# 500 Class 05 (Zoom)

https://thomaselove.github.io/500-2025/

2025-02-13

# Agenda for Zoom Call

Thursday 2025-02-13 from 10 to 11 AM. Zoom details in your email and on Canvas.

- Feinstein's Model for Research Architecture
  - 7 Key Aspects for Making Fair Judgments about Causation
- A Published Example of My Early Propensity Score Work
  - M.I. Ahmed et al. International Journal of Cardiology 154 (2012) 128–133.
- Reviewing the Project Proposals
- Discussing Rosenbaum, Causal Inference, Chapter 6 (Quasi-Experimental Designs)

# Section 1

## Feinstein's Model for Research Architecture (expanded by Neal Dawson)

# 7 Key Aspects of Research Architecture*:
## Making Fair Judgments about Causation


- Possibility of distorted assembly – sample doesn't reflect the population to which the results will be generalized.

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

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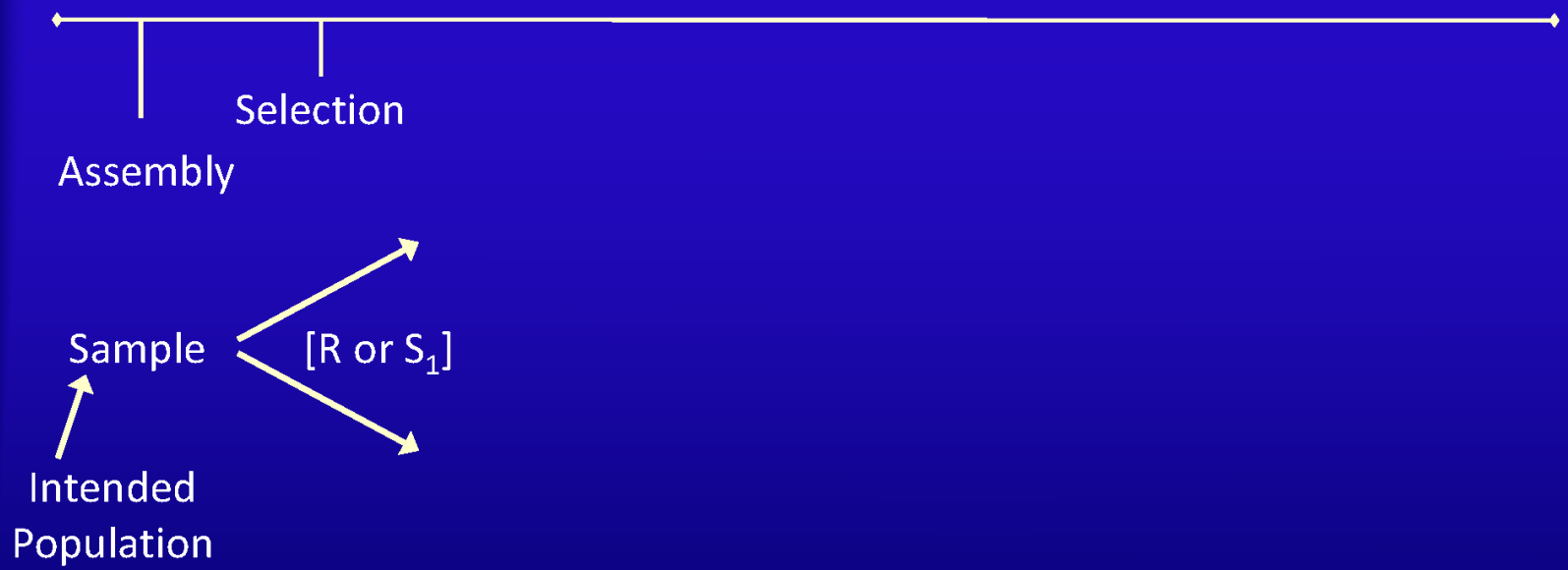
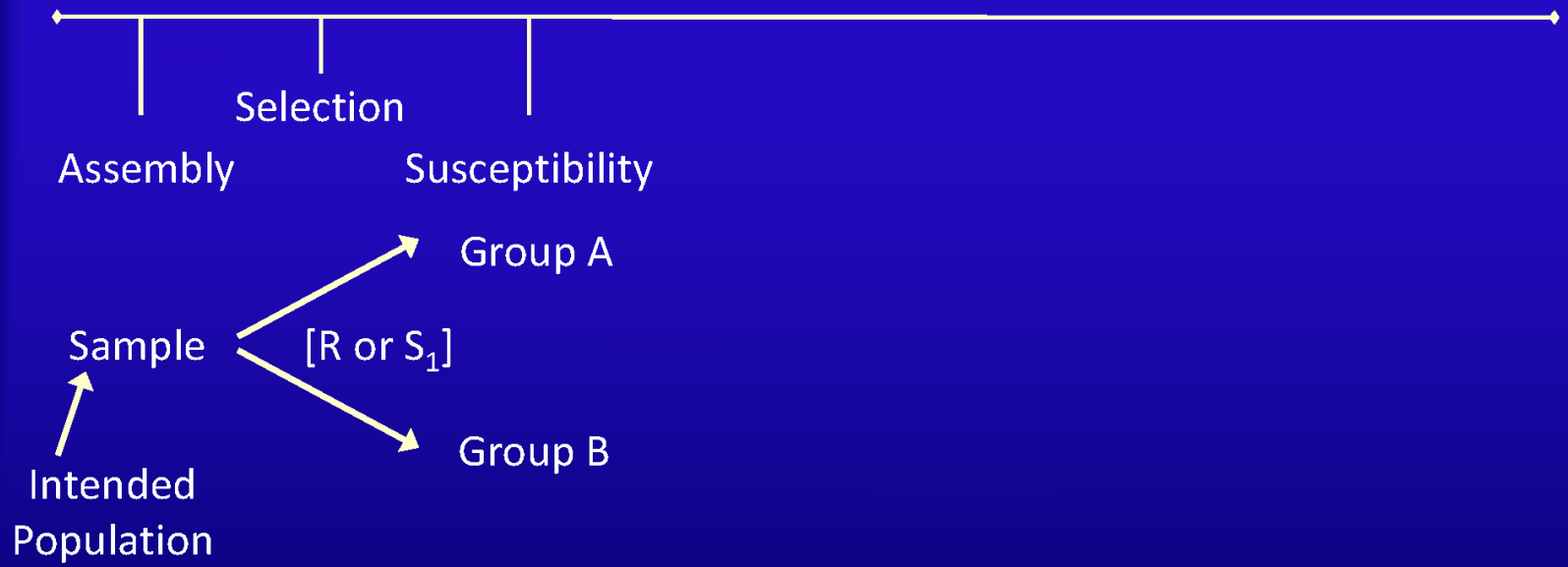
# 7 Key Aspects of Research Architecture*:
## Making Fair Judgments about Causation




