CLEAR Center-PM&R Journal
Methods Webinar Series

Methods for Dealing with Confounding in Observational Studies: Propensity Scores

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Propensity scores

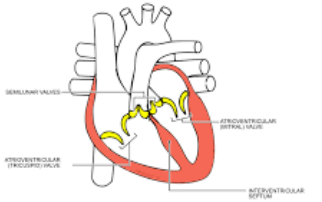
- A data compression technique specifically for confounders

Why propensity scores?

- Observational treatment studies are limited by the lack of randomization.
  - Factors that affect treatment selection also affect outcomes (confounding by indication).
- Propensity scores aim to address this treatment selection bias.

Example 1: Ross procedure vs. mechanical valves

- Retrospective cohort study comparing two treatments for aortic valve replacement: Ross procedure (autograft) versus mechanical valve (with optimal anticoagulation therapy).
- Outcome: late survival
- Previous studies had suggested a survival advantage for Ross patients, but could not rule out bias due to patient selection.
  - Those selected for the Ross procedure tend to be younger and in better physical condition.



[1]Mokhles MM, Körtke H, Stierle U, et al. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. *Circulation* 2011;123:31-38.

Treatment groups differ greatly!

Examples of imbalances, from Table 1:

Table 1. Baseline Characteristics: Unmatched Cohort

Covariates	Mechanical AVR (n=406)	Ross Procedure (n=918)	*P*
Male gender, n (%)	310 (76.4)	691 (75.3)	0.672
Mean age at surgical intervention, y	**49.5±10.3**	**41.6±11.0**	**<0.001**
Cause, n (%)			
Rheumatic	23 (5.7)	37 (4.0)	0.054
Missing	58 (14.3)		
Calcified/degenerative	**311 (76.6)**	**333 (36.3)**	**<0.001**
Preoperative DM, n (%)	20 (4.9)	26 (2.8)	0.055
Preoperative hypertension, n (%)	**161 (39.7)**	**245 (26.7)**	**<0.001**
Concomitant CABG, n (%)	**145 (35.7)**	**38 (4.1)**	**<0.001**

●AVR indicates aortic valve replacement; NYHA, New York Heart Association; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; CABG, coronary artery bypass grafting; and MV, mitral valve.

Example 2: rehabilitation vs. no rehabilitation post-stroke

- Retrospective cohort study comparing rehabilitation in nursing homes versus no rehabilitation for stroke patients
- Outcome: community discharge; functional status
- Patients who receive rehabilitation have better outcomes than those who do not receive rehabilitation, but they are also less disabled, better insured, and have more social support at baseline.
  - Does the rehabilitation itself improve outcomes or would these patients have done well regardless?

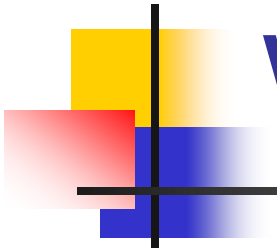
Murray PK, Dawson NV, Thomas CL, Cebul RD. Are we selecting the right patients for stroke rehabilitation in nursing homes? *Arch Phys Med Rehabil* 2005;86:876-880.

Traditional ways to control for these confounders...

- Stratification
- Matching
- Statistical adjustment

Issues with these methods...

- Stratification
  - How can we stratify on so many confounders?
- Matching
  - How can we match on so many confounders?
- Statistical adjustment
  - Groups may simply be incomparable.
  - High chance of residual confounding.
  - Cannot control for 24 confounders when there are only 36 events (36 deaths)!



With propensity scores...

- Stratification
  - Easy to stratify on a single number!
- Matching
  - Easy to match on a single number!
- Statistical adjustment
  - Easy to adjust for a single number, even if event rate is low!

Propensity scores

- In a randomized trial, all participants have the same probability of receiving each treatment.
- In an observational study, participants vary in these probabilities.
  - Propensity scores estimate these probabilities for each individual, given their covariates (clinical, social, demographic characteristics).

