EPID 765

Pharmacoepidemiology

Lesson 15:
Variability in Treatments & Variable Selection

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Variability in Treatments

- Predictable?
  - No
  - Yes (but: do we want/need to?)
- Affected by risk factors for outcome?
  - No — The GOOD,
  - Yes -> confounding
    - Measured — the BAD,
    - Unmeasured
      - Known — and the UGLY
      - Unknown

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Conditioning on IVs is Bad

- Removes "good" variability
- Increases variance of effect estimates
- Leads to bias amplification

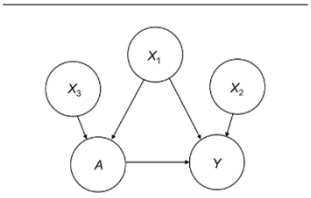

FIGURE 1. Causal diagram for simulation experiment 1.

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Conditioning on IVs

TABLE 1. Simulation experiment 1, with results based on an analysis in which the propensity score is entered into an outcome model as a parametric spline term[a]

	Variable(s) in propensity score model							
	X_1	X_2	X_3	X_1, X_2	X_1, X_3	X_2, X_3	X_1, X_2, X_3	None
$n = 500$								
Bias × 10^1	−0.03	5.97	7.34	−0.03	−0.07	7.38	−0.06	5.94
Var × 10^1	0.32	0.22	0.46	0.22	0.44	0.36	0.31	0.39
MSE × 10^1	0.32	3.79	5.85	0.22	0.44	5.77	0.31	3.92
Average *c* statistic	0.67	0.52	0.76	0.67	0.82	0.76	0.82	
$n = 2{,}500$								
Bias × 10^1	0.00	5.93	7.33	−0.01	−0.04	7.33	−0.03	5.95
Var × 10^2	0.66	0.53	0.96	0.49	0.89	0.79	0.69	0.80
MSE × 10^2	0.66	35.65	54.72	0.49	0.89	54.56	0.70	36.16
Average *c* statistic	0.67	0.51	0.76	0.67	0.81	0.76	0.81	

[a] The table shows the estimated bias, variance (Var), and mean squared error (MSE) of all possible estimators and the average *c* statistic for the corresponding propensity score model.

Brookhart et al. Variable Selection for Propensity Score Models. AJE 2006 – note: bias amplification not discussed!

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Conditioning on IV in Practice

Table 3. Effect of outcome-association cut-point used as variable selection criterion

Model	PS Characteristics		Outcome effect estimate[1]	
	N covariates	C statistic	Estimate	HR
Mortality				
Non-parsimonious	202	0.91	−0.18	0.83
Outcome +/− 5%	181	0.91	−0.20	0.82
Outcome +/− 7.5%	172	0.90	−0.21	0.81
Outcome +/− 10%	163	0.90	−0.21	0.81
Outcome +/− 12.5%	157	0.90	−0.22	0.81
Outcome +/− 15%	151	0.90	−0.22	0.80
Outcome +/− 17.5%	149	0.90	−0.22	0.81
Outcome +/− 20%	144	0.90	−0.20	0.82
+ glaucoma diagnosis				
Outcome +/− 20%	143	0.82	−0.18	0.84
Outcome +/− 22.5%	139	0.81	−0.17	0.84
Outcome +/− 25%	135	0.81	−0.17	0.84
Outcome +/− 27.5%	130	0.81	−0.18	0.83
Outcome +/− 30%	127	0.81	−0.19	0.83

Table 3. Effect of outcome-association cut-point used as variable selection criterion

Model	PS Characteristics		Outcome effect estimate[1]	
	N covariates	C statistic	Estimate	HR
Hip fracture				
Non-parsimonious	201	0.91	−0.32	0.72
Outcome +/− 5%	177	0.90	−0.37	0.69
Outcome +/− 7.5%	170	0.90	−0.36	0.70
Outcome +/− 10%	160	0.90	−0.36	0.70
Outcome +/− 12.5%	151	0.90	−0.37	0.69
Outcome +/− 15%	146	0.90	−0.38	0.68
Outcome +/− 17.5%	137	0.89	−0.37	0.69
Outcome +/− 20%	121	0.89	−0.37	0.69
+ glaucoma diagnosis				
Outcome +/− 20%	120	0.81	−0.27	0.76
Outcome +/− 22.5%	108	0.81	−0.31	0.74
Outcome +/− 25%	100	0.81	−0.28	0.75
Outcome +/− 27.5%	91	0.80	−0.35	0.71
Outcome +/− 30%	87	0.80	−0.35	0.71

