Delineating the Possible Mechanisms Underlying Longitudinal Associations in Observational Studies on Aging

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“Aging seems to be the only available way to live a long life.”

Daniel Francois Esprit Auber

Via Troen, Mt Sinai J Med 70:3-22
Introduction

• **Holy grail?**: What causes adverse aging?
  - Experimental data on humans: hard to come by
  - Observational, longitudinal data: central

• Cohort studies on aging abound
  - EPESE; CHS; HRS/ALIVE
  - Women’s Health and Aging Study (WHAS)
  - InCHIANTI
Introduction

• Inflammation & Accelerated Aging
  – Cellular repair
  – 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)

• Two themes
  – Homeostasis/balance: cytokines, hormones, nutrition, immune response
  – “Causal pathways”
Outline

• Goals
  – To what extent “causal mechanisms”?
  – Balance of ideas, methods

• Two challenges in research on aging

• Causality in research on aging

• Methodology / Analysis
  – Focus: Imprecise measurement
  – Bidirectionality: an allusion
Classic Conceptual Framework

Pathology → Impairment → Functional Limitation → Disability → Death

A Challenge: Determining Roles Amid Complex Measurement

$X_1 \ldots X_p \rightarrow \text{Inflammation} \rightarrow \text{Mobility} \rightarrow Y_1 \ldots Y_M \rightarrow \text{Confounders} C$
Another Challenge:
Bidirectionality

$X_1$  $\ldots$  $\ldots$  $Y_1$

$X_p$  $\ldots$  $\ldots$  $Y_M$

Inflammation  Mobility

Confounders  $C$
Causal Models

- **Three queries** *(Pearl, 2000)*
  - Predictions
    - “Probabilistic causality” *(von Suppes, 1970)*
    - Is bad function probable among the inflamed?
  - Interventions / Experiments *(Bollen, 1989)*
    - Association, temporality, isolation
    - Does bad function follow inflammation?
  - Counterfactual
    - Does one’s function change if inflamed vs. not?
    - Neyman, 1923; Stalnaker, 1968; Lewis, 1973; Rubin, 1974; Robins 1986; Holland 1988
Challenge #1: Complex Measurement

- IL-18
- IL-1RA
- IL-6
- CRP
- TNF-α

Inflammation 1

Inflammation 2
Toward “causal” inferences?

Inflammation → Mobility

Age, Gender, Smoking

Hx: CVD, Cancer, Diabetes

- Propensity scoring (Rosenbaum & Rubin, 1983; Imai & Van Dyk, 2004)
- My work: Implementation amid latent variables
Success of Approach: 
Counterfactual interpretation or no?

- $\{Y^{(t)}\} \perp I \mid c$
- $I$ varies at all levels of $c$
- **Critical**: characteristics violating strong ignorability
- **Perhaps**: strong ignorability of $[I, \text{other}]$ given “external” confounders
Application: Study
InCHIANTI (Ferrucci et al., JAGS, 48:1618-25)

• **Aim**: Causes of walking decline
• **Brief design**
  - Random sample ≥ 65 years (n=1270)
  - Enrichment for oldest-old, younger ages
  - Participation: > 90% in the primary sample
• **Data**
  - Home interview, blood draw, physical exam
  - This talk: one evaluation
Application: Data
InCHIANTI (Ferrucci et al., JAGS, 48:1618-25)

• Inflammation – 5 cytokines
  *IL-6, CRP, TNF-α, IL-1RA, IL-18*

• Functional elements – Z-score average
  *Usual & rapid speed; muscle power; range of motion; neurological intactness*

• Confounders
  *Age, gender, history of: cancer, cardiovascular disease, diabetes, smoking*
Propensity Score Model

- $I_1 \sim \text{age, cancer hx, CVD hx}$
- $I_2 \sim \text{age, gender, diabetes hx, smoking hx}$
Summary

• “Causality” re natural history of aging: not an immediate concept

• Discussed here: Analytic strategies to advance toward causal inferences

• Needed: Assessment of extent to which causal mechanisms can be delineated with observational data on aging