Propensity scores

- The propensity score is the probability of receiving a treatment given one's covariates:
  - P (treatment A / covariates)
- For example, a young patient in good physical condition might have a 70% chance of receiving a Ross procedure; an older patient in poor physical condition might have a 30% chance.

70% chance of Ross procedure

30% chance of Ross procedure

Propensity scores

- Propensity scores are estimated using logistic regression:

  Logit (treatment A) = intercept + covariate 1 + covariate 2 + covariate 3 + covariate 4...
- Yields a predicted probability of treatment A for each individual.
- Reduces a large number of covariates to a single number (a probability).

Propensity scores

- Patients with similar propensity scores are comparable, even if they vary greatly in their underlying characteristics.
  - If a patient with a 70% propensity score received the Ross procedure and another with a 70% propensity score received a mechanical valve, then, in theory, any difference in outcome can be attributed to the treatment rather than to patient selection.

70% chance of Ross procedure; and <u>HAD ROSS PROCEDURE</u>

VS.

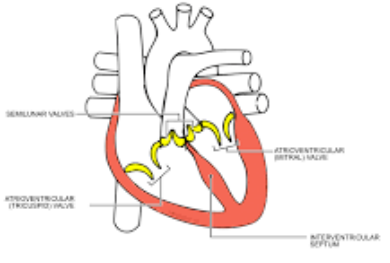
70% chance of Ross procedure; and <u>HAD MECHANICAL VALVE</u>

Propensity scores vs. Randomization

- Matching or stratifying participants based on propensity scores yields treatment groups that are balanced with respect to *measured* covariates.
- Randomization yields treatment groups that are balanced with respect to *measured and unmeasured* covariates.
- Propensity scores do not eliminate unmeasured or residual confounding!

Building the propensity score model

- Logit (Ross Procedure) = intercept + preoperative LVESD + preoperative creatinin + age + concomitant CABG + mixed valve disease + gender +...
- Included 23 predictors



Building the propensity score model

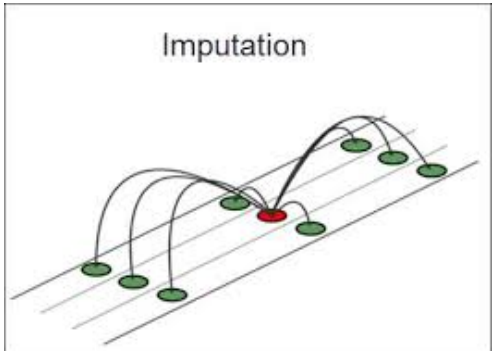
- Logit (Rehabilitation) = intercept + age + medicaid insurance + vision score + mood score + activities of daily living score + use of assistive devices + ...
- They used 112 predictors!

Building the propensity score model, steps

- 1. Identify potential confounders (related both to treatment and outcome).
- 2. Impute missing data.
- 3. Build a non-parsimonious model, potentially including quadratics and interactions.
- 4. Stratify or match on the resulting propensity scores; assess the balance of covariates in the treatment groups.
- 5. If balance is poor, refit the model including additional confounders or higher order terms.

Building the propensity score model: missing data

- If an individual is missing one datapoint for one covariate, they will be omitted from the logistic regression.
- Must impute missing data!
- For example, in the rehabilitation study, 7 of the 112 predictors were missing values for 0.5% to 5.5% of the sample. The authors appropriately replaced these missing values with the mean values from the non-missing data.



Building the propensity score model: fit the model

- Normal rules of model building don't apply!
  - Don't worry about parsimony
  - Don't worry about overfitting
  - Try multiple interactions and quadratic terms
- But... do consider omitting variables that are unrelated to outcomes (which cannot be confounders):
  - simulations show that including these does not improve balance or reduce bias, but may make it harder to find matches

Building the propensity score model: evaluate the model

- The model is a success if it balances the treatment groups with respect to covariates!
- If balance is not achieved, refit the logistic model.