- Selection Bias – who receives the exposure? Basis: (possibly unmeasured) covariates linked to outcomes? Why randomize?

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

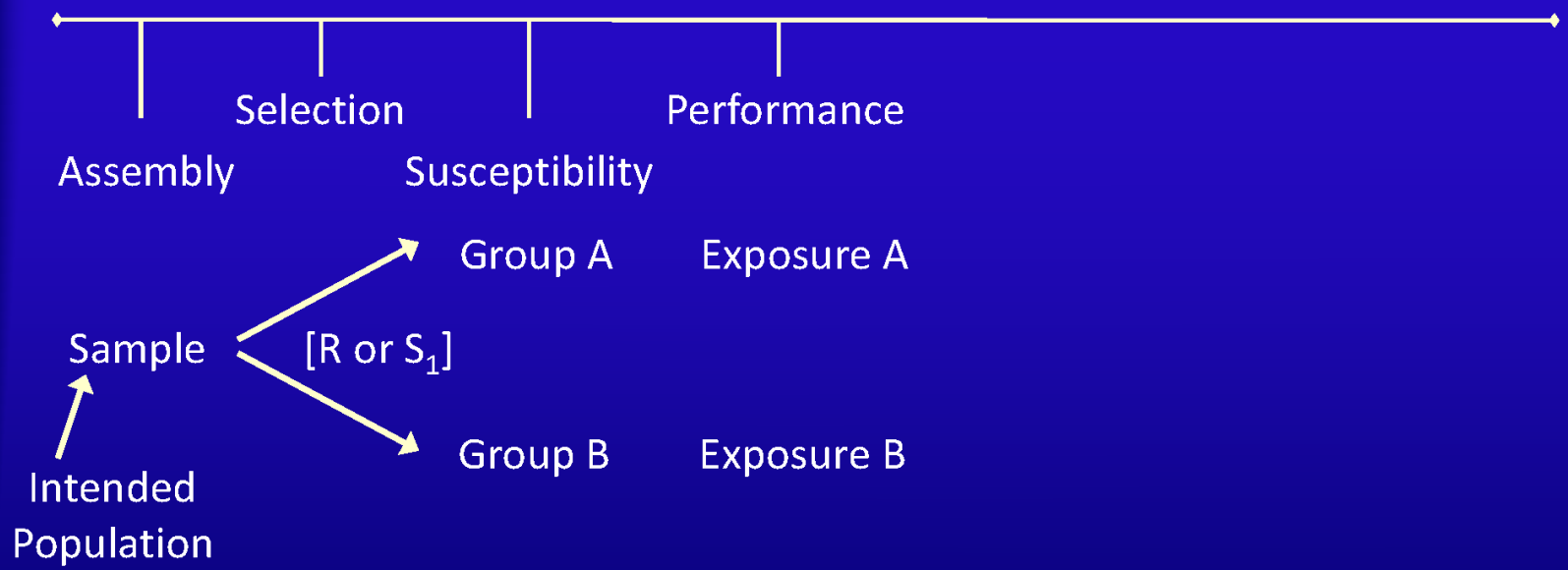
# 7 Key Aspects of Research Architecture*: Making Fair Judgments about Causation




- Are there importantly different expectations at baseline, for the eventual outcomes? Susceptibility reflects covariate differences.

