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

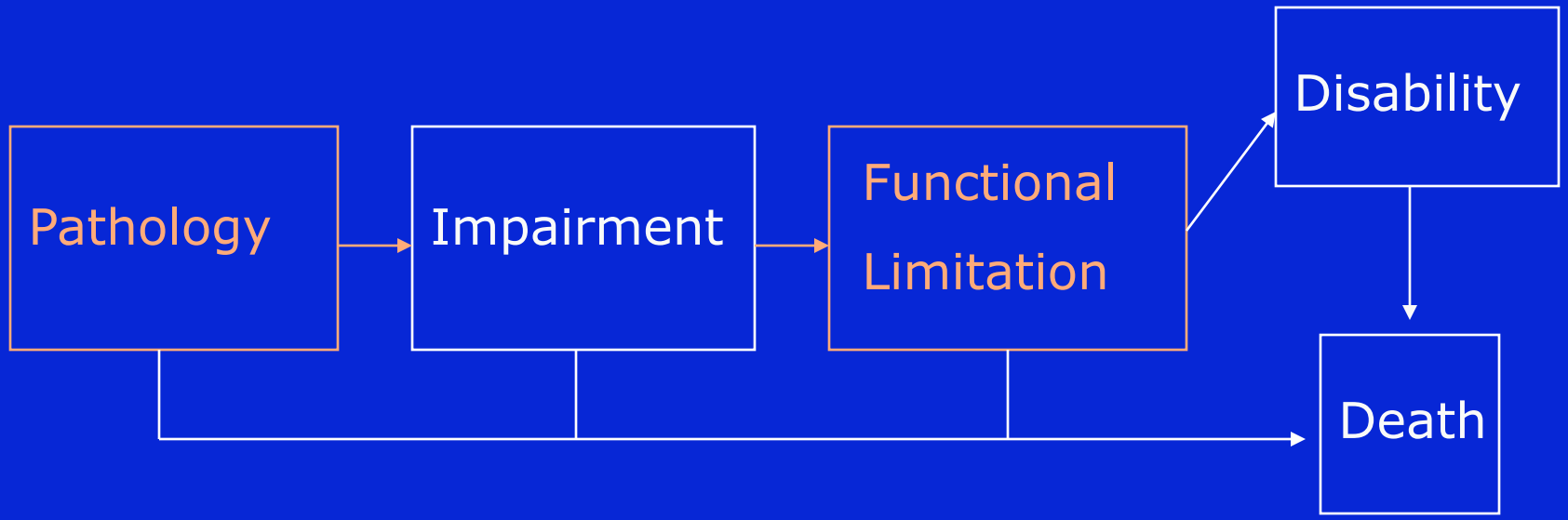
- Inflammation & Accelerated Aging
  - Cellular repair
  - Muscle wasting (*Ferrucci et al., JAGS 50:1947-54; Cappola et al, J Clin Endocrinol Metab 88:2019-25*)
  - Receptor inhibition: erythropoetin production / anemia (*Ershler, JAGS 51:S18-21*)

- Two themes
  - ***Homeostasis/balance***: cytokines, hormones, nutrition, immune response
  - "Causal pathways"