Evaluating the propensity score model

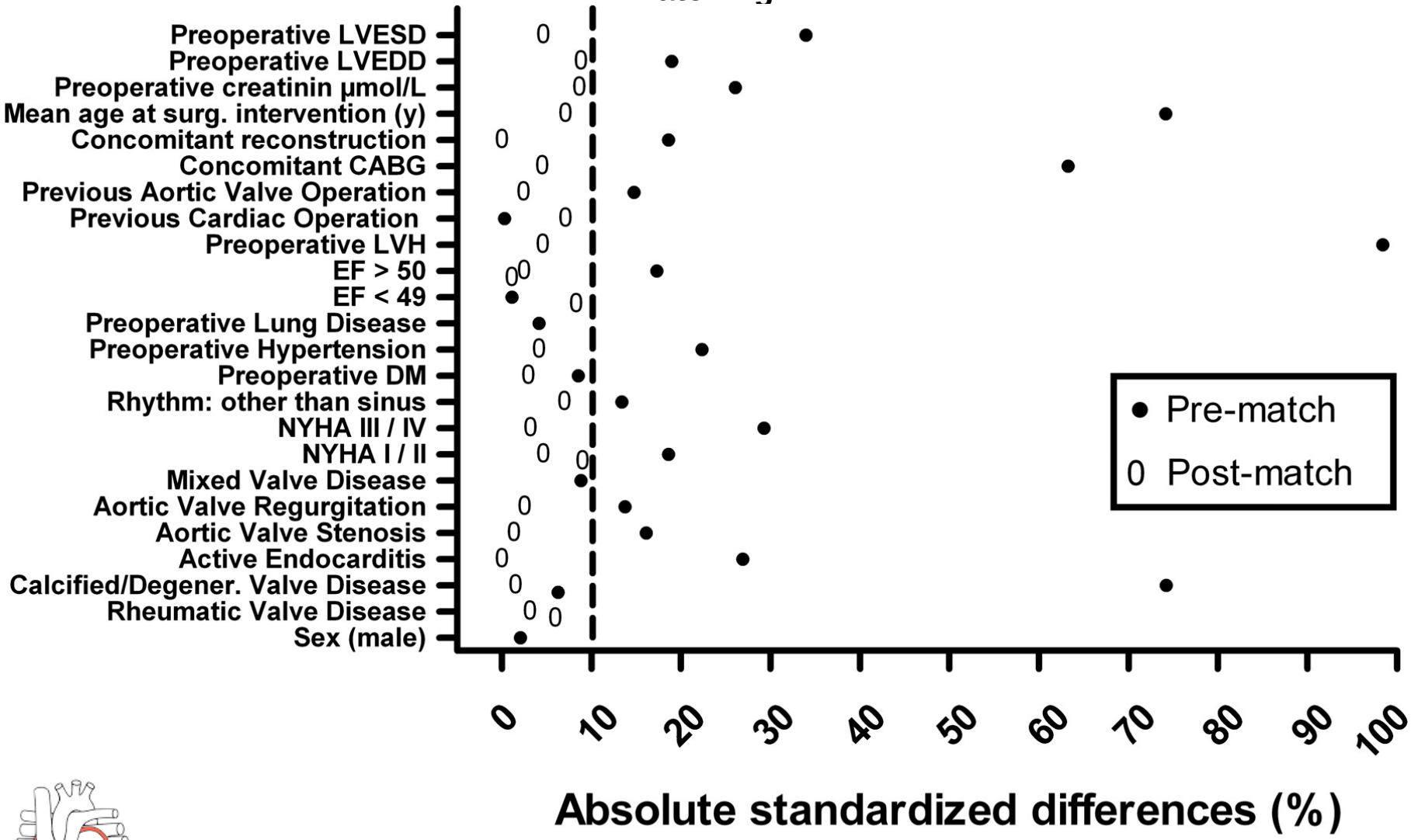
- Evaluate balance with “standardized differences” in lieu of p-value tests.
  - P-value tests depend highly on sample size.
  - A non-significant p-value does not guarantee that the groups are balanced.
- Standardized difference is the mean difference between groups expressed as the percent of 1 standard deviation.
- Standardized differences < 10% are considered balanced.