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

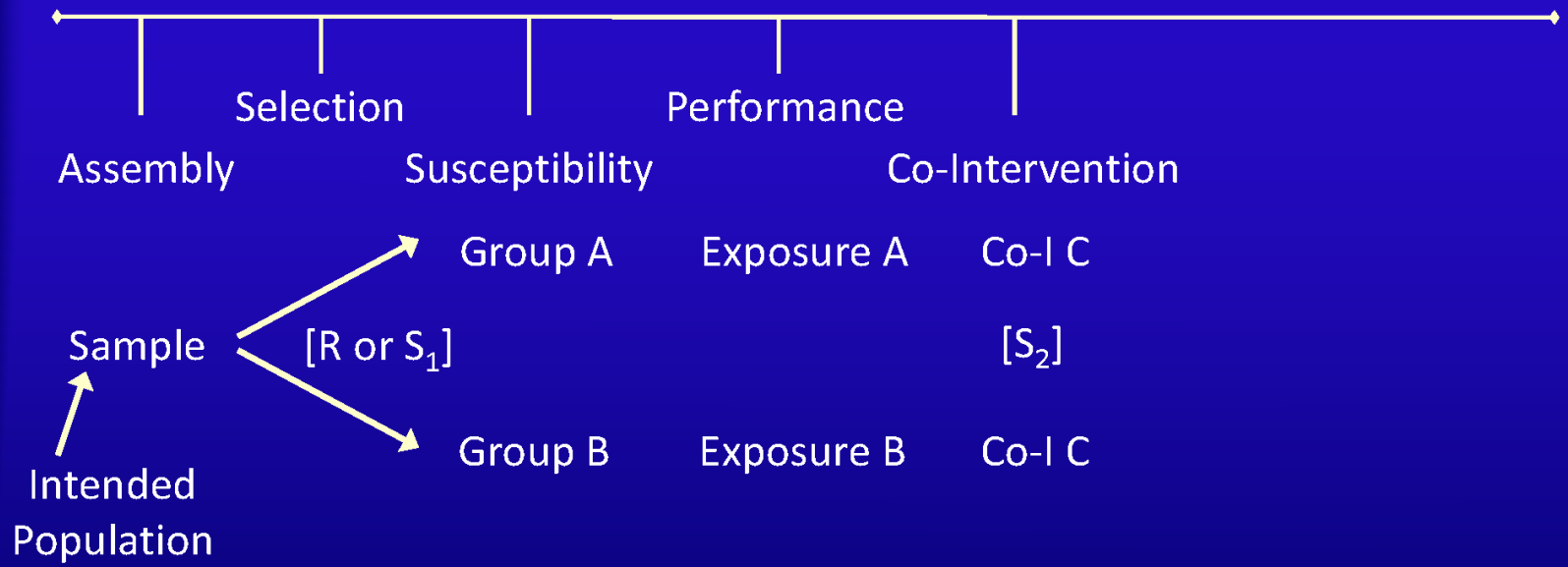
# 7 Key Aspects of Research Architecture*: Making Fair Judgments about Causation




- Are exposures applied with the same proficiency? How "well" do pts receive the exposures (dosage schedules, compliance)?

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

# 7 Key Aspects of Research Architecture*: Making Fair Judgments about Causation




- Additional selection opportunities – co-interventions (beyond exposure of interest) may influence likelihood of outcomes.

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

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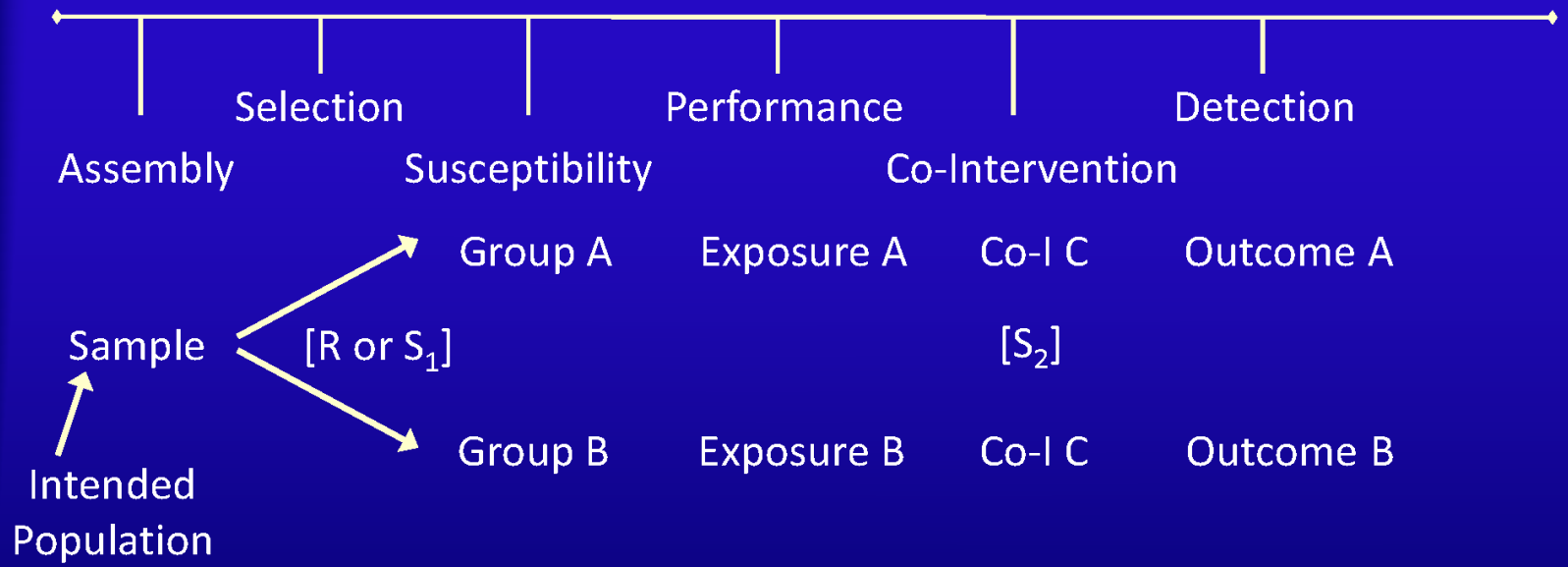
# 7 Key Aspects of Research Architecture*: Making Fair Judgments about Causation




- Is process for determining outcomes applied unequally? Differences in surveillance, diagnostic testing, or interpretation?

