Discussing and Displaying the Effectiveness of Causal Models for Observational Studies

Joint Statistical Meetings Luncheon Roundtable: August 4, 2003 from 12:30 to 1:50 PM
Renaissance Parc 55 Hotel: Barcelona Room I and II, Session 139: **ML-11**

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Abstract:
There has been rising interest in approaches designed to draw causal inferences from observational or quasi-experimental data in studies of health outcomes and policy. Causal interpretations of observed associations in such settings can be tricky, largely due to the problems of selection bias. Methodologies such as propensity scores and instrumental variables are increasingly part of the statistician's toolbox. Statisticians involved with health policy research need to communicate with an audience of physicians and other consumers, who are often skeptical of these techniques.

At this roundtable, we will discuss the role of statisticians in [1] arguing the need for appropriate methodologies for dealing with self-selection in observational studies; [2] producing effective displays for validating assumptions and documenting findings, and [3] describing an observational study's results, assumptions, caveats and conclusions accurately and usefully for a clinical or policy-oriented audience.

Arguing the Need for Dealing with Self-Selection in Observational Studies

Randomized experiments are the "gold standard" – they ensure that subjects receiving different exposures are comparable. Yet, we cannot always do experiments – exposures may be harmful, controlled by a systemic process that will not yield control, beyond reach legally or financially. We're frequently interested in phenomena that do not lend themselves to randomized trials. Such trials often have limited external validity as well – due in many cases to exclusion criteria, and other phenomena that limit our ability to study "entrenched practices".

In an observational study concerning exposures and their effects, the researcher does not control the assignment of exposures. Despite this, we want to be able to compare groups who "looked similar" prior to exposure assignment – thus, analytical adjustments are need to account for baseline differences in covariates. A study is biased if the exposed and unexposed groups differ in ways that matter for the outcomes of interest. We need to think hard about how exposure was determined.

Patients who receive an exposure are usually different from patients who don't receive it in important ways. We capture reasons behind exposure assignment in covariates, then adjust for covariate differences in estimating effects on outcomes.

> "… the elucidation of causal relationships from observational studies must be shaped by knowledge (or assumptions) about how the data were generated; ***such assumptions are crucial to causal inference***."
>
> - Judea Pearl (2001) *HS&ORM*

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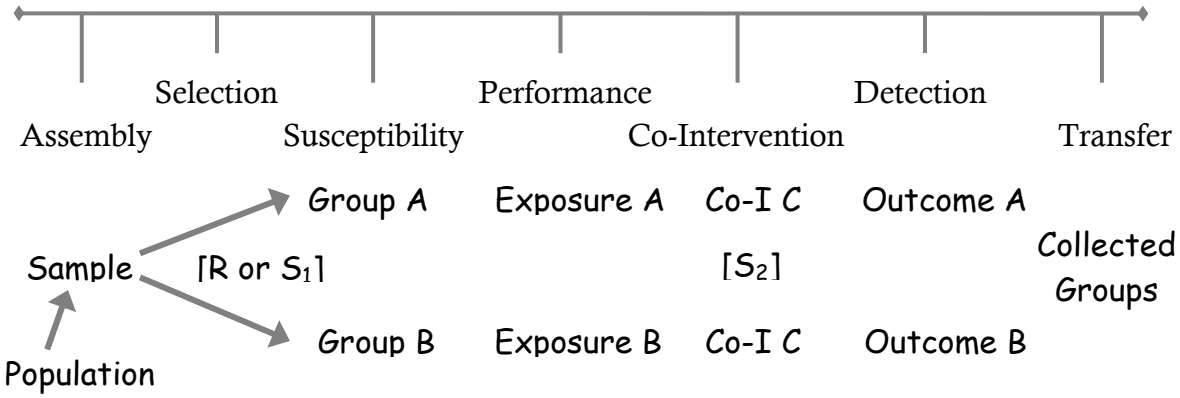
Seven Key Aspects of Research Architecture: Judgments About Causation

(**Feinstein Model** for the evaluation of the scientific quality of cause-effect research, as modified by Neal V. Dawson, MD nvd@cwru.edu)

Goal: Comparability of the Groups Who Did and Did Not Receive the Exposure of Interest (Except for the Actual Receipt of Exposure)