Outline

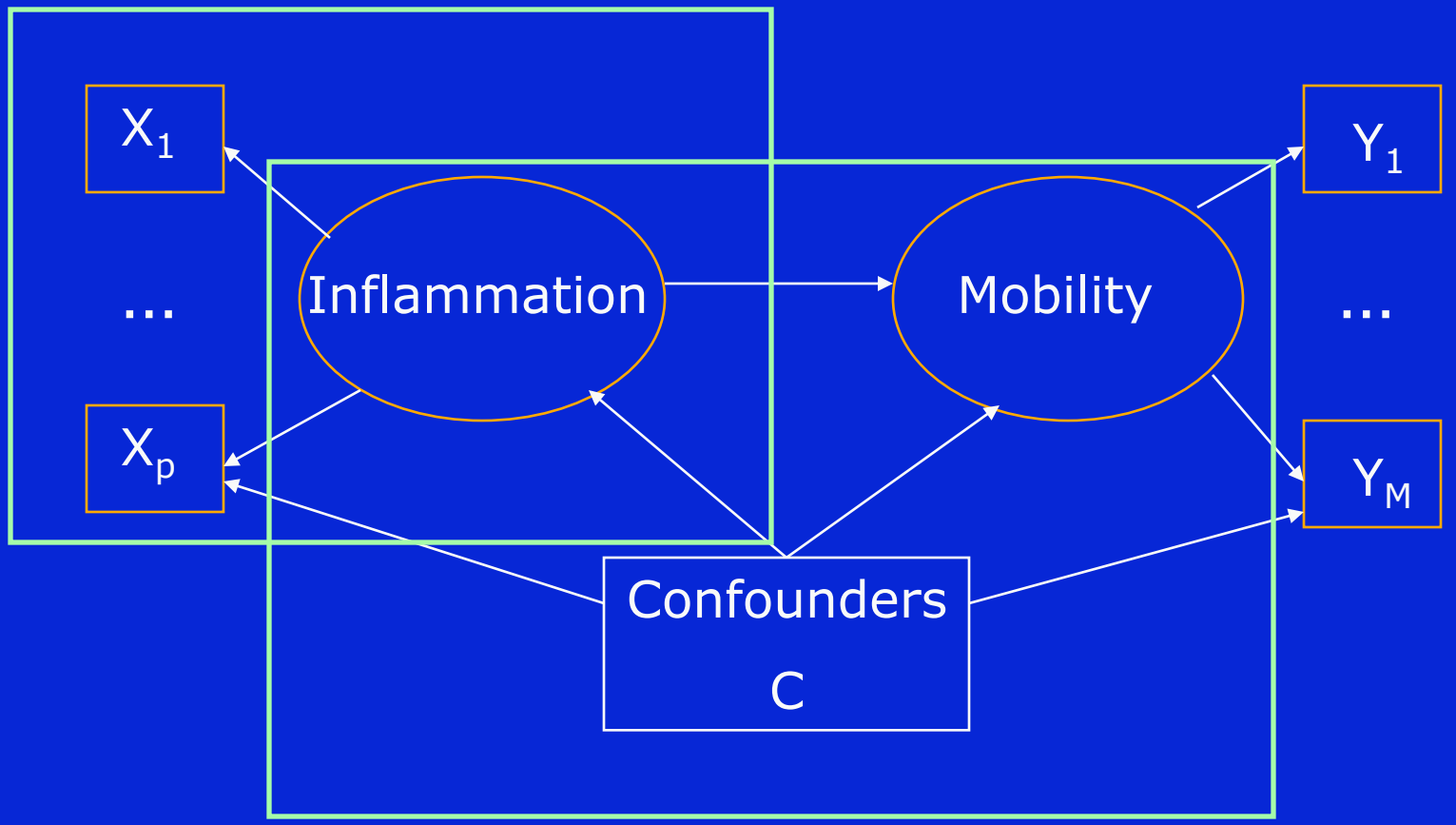
- Goals
  - To what extent "causal mechanisms"?
  - Balance of ideas, methods
- Two challenges in research on aging
- Causality in research on aging
- Methodology / Analysis
  - Focus: Imprecise measurement
  - Bidirectionality: an allusion