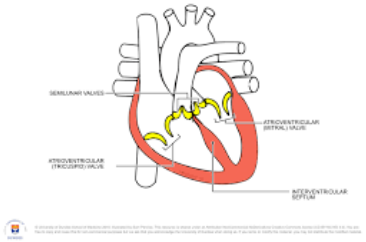
Standardized differences

- Standardized difference = $\frac{\bar{x}_1 - \bar{x}_2}{\left(\frac{s_1 + s_2}{2}\right)} x\ 100$

- Example, Ross study, unmatched cohort:
- Mean (SD) of age for Ross patients = 41.6 (11.0) years
- Mean (SD) of age for mechanical valve patients = 49.5 (10.3) years
- Average SD = 10.65 years
- Standardized difference = $\frac{49.5 - 41.6}{10.65} \times 100 = 75\%$

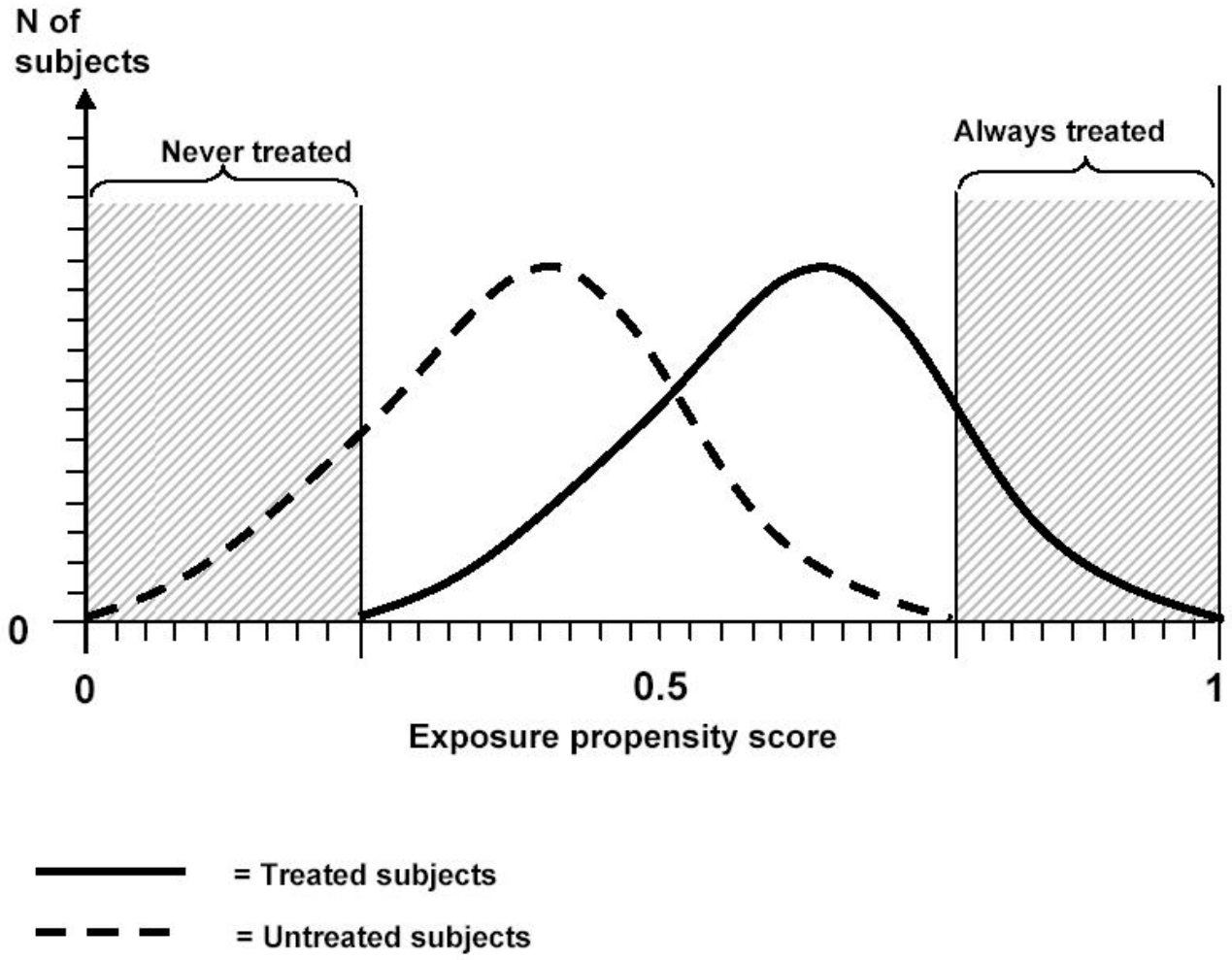
Love plots for absolute standardized differences for baseline covariates between patients with mechanical valve and patients with the Ross procedure, before and after propensity score matching.