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

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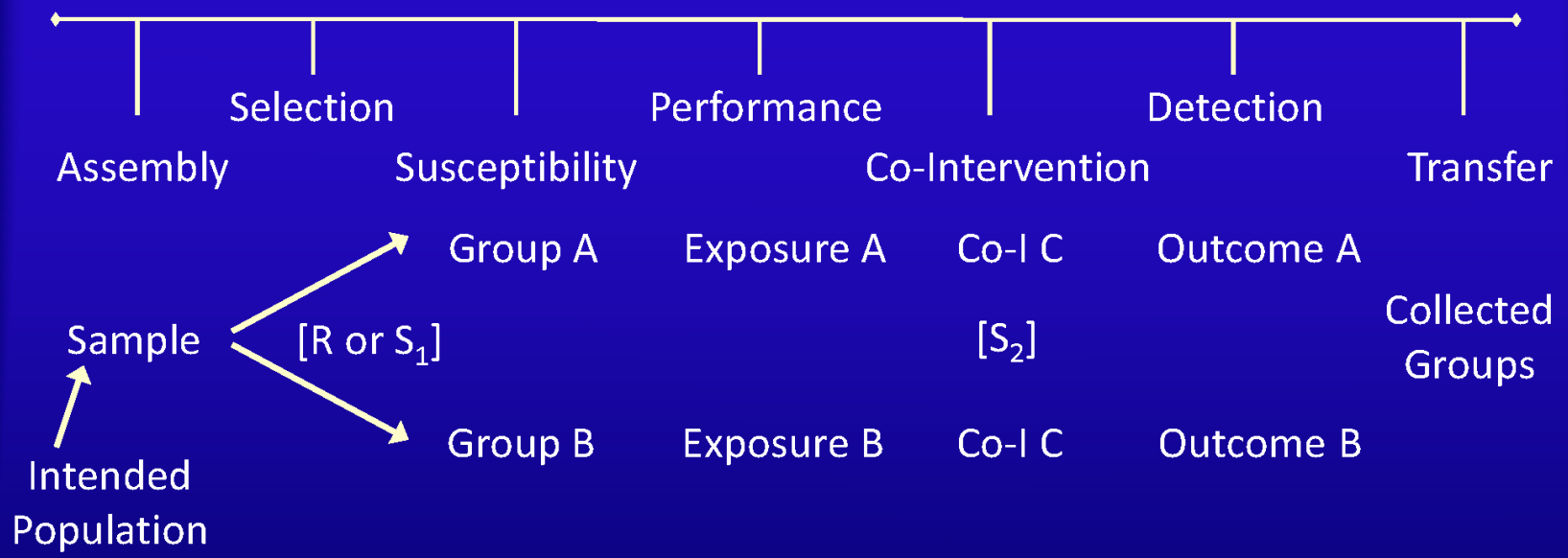
# 7 Key Aspects of Research Architecture*:
## Making Fair Judgments about Causation




- Comparison of members of original cohorts of A and B – dropouts, in-study exclusions, crossovers, dealing with missing data…

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

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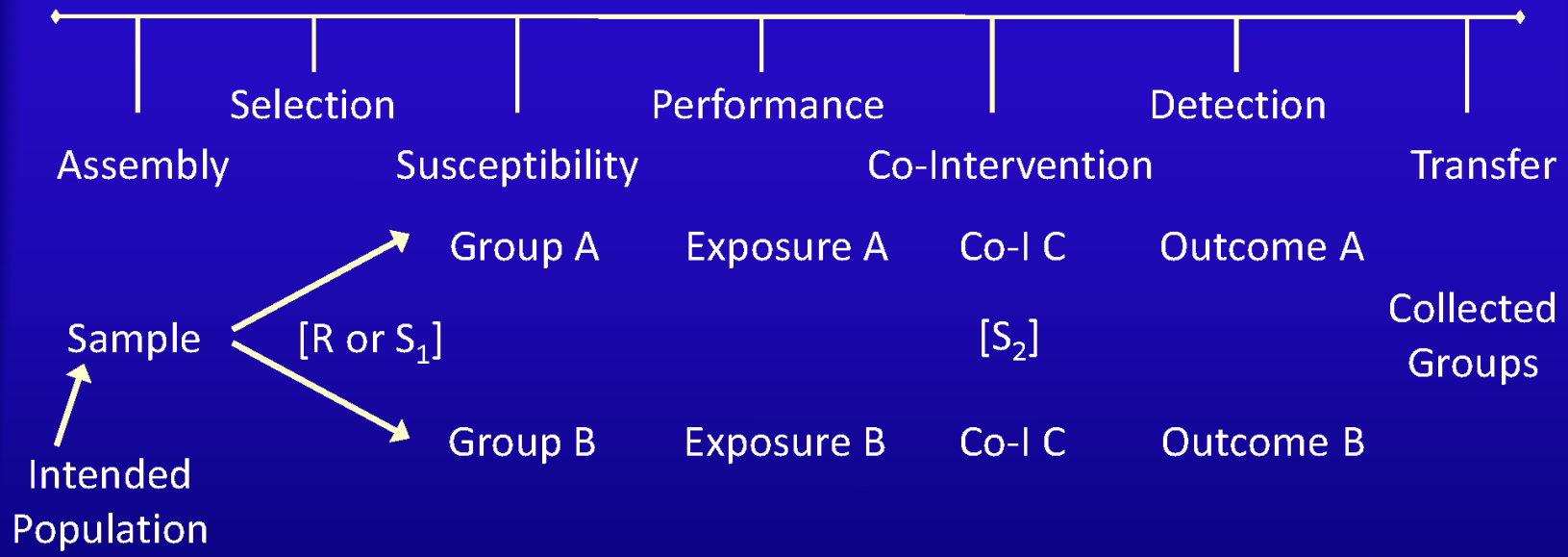
# 7 Key Aspects of Research Architecture*:
## Making Fair Judgments about Causation




