On the Next Generation of Frailty Measures: Unification of Physiologic and Clinical Manifestations

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Conceptual model for frailty

Weight Loss

Physical Activity

Sarcopenia

Clinical Presentation

↓ Motor Performance

↓ Strength

Exhaustion/↓ Exercise Tolerance

Physiologic Dysregulation

Cellular Function, Molecular and Genetic Characteristics
Ultimate Scientific Aims

- We argue that frailty is:
  - More than a marker of disease
  - More than severe disability
  - A syndrome: more than the component parts

- Aim: Advancement beyond progress made
  - Drilling down: from phenotype to etiology
  - Specificity: a measure tied explicitly to dysregulation
  - Product: a refined summary variable
Statistical Contribution to Achievement of Aims

• Long psychometric tradition
  – Validity, (reliability)
  – Framework: frailty as a latent variable

• Role of latent variable modeling?
  – Reveal underlying truth?
  – Operationalize theory?
  – Sensitivity analyses?
  – Commonality vs. uniqueness
Existence / Summary Paradigm

determinants

\[ Y_1 \]

\[ \cdots \]

Frailty

\[ \text{theory} \]

Adverse outcomes

\[ D \]

\[ e_1 \]

\[ e_p \]
Conceptual framework

Determinants D

Biological dysregulation

Clinical Frailty

Statistical methodology: SEM with latent variables (AMOS)
Methods: Data

InCHIANTI (*Ferrucci et al., JAGS, 48:1618-25*)

- **Dysregulation:** inflammation – 5 cytokines
  - *IL-6, CRP, TNF-α, IL-1RA, IL-18*

- **Frailty:** Consensus criteria (*Fried et al., 2001*)
  - Exhaustion; grip strength; physical activity; walking speed; weight loss
  - Continuously measured versions

- **Analyses accounting for:** *age, gender*
Benefit # 1: Theory Infusion

- Central role: cellular repair

- A hypothesis: dysregulation = key in accelerated aging
  - Muscle wasting (*Ferrucci et al., JAGS 50:1947-54; Cappola et al, J Clin Endocrinol Metab 88:2019-25*)
  - Receptor inhibition: erythropoietin production / anemia (*Ershler, JAGS 51:S18-21*)

\[
\text{Stimulus (e.g. muscle damage)} \rightarrow \text{IL-1#} \rightarrow \text{TNF} \rightarrow \text{IL-6} \rightarrow \text{CRP}
\]

- # Difficult to measure. IL-1RA = proxy
- up-regulation
- inhibition
Theory infusion
Construct Definition

- LV method: measured = physiology + noise
  - Multivariate normal underlying variables, errors
  - Conditional independence of errors
Benefit 2: Specificity

- Inflammation 1: Up-reg.
- Inflammation 2: Down-reg.
- Age
- Exh.
- Str.
- PA
- Spd.
- Clinical Frailty

Weights:
- .18
- .14
- .37
- .34
- .35
- .80
- .04
- .58
Benefit 3: Variable Refinement

- More balanced IL6, CRP contributions than I
- Higher TNF, lower IL6, contributions than in I

\[ j = .98, \quad j = .74, \quad j = .66, \quad j = .09, \quad j = .14 \]
Discussion

• Demonstrated: A framework for
  – Incorporating bio-regulation into frailty measurement
  – Distinguishing risk factor effects on frailty (i) status;
    (ii) measurement
  – Refining frailty characterization

• Needed:
  – More explicit incorporation of theory in models
  – Best methods for deriving measures from models
  – Performance comparison
Implications

• Refined understanding of frailty and its measurement
  – Integrating systems biology
  – Increasing specificity

• Heightened accuracy and precision for
  – Delineating etiology
  – Developing and targeting interventions