1. **Distorted Assembly**: The sample should reflect the population to which results will be generalized. Application of specific inclusion/exclusion criteria will determine the pool of baseline characteristics of the sample.
2. **Selection Bias**: Bias can occur when subjects are selected to receive an exposure or co-intervention – especially when exposure is based on baseline covariates, and covariates are related to different likelihoods of outcome. Unmeasured covariates may or may not also be associated with measured characteristics.
3. **Susceptibility Bias / Case Mix / Severity**: Comparability of baseline characteristics of the exposure groups – are there importantly different expectations at baseline of the outcome of interest.
4. **Performance Bias**: How "well" do patients receive exposures (i.e. differences in dosage schedules, compliance rates, etc.)
5. **Co-Interventions** (Another Opportunity for Selection): Additional (medical) interventions beyond the exposure of interest that may influence the likelihood of achieving the outcome.
6. **Outcome Bias**: Process for determining the status of the outcome of interest in each group is applied unequally – differences in surveillance, diagnostic interpretation or testing, etc.
7. **Transfer Bias**: Members of the original or complete cohorts of A and B may be lost to dropout, intra-study exclusions, crossover, during statistical manipulations, etc.

"*Care in design and implementation will be rewarded with useful and clear study conclusions… Elaborate analytical methods will not salvage poor design or implementation of a study.*"

- National Academy of Sciences Report (Meyer and Feinberg 1992, p. 106)

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The **standard ANCOVA procedure for mitigating selection bias**: (***Risk Adjustment***)

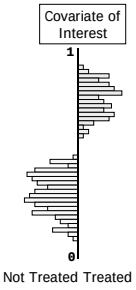
1. Capture as many important variables as possible and include them in the model, along with an indicator I_T or whether or not the subject received the treatment.
2. Identify the coefficient of the I_T indicator as a measure of the risk-adjusted "association" between receipt of treatment and the outcome.
3. Discuss and evaluate alternative explanations for the observed association other than "causality".

There is a clear need to …

> *"move beyond these informal techniques (that often perform well in the hands of 'master users') to established conceptual frameworks and "user-friendly" protocols."*
>
> –Ash, Normand, Duan (2001) *HS&ORM*

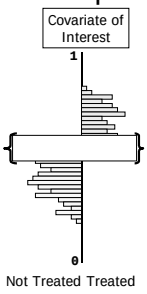
Validating Assumptions: The Issue of Overlap

How Much Overlap In The Covariates Do We Want?



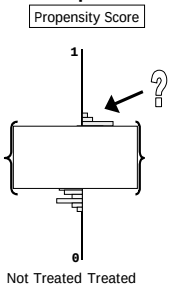
- If those who receive treatment don't overlap (in terms of covariates) with those who receive the control, we've got nothing to compare.
- Modeling, no matter how sophisticated, can't help us to develop information out of thin air.

What if Treated and Untreated Groups Overlap, but minimally?



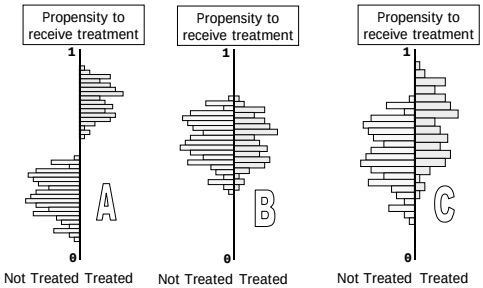
- No help.
- The information available to infer treatment effect will reside almost entirely in the few patients who overlap.
- Need to think hard about whether useful inferences will be possible.

What if Treated and Untreated Groups Don't Overlap Completely?



- Inferences for the causal effects of treatment on the subjects with no overlap cannot be drawn without heroic modeling assumptions.
- Usually, we'd exclude these treated subjects, and explain separately.

How Much Overlap In The Propensity Scores Do We Want?



Aspirin Use and Mortality Example from Gum et al. (2001) *JAMA*

Aspirin Use and Mortality

- 6174 consecutive adults undergoing stress echocardiography for evaluation of known or suspected coronary disease.
- 2310 (37%) were taking aspirin (treatment).
- Main Outcome: all-cause mortality
- Median follow-up: 3.1 years
- Univariate Analysis: 4.5% of aspirin patients died, and 4.5% of non-aspirin patients died…
- Unadjusted Hazard Ratio: 1.08 (0.85, 1.39)

Gum PA et al. (2001) *JAMA*, 1187-1194.

What Would Be Relevant Covariates for Adjustment?