- Goal: Comparability of groups who did and did not receive the exposure (except for the actual receipt of the exposure)

*Adapted by Neal Dawson from Alvan Feinstein's intellectual model (5 key aspects)

Section 2

# A Published Example of My Early Propensity Score Work

# Ahmed et al. 2012

## Outcomes in younger and older adults with chronic advanced systolic heart failure: A propensity-matched study

Mustafa I. Ahmed [a], Marjan Mujib [a], Ravi V. Desai [a], Margaret A. Feller [a], Casey Daniel [a], Inmaculada B. Aban [a], Thomas E. Love [b], Prakash Deedwania [c], Bertram Pitt [d], Wilbert S. Aronow [e], Ali Ahmed [a,f,*]

[a] *University of Alabama at Birmingham, Birmingham, AL, USA*
[b] *Case Western Reserve University, Cleveland, OH, USA*
[c] *University of California-San Francisco, Fresno, CA, USA*
[d] *University of Michigan, Ann Arbor, MI, USA*
[e] *New York Medical College, Valhalla, NY, USA*
[f] *VA Medical Center, Birmingham, AL, USA*

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- M.I. Ahmed et al. *International Journal of Cardiology* 154 (2012) 128–133.

# Abstract of Ahmed et al.


A B S T R A C T

*Background:* Older age is an independent predictor of all-cause mortality in patients with mild to moderate heart failure (HF). Whether older age is also an independent predictor of mortality in patients with more advanced HF is unknown.

*Methods:* Of the 2707 Beta-Blocker Evaluation of Survival Trial (BEST) participants with ambulatory chronic HF (New York Heart Association class III/IV and left ventricular ejection fraction <35%), 1091 were elderly (≥65 years). Propensity scores for older age, estimated for each of the 2707 patients, were used to assemble a cohort of 603 pairs of younger and older patients, balanced on 66 baseline characteristics.

*Results:* All-cause mortality occurred in 33% and 36% of younger and older matched patients respectively during 4 years of follow-up (hazard ratio {HR} associated with age ≥65 years, 1.05; 95% confidence interval {CI}, 0.87–1.27; $P = 0.614$). HF hospitalization occurred in 38% and 40% of younger and older matched patients respectively (HR, 1.01; 95% CI, 0.84–1.21; $P = 0.951$). Among 603 pairs of unmatched and unbalanced patients, all-cause mortality occurred in 28% and 36% of younger and older patients respectively (HR, 1.34; 95% CI, 1.10–1.64; $P = 0.004$) and HF hospitalization occurred in 34% and 40% of younger and older unmatched patients respectively (HR, 1.24; 95% CI, 1.03–1.50; $P = 0.024$).

*Conclusion:* Significant bivariate associations suggest that older age is a useful marker of poor outcomes in patients with advanced chronic systolic HF. However, lack of significant independent associations suggests that older age per se has no intrinsic effect on outcomes in these patients.

# From the Introduction

> *The majority of heart failure (HF) patients are 65 years, and most deaths and HF-related hospitalizations in HF patients occur in this patient group. We have previously demonstrated that in a propensity-matched cohort of ambulatory patients with mild to moderate chronic HF, older age ($\geq 65$ years) was associated with increased mortality but not hospitalization.*

The objective of the current study was to examine the independent effect of older age on outcomes in chronic advanced systolic HF patients using a propensity-matched design.

# Data Source and Subjects

> *This study was conducted using retrospective analysis of public-use copies of the Beta-Blocker Evaluation of Survival Trial (BEST) datasets obtained from the National Heart, Lung, and Blood Institute (NHLBI).*
>
> *BEST was a multicenter randomized controlled trial of the beta-blocker bucindolol in chronic systolic HF.*

Patients with advanced systolic HF were enrolled from 90 different sites across the United States and Canada. All patients had New York Heart Association class III or IV symptoms and a left ventricular ejection fraction below 35%.

# Exposure and Outcomes

Exposure: We categorized (2707) patients into two age groups: younger ($< 65$ years) and older ($\geq 65$ years; n $= 1091$ or 40%).