Patrick et al. The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. PDS 2011

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Emerging Therapies

- Is calendar time a confounder/proxy for confounder?
  - Yes (e.g., stage shift, surgery technique)
    - The BAD: condition on calendar year
    - Consider calendar-time specific PS
  - No
    - The GOOD: Do not condition on calendar year
    - Consider using calendar time as IV
- Not an easy decision (do both?)

CER of oxaliplatin vs. 5-FU in patients with stage III colon cancer
Mack et al. PDS 2013, Epidemiology 2016

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Emerging Therapies

Table 1. Baseline Demographic Characteristics for the IMRT vs CRT Comparison

Characteristics	Before Propensity Weighting	
	IMRT (n = 6666)	CRT (n = 6310)
Year of radiation		
2002	448 (6.7)	2402 (38.1)
2003	917 (13.8)	1846 (29.3)
2004	1334 (20.0)	1149 (18.2)
2005	1841 (27.6)	601 (9.5)
2006	2126 (31.9)	312 (4.9)

Intensity Modulated Radiation Therapy vs. Conformal Radiation Therapy; Sheets et al. JAMA 2012

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High Dimensional Propensity Score

- Data driven approach for covariate creation and selection
- Developed and applied in claims data
- Each code is a potential covariate
- Codes with a prev >2% (<98%) are retained
- Estimate association with treatment and outcome (conditioning on treatment)
- Calculate confounding using Bross equation
- Rank according to magnitude of confounding
- Select certain number of codes into PS
  - Within and across data dimensions

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Bross Confounding Equation

$$ARR = RR \times \frac{P_{C1}(RR_{CD}-1)+1}{P_{C0}(RR_{CD}-1)+1}, \text{ if } RR_{CD} \geq 1$$

$$ARR = RR \times \frac{P_{C1}(\frac{1}{RR_{CD}}-1)+1}{P_{C0}(\frac{1}{RR_{CD}}-1)+1}, \text{ if } RR_{CD} < 1$$

Bross IDJ. Spurious effects from an extraneous variable. J Chron Dis 1966 – notation from Schneeweiss et al

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High Dimensional Propensity Score

- Has been shown empirically to often outperform investigator specified variable sets
- Is highly likely to include IVs and colliders
- Can perform worse than investigator specified variable sets with rare outcomes
  - Add hdPS to investigator specified variable sets!
- Is a great tool to learn more about data
  - Data errors
  - Indications/contraindications/required tests
- Should only be used in addition to rather than to replace investigator specified variable sets
- Does NOT control for unmeasured confounding!

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Variable Selection

Recent theoretical studies have shown that conditioning on an instrumental variable (IV), a variable that is associated with exposure but not associated with outcome except through exposure, can increase both bias and variance of exposure effect estimates. Although these findings have obvious implications in cases of known IVs, their meaning remains unclear in the more common scenario where investigators are uncertain whether a measured covariate meets the criteria for an IV or rather a confounder. The authors present results from two simulation studies designed to provide insight into the problem of conditioning on potential IVs in routine epidemiologic practice. The simulations explored the effects of conditioning on IVs, near-IVs (predictors of exposure that are weakly associated with outcome), and confounders on the bias and variance of a binary exposure effect estimate. The results indicate that effect estimates which are conditional on a perfect IV or near-IV may have larger bias and variance than the unconditional estimate. However, in most scenarios considered, the increases in error due to conditioning were small compared with the total estimation error. In these cases, minimizing unmeasured confounding should be the priority when selecting variables for adjustment, even at the risk of conditioning on IVs.

- The final word for PE based on claims data?
- What about DAGs (see Pearl commentary)?
- What about non-claims data?

Myers et al. Effects of Adjusting for Instrumental Variables on Bias and Precision of Effect Estimates. AJE 2011

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