Mokhles M M et al. Circulation 2011;123:31-38

Use of propensity scores: Evaluating overlap



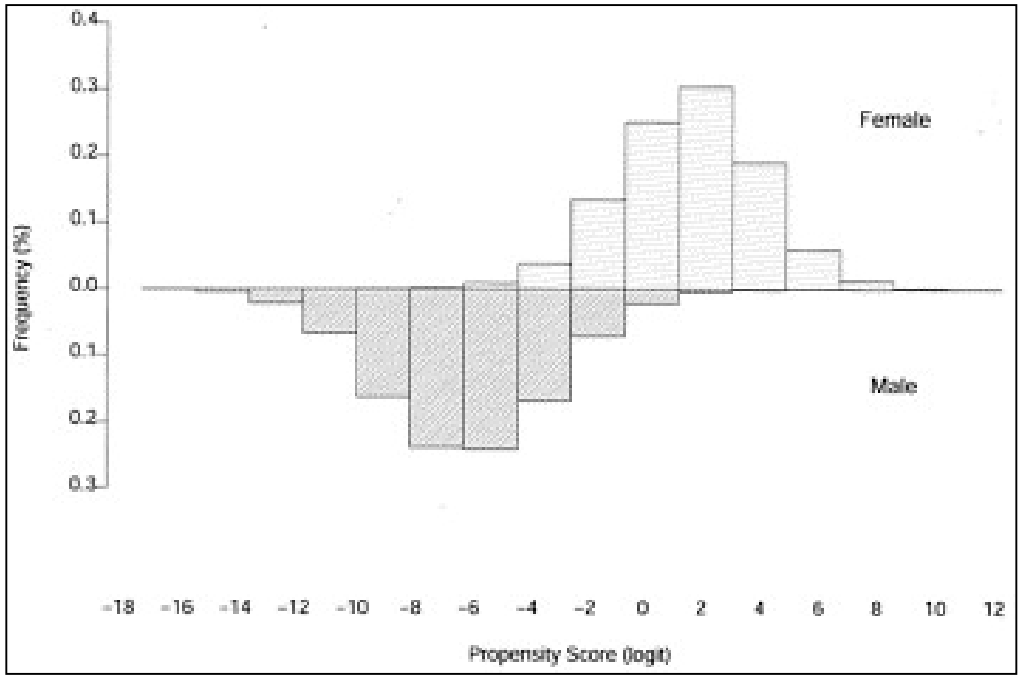
Comparing the distributions of propensity scores in different treatment groups may reveal:

-Certain subjects for whom there are no good comparators. These subjects should be excluded from the analysis.

Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol* 2006;98:253–259.

Evaluating overlap

- Propensity score distributions may reveal when patient populations are too divergent to make meaningful comparisons, e.g.:



Gorman Koch C, Khandwala F, Nussmeier N, Blackstone EH. Gender and outcomes after coronary artery bypass grafting: a propensity-matched comparison. *The Journal of Thoracic and Cardiovascular Surgery* 2003; 126: 2032-2043.