Primary outcomes were all-cause mortality and HF hospitalization. Secondary outcomes included cardiovascular mortality, HF mortality and all-cause hospitalization. All outcomes were centrally adjudicated.

# Greedy Matching Approach

> *Using a greedy matching protocol described elsewhere in detail, we were able to match 603 of the 1091 older patients with 603 patients* $< 65$ *years old who had similar propensity scores.*

We began by using a non-parsimonious multivariable logistic regression model to estimate propensity score for age $\geq 65$ years for each of the 2707 participants. In the model, an age $\geq 65$ years was used as the dependent variable and all clinically relevant baseline characteristics (see Fig. 1, in two slides) were included as covariates.

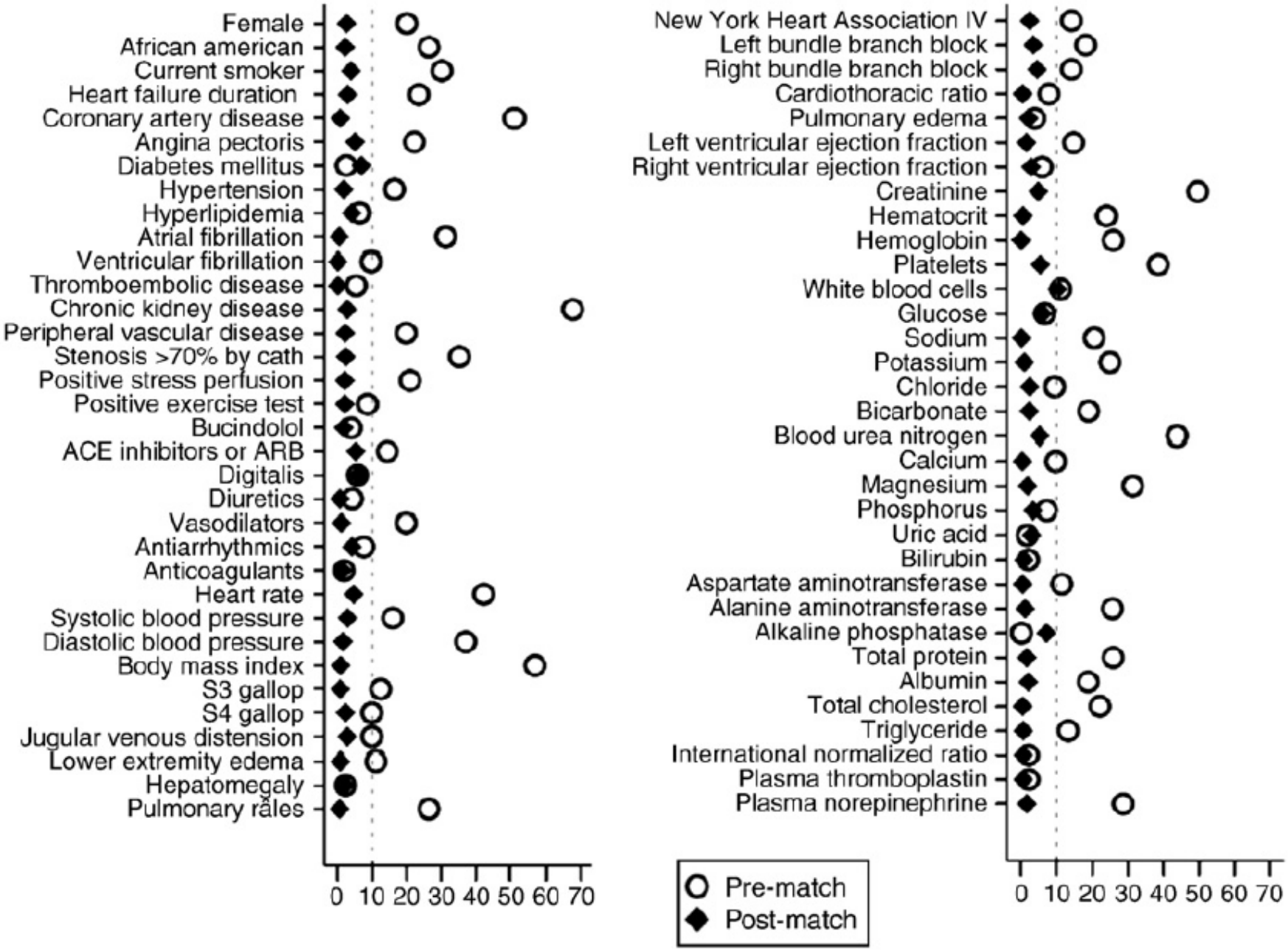
- The matching process used an SPSS macro published in the second edition of Levesque R, ed. *A Guide for SPSS and SAS Users* 2005.

# Propensity Matching Results

Before matching, older patients were more likely to have coronary artery disease, atrial fibrillation and chronic kidney disease than younger patients.

After matching, absolute standardized differences between age groups were $< 10\%$ for all measured covariates (with the exception of white blood cell count which was 10.2%) with most values $< 5\%$ demonstrating substantial covariate balance across the groups (Love plot, next slide.)