Classic Conceptual Framework

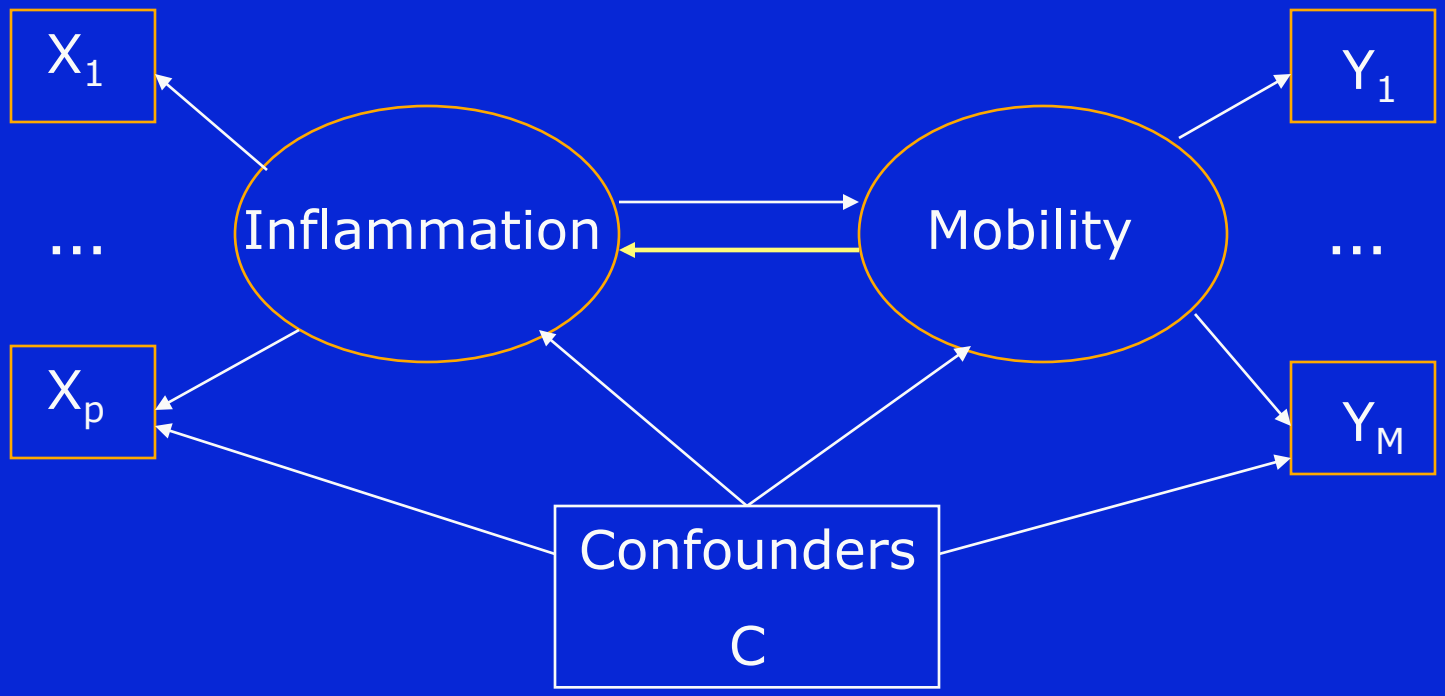


WHO, 1980; IOM, 1991; Nagi, 1991

A Challenge: Determining Roles Amid Complex Measurement



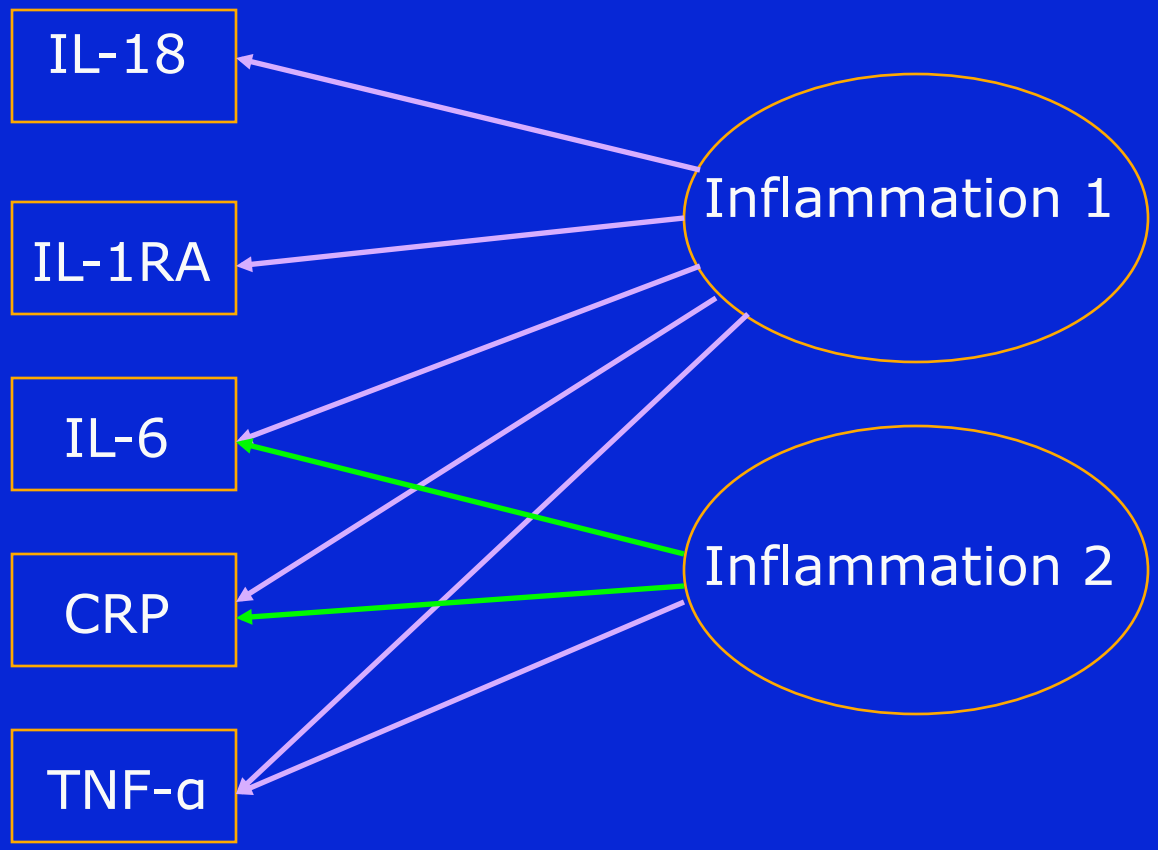
Another Challenge: Bidirectionality



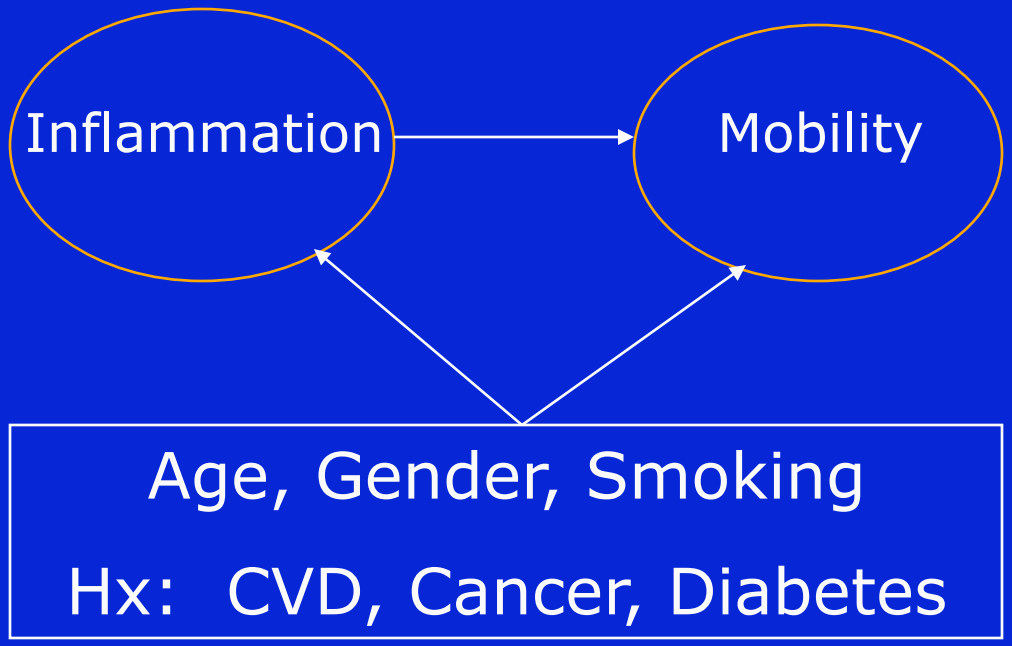
Causal Models

- 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