- Demographics (Age, Sex)
- Cardiovascular risk factors
- Coronary disease history
- Use of other medications
- Ejection fraction
- Exercise capacity
- Heart rate recovery
- Echocardiographic ischemia

Result of adjusting for these factors: Aspirin use now associated with reduced mortality: Hazard Ratio: 0.67 95% CI: (.51, .87) p = .002

Baseline Characteristics According to Aspirin Use (before matching)

Variable	Aspirin* (n = 2310)	No Aspirin* (n = 3864)	P value
Age, years	62 (11)	56 (12)	< .001
Body mass index, kg/m^2	29 (5)	30 (7)	< .001
Ejection fraction, %	50 (9)	53 (7)	< .001
Resting heart rate, beats/min	74 (13)	79 (14)	< .001
Resting systolic BP, mm Hg	141 (21)	138 (20)	< .001
Resting diastolic BP, mm Hg	85 (11)	86 (11)	.04
Heart rate recovery, beats/min	28 (11)	30 (12)	< .001
Peak exercise cap., men (METs)	8.6 (2.4)	9.1 (2.6)	< .001
Peak exercise capacity, women	6.6 (2.0)	7.3 (2.1)	< .001

*Cells contain mean (SD)

Baseline Characteristics By Aspirin Use (in %) (before matching)

Variable	Aspirin (n = 2310)	No Aspirin (n = 3864)	P value
Men	77.0	56.1	< .001
Clinical history: diabetes	16.8	11.2	< .001
hypertension	53.0	40.6	< .001
prior coronary artery disease	69.7	20.1	< .001
congestive heart failure	5.5	4.6	.12
Medication use: Beta-blocker	35.1	14.2	< .001
ACE inhibitor	13.0	11.4	< .001

- Baseline characteristics appear very dissimilar: 25 of 31 covariates have p < .001, 28 of 31 have p < .05.
- Aspirin user covariates indicate higher mortality risk.

Baseline Characteristics According to Aspirin Use (after matching)

Variable	Aspirin* (n = 1351)	No Aspirin* (n = 1351)	P value
Age, years	60 (11)	61 (11)	.16
Body mass index, kg/m^2	29 (6)	29 (6)	.83
Ejection fraction, %	51 (8)	51 (9)	.65
Resting heart rate, beats/min	77 (13)	76 (14)	.13
Resting systolic BP, mm Hg	141 (21)	141 (21)	.68
Resting diastolic BP, mm Hg	85 (11)	86 (11)	.57
Heart rate recovery, beats/min	28 (12)	28 (11)	.82
Peak exercise cap., men (METs)	8.7 (2.5)	8.3 (2.5)	**.01**
Peak exercise capacity, women	6.5 (2.0)	6.7 (2.0)	.13

*Cells contain mean (SD)

Baseline Characteristics By Aspirin Use [%] (after matching)

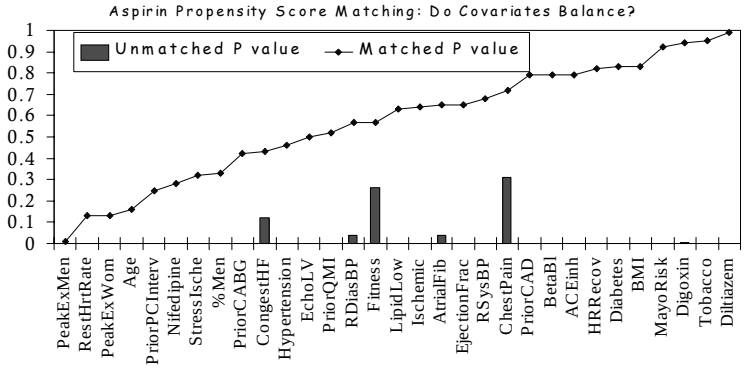
Variable	Aspirin (n = 1351)	No Aspirin (n = 1351)	P value
Men	70.4	72.1	.33
Clinical history: diabetes	15.0	15.3	.83
hypertension	50.3	51.7	.46
prior coronary artery disease	48.3	48.8	.79
congestive heart failure	5.8	6.6	.43
Medication use: Beta-blocker	26.1	26.5	.79
ACE inhibitor	15.5	15.8	.79

- Baseline characteristics similar in matched users and non-users.
- 30 of 31 covariates show NS difference between matched users and non-users. [Peak exercise capacity for men is p = .01]

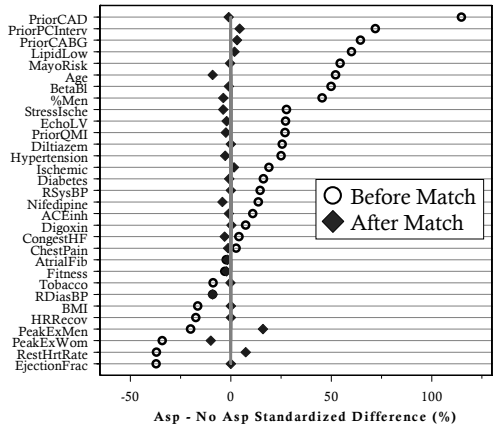
Displays for Validating Assumptions: Covariate Balance After Adjustment

