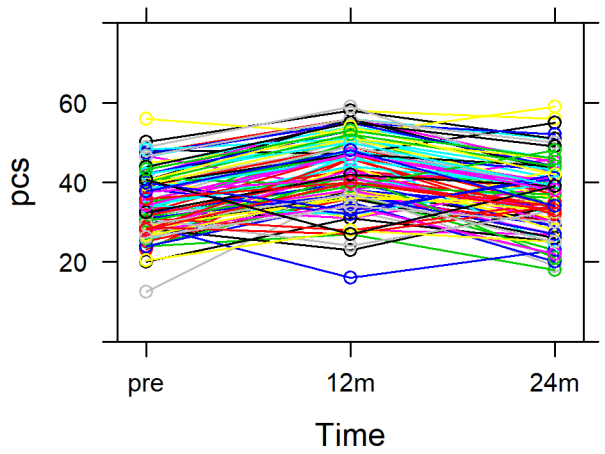


Unpublished Data from FORCE-TJR









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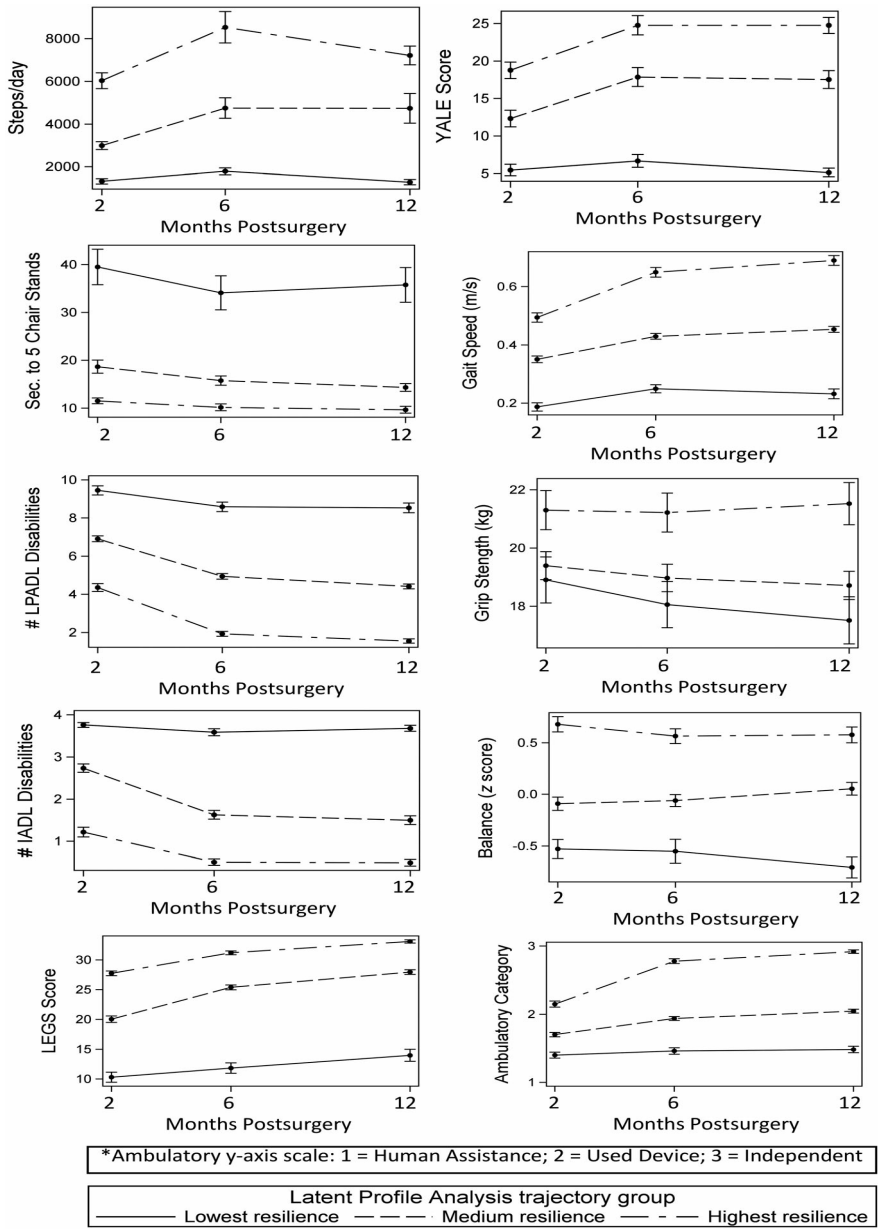

Latent Profiles

Colon-Emeric et al. 2019

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Handling Death

- How to account for death?
  - Simple censoring is seldom appropriate
  - Mixed-effects model extrapolate phenotypes beyond death

- Is death a competing risk or does it denote lack of resilience?
  - Model death as a separate process – joint modeling
  - Death as part of resilience itself
  - Survival as resilience!

What Constitutes a Resilient Phenotype?

- Resilience is a rich, multi-dimensional concept
- Stressor-specific clinical outcomes
  - for example in bone-marrow transplantation for treating leukemia, major clinical outcomes are: graft failure, GVHD, relapse, and death
- Physical and cognitive function
- Quality of life
- Patient-reported outcomes
- Modeling and characterization is challenging

Thank you!