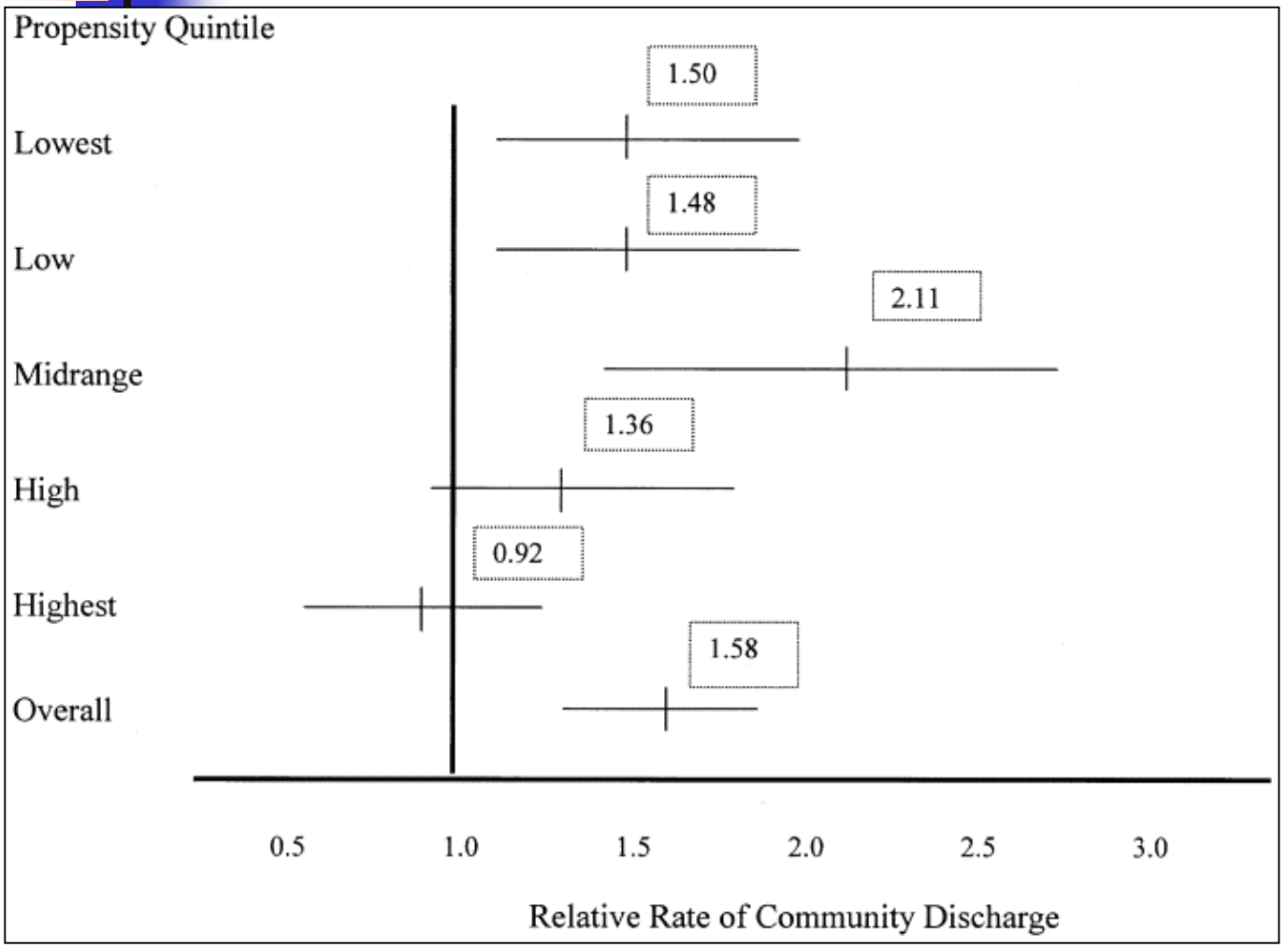
Use of propensity scores

- 1. Stratification
- 2. Matching
- 3. Statistical adjustment

1. Propensity score stratification

- Stratify on propensity score.
- E.g., in the rehabilitation study, authors stratified on quintiles of propensity score.
- Data are analyzed with Mantel-Haenzel methods for stratified data.