# Love Plot (Figure 1)

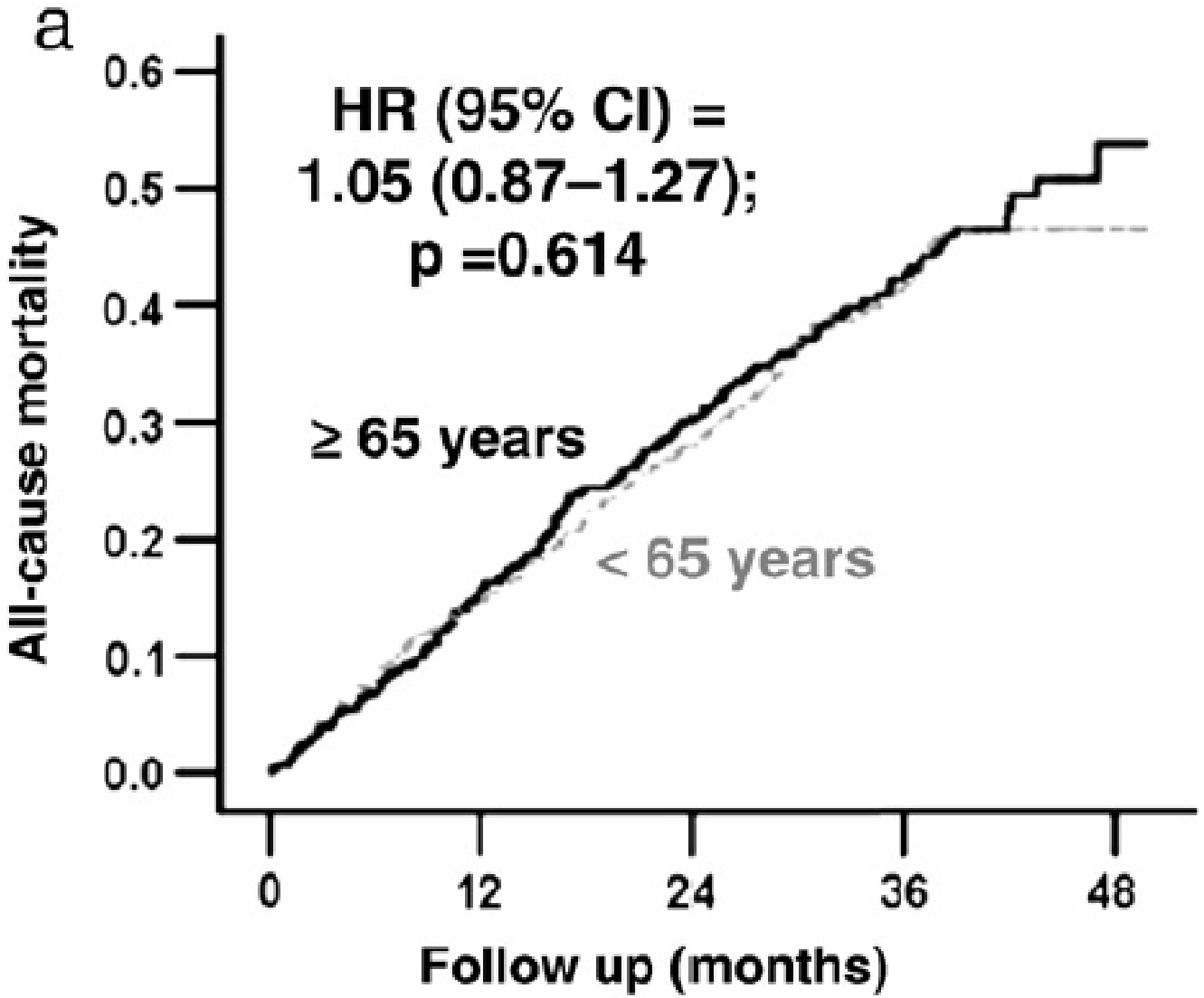


# All-Cause Mortality Effect?

All-cause mortality occurred in 33% (202/603) and 36% (215/603) of matched younger and older patients respectively during 4 years of follow-up.

The hazard ratio (HR) for all-cause mortality when older patients are compared to younger patients was HR = 1.05, 95% CI: 0.87 - 1.27.

# Kaplan-Meier Plot for All-Cause Mortality




**Number of patients at risk**

| | | | | | |
|---|---|---|---|---|---|
| <65 years | 603 | 460 | 289 | 117 | 16 |