Are The Covariates Balanced?
"P values Plot"

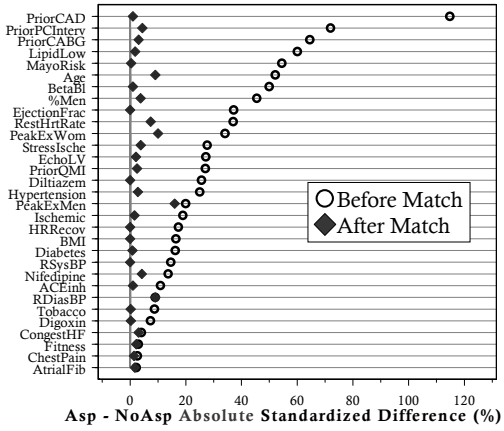
31 covariates provided in paper's Tables.



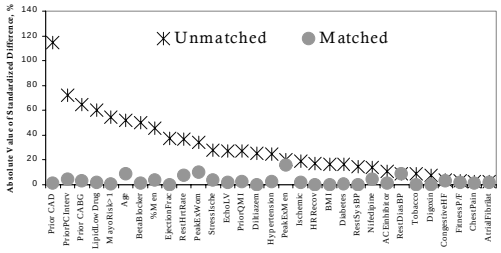
Covariate Balance for Aspirin Study



Absolute Standardized Differences



Covariate Balance for Aspirin Study



Absolute Value of Standardized Difference
plotted for 31 covariates (in Excel).

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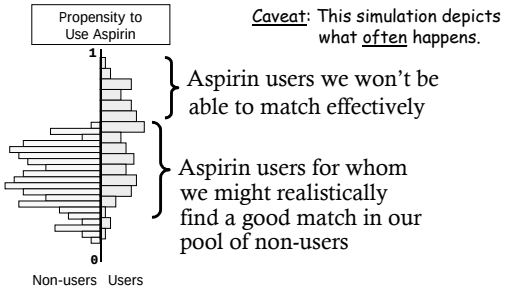
Who's Getting Matched Here?

Where Do The Propensity Scores Overlap?



Which Aspirin Users Get Matched?

- 652 of the 1351 matched aspirin users had had prior coronary artery disease (48.3%).
- 957 of the 959 unmatched aspirin users had had prior coronary artery disease (99.8%).

Variable	% of Matched	% of Unmatched	Stdzd Diff
Prior CAD	48.3	99.8	-145
Prior PCI	12.3	52.2	-95
Lipid-low th	20.8	51.5	-68
Prior CABG	18.6	45.7	-61
β-blocker	26.1	47.9	-46
Tobacco	11.9	7.3	+16

Describing the Results of an Observational Study Accurately and Usefully

Rosenbaum's Four Specific Suggestions (2002 book, p. 368)

- Design Observational Studies
  - Exert as much experimental control as possible, carefully consider the selection process, and anticipate hidden biases.
- Focus on Simple Comparisons
  - Increase impact of results on consumers
- Compare Subjects Who Looked Comparable Prior to Treatment
- Use Sensitivity Analyses to Inform Discussions of Hidden Bias Due to Unobserved Covariates
  - **Sensitivity analysis** asks how much hidden bias would need to be present to explain the differing outcomes in the exposed and control groups.

What Should Always Be Done in an Observational Study and Often Isn't

- Collect data so as to be able to model selection
- Demonstrate selection bias
- Ensure covariate overlap for comparability
- Evaluate covariate balance after adjustment
- Specify relevant post-adjustment population with care
- Model or estimate treatment effect in light of selection bias adjustments
- Estimate sensitivity of results to potential hidden biases

On Instrumental Variables vs. Propensity Methods vs. "Standard Risk Adjustment"

IV analysis has a long history in economics, where we are often facing "weak" data. The methods are attractive because they mirror RCT – instrument should adjust for both overt and hidden biases, and the resulting local average treatment effect estimates are sometimes more interesting than estimates from propensity models. It remains awfully difficult to justify the IV assumptions, although some specific examples (noncompliance in randomized trials) look well-suited to instruments. See

the Special Issue of HS&ORM described on page 10 of this handout for more details and comparisons (especially the Landrum/Ayanian and Posner et al. articles).

A Partial Bibliography

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Causation, Confounding and The Role of Observational Studies

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Special Issue of Health Services & Outcomes Research Methodology

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