Toward "causal" inferences?

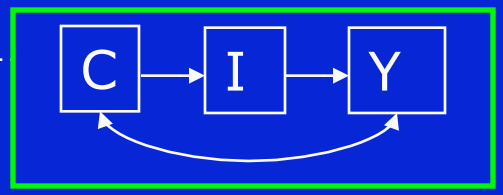


- Propensity scoring *(Rosenbaum & Rubin, 1983; Imai & Van Dyk, 2004)*
- My work: Implementation amid latent variables

Success of Approach:

Counterfactual interpretation or no?

- $\{Y^{(t)}\} \perp\!\!\!\perp I \mid c$ ----------



- I varies at all levels of c
- **Critical**: characteristics violating strong ignorability
- Perhaps: strong ignorability of [I,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-a, IL-1RA, IL-18

- **Functional elements – Z-score average**

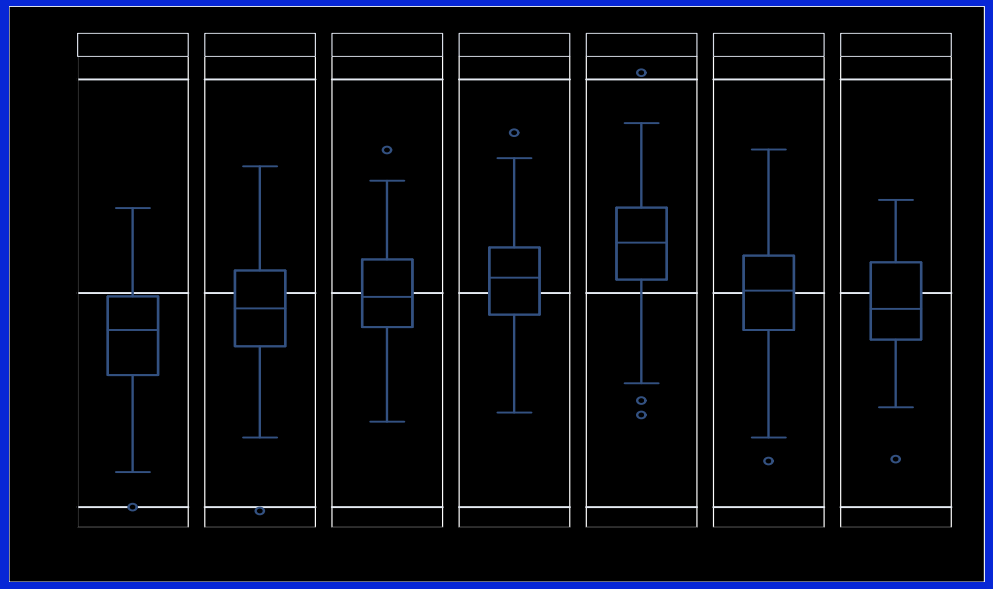
  Usual & rapid speed; muscle power; range of motion; neurological intactness