Propensity score stratification



Their analysis revealed a significant interaction between propensity score and treatment effect!

The summary relative rate is 1.58, but the relative rate varies significantly by propensity for treatment.

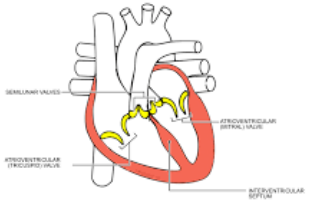
Murray PK, Dawson NV, Thomas CL, Cebul RD. Are we selecting the right patients for stroke rehabilitation in nursing homes? *Arch Phys Med Rehabil* 2005;86:876-880.

2. Propensity score matching

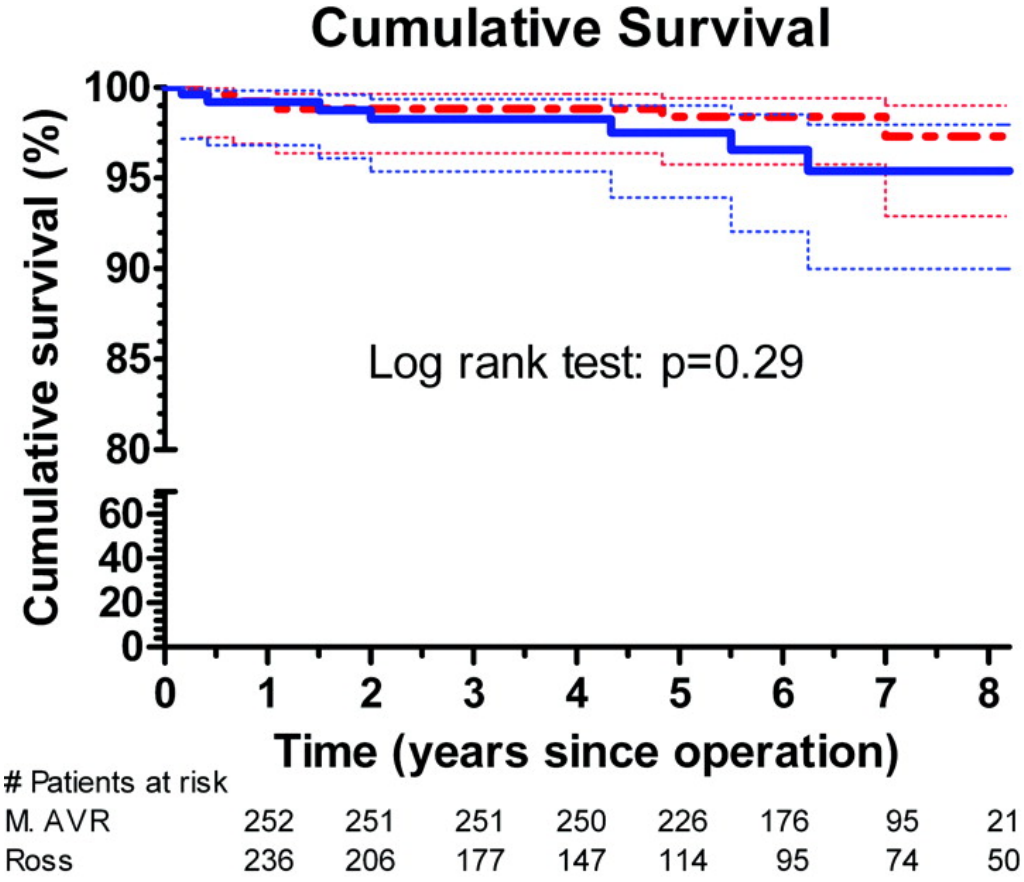
- Matching on the propensity score optimizes matching.
- Many algorithms for propensity score matching:
  - Nearest-neighbor
  - Caliper matching
  - Mahalanobis metric matching in conjunction with propensity score
  - Others...