# Table 2

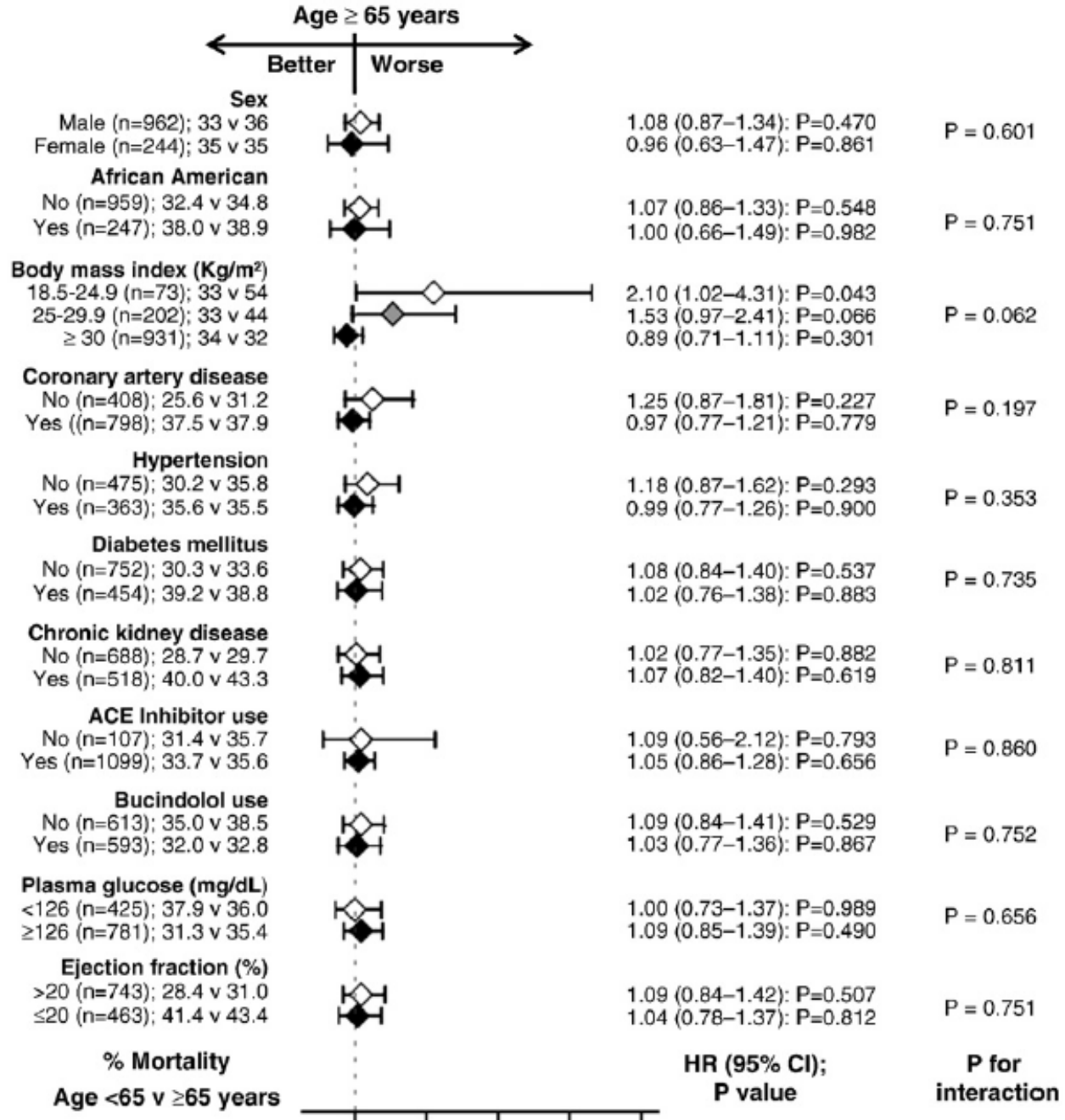
**Table 2**
Age ≥ 65 years and outcomes in the matched cohort.

| Outcomes | Events (%) | | Absolute risk difference[a] (%) | Hazard ratio (95% confidence interval) | *P* value |
|---|---|---|---|---|---|
| | <65 years ($n = 603$) | ≥65 years ($n = 603$) | | | |
| All-cause mortality | 202 (33%) | 215 (36%) | +2 | 1.05 (0.87–1.27) | 0.614 |
| Cardiovascular mortality | 182 (30%) | 168 (28%) | −2 | 0.91 (0.74–1.12) | 0.379 |
| Heart failure mortality | 52 (9%) | 80 (13%) | +5 | 1.51 (1.07–2.14) | 0.020 |
| All-cause hospitalization | 375 (62%) | 409 (68%) | +6 | 1.07 (0.93–1.23) | 0.372 |
| Heart failure hospitalization | 229 (38%) | 240 (40%) | +2 | 1.01 (0.84–1.21) | 0.951 |

[a] Absolute risk differences were calculated by subtracting percent events in the <65 year group from the percent events in the ≥65 year group (before rounding).

- Significant association of older age with increased risk of HF mortality.

# Figure 3 (Subgroup Analyses)



# Conclusions

In conclusion, in patients with advanced chronic systolic HF, older age is an important marker of increased mortality and hospitalization, but has no intrinsic effect on outcome. Therapeutic decisions in older adults with advanced HF should not be biased on the basis of age alone.

# Funding and Acknowledgements

Dr. Ahmed is supported by the National Institutes of Health through grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama.

"The Beta-Blocker Evaluation of Survival Trial (BEST) study was conducted and supported by the NHLBI in collaboration with the BEST Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the BEST Study or the NHLBI." The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the *International Journal of Cardiology*.

# Discussion of Project Proposals (Draft 1)

To be discussed in class.

# Brief discussion of Rosenbaum Chapter 6

Quasi-Experimental Designs and the use of Two Control Groups

- What was the most **important** thing you learned from reading Chapter 6?
- What was the **muddiest**, least clear thing that arose in your reading?

# Next Week (Class 6: 2025-02-20)

Recorded Session

- Rubin 2001 discussion (bulk of the recorded materials)
- Rubin's Rules in Context
    - toy, lindner and dm2200 examples

Zoom Call and Reminders

- Discussion of Austin and Mamdani case study (2006)
- Kubo 2020 as an example of OSIA
- Review of OSIA selections (due Wednesday 2025-02-19 at noon)
- Lab 2 due to Canvas at 9 AM on Thursday 2025-02-20
- We'll next discuss Rosenbaum in Class 08.