- **Confounders**

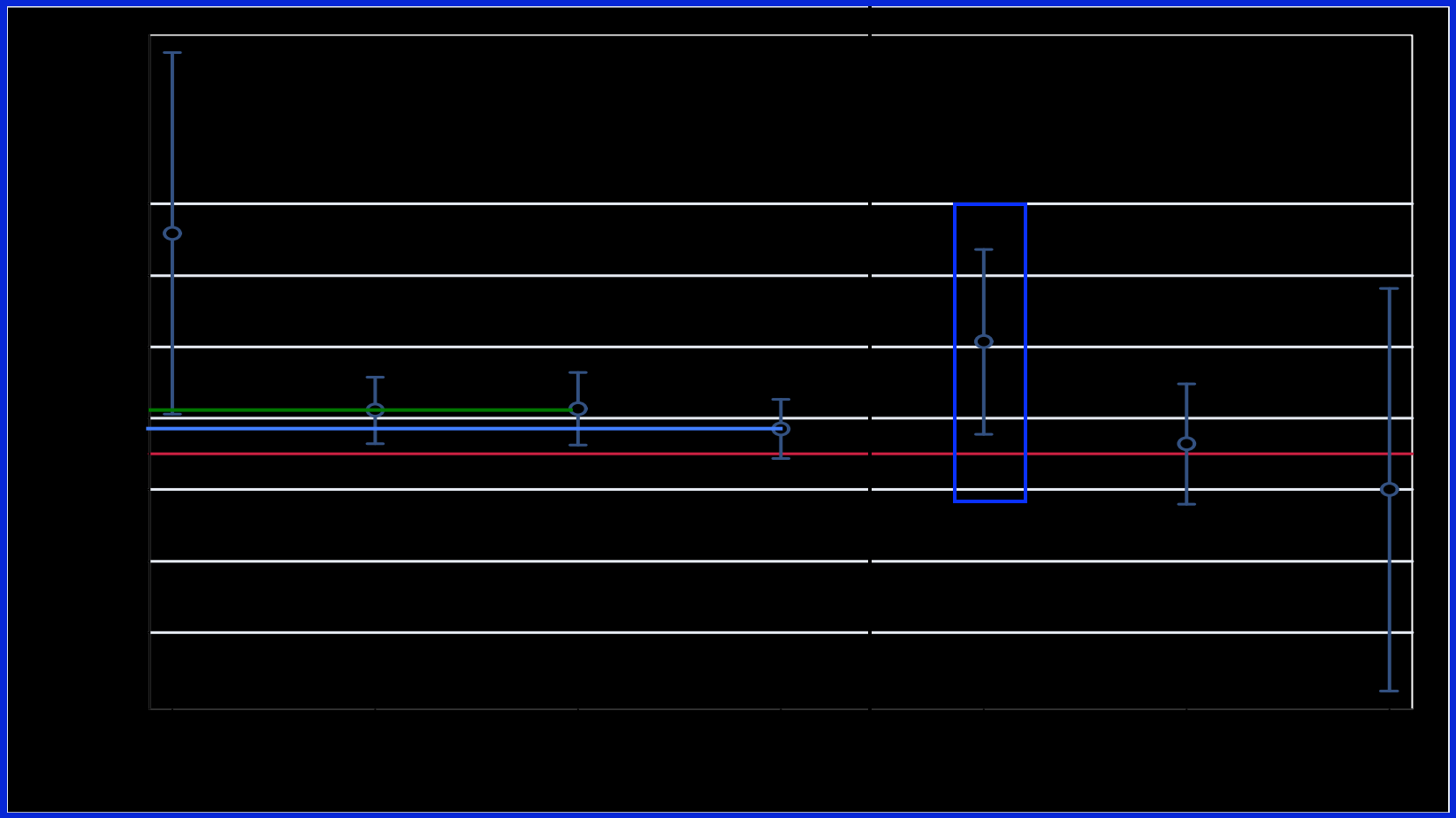
  Age, gender, history of: cancer, cardiovascular disease, diabetes, smoking

Propensity Score Model

- I_1 ~ age, cancer hx, CVD hx
- I_2 ~ age, gender, diabetes hx, smoking hx



Inflammation Effects (Summary 2)



raw adjusted PS-full PS-red. diab/sm young cancer

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