Propensity score matching

- Nearest-neighbor method:
  - In the Ross study, authors randomly ordered the mechanical valve patients and then sequentially matched each one to the Ross patient with the closest propensity score. If no Ross patients had a propensity score within 25%, the patient was left unmatched and excluded.
  - In fact, matches could be found only for 253 of 406 mechanical valve patients.



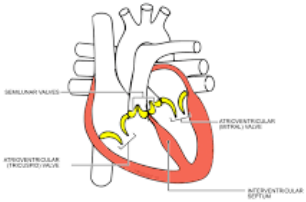
Results, matched cohort (n=253 pairs)



Mechanical AVR
with optimal anticoagulation therapy

Ross-procedure

Survival at 7 years:
Mechanical AVR: 97%
Ross procedure: 95%



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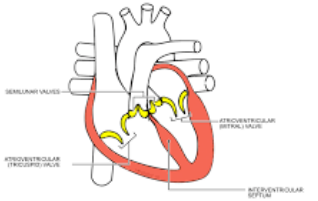
Results, matched cohort (n=253 pairs)

Table 3.
Association of Procedure With Late Mortality

	Events, n/Total Follow-Up, y			
	Mechanical Valve	Ross Procedure	Hazard Ratio (95% Confidence Interval)	*P*
After matching, n	253	253		
All-cause mortality	**5/1682**	**7/1310**	**1.86 (0.58–5.91)**	**0.29**
Valve-related mortality	0	4/1310		
Non–valve-related cardiac mortality	3/1682	1/1310		
Non–valve-related noncardiac mortality	1/1682	2/1310		
Unknown	1/1682	0		



Propensity score matching

- Tradeoff between inexact matching and incomplete matching.
  - Inexact matching increases residual confounding.
  - Incomplete matching decreases statistical power and generalizability of results.

Propensity score matching

- Matched data may be correlated and should be analyzed as matched pairs.
- There is some ongoing debate on this issue.

3. Statistical adjustment with propensity scores

- Outcome = intercept + treatment + propensity scores (+ other covariates?)

Assumptions!

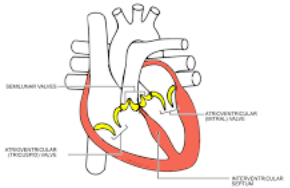
- Assumes a certain relationship between the propensity score and outcome (e.g., linear in the logit)
- Assumes no interaction between propensity score and treatment (unless you add an interaction term between PS and tx).

Statistical adjustment with propensity scores

- Is similar to adjusting for all the covariates used to calculate the propensity score.
- But...is beneficial compared with traditional adjustment when the ratio of events: confounders <10

Cox regression for mortality, Ross study (unmatched cohort)

- Ln (rate of death) = Ross (vs. mechanical valve) + propensity score
- HR = 3.64 (95% CI: 1.22 – 10.88)
- Could be driven by extreme skewness of the propensity scores in the Ross group…



Ways to address unmeasured confounding…

- Propensity score calibration
  - Collect more detailed confounder information in a subset of the sample.
  - Use this information to adjust or “calibrate” the propensity score estimates in the full set of data.
  - Use the corrected, or calibrated, propensity score for analyses of outcomes.

Summary: Advantages of propensity scores

- Focus the researcher on the problem of confounding by indication.
- Reduce a large set of confounders to a single, intuitive variable.
- Reveal subjects that cannot be compared or instances when whole groups cannot be compared.
- Make statistical adjustment possible when the number of confounders is large relative to the number of outcome events.

Summary: Disadvantages of propensity scores

- Are inferior to randomization.
- Do not solve the problems of residual and unmeasured confounding.
- May give the researcher/reader a false sense of security.
- Offer little benefit over traditional statistical adjustment when the ratio of outcomes/sample size:confounders is large.
- Are the subject of ongoing statistical debate, e.g.: “Why Propensity Scores Should Not Be Used for Matching” King and Neilson, November 2018 preprint.