Slide 1

EPID 765

Pharmacoepidemiology

Lesson 14:
Patients Treated Contrary to Prediction

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Slide 2

Approaches to Reduce Unmeasured Confounding

- Active comparator, new user design (equipoise)
- Instrumental variables
- Internal validation study (e.g., linkage to EHR)
- External validation study (e.g., PSC, 2-stage)
- Additional restrictions on measured covars
  - DPP4 vs. TZD: Restrict to patients without CHF or on first line treatment (metformin)
- Restrict study population based on measure of equipoise (the estimated propensity score)

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Slide 3

Limited Equipoise in Tails of the Overlapping PS (None Outside!)

Figure 2. Distribution of the linear predictor of the propensity score among exposed and unexposed subjects, without adjustment. ——, untreated; – – –, treated.

Lunt M et al. AJE 2009

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Slide 4

Mortality in Patients with Stroke Treated Contrary to Predcition

TABLE 2. Proportion of deaths among 6,269 ischemic stroke patients registered in a German stroke registry between 2000 and 2001 who were treated or not treated with tissue plasminogen activator, according to percentiles of the propensity score for the entire study population

Percentile	Treated (n = 212)				Not treated (n = 6,057)				Empirical OR*
	Score†	No.	Deaths No.	Deaths %	Score†	No.	Deaths No.	Deaths %	
99 to 100	0.5809	36	3	8.3	0.5474	26	7	26.9	0.25
95 to <99	0.3143	73	13	17.8	0.2912	178	27	15.2	1.21
90 to <95	0.1393	55	8	14.6	0.1363	258	19	7.4	2.14
75 to <90	0.0585	31	3	9.7	0.0459	910	82	9.0	1.08
50 to <75	0.0115	10	4	40.0	0.0084	1,558	87	5.6	11.27
25 to <50	0.0017	5	2	40.0	0.0014	1,561	54	3.5	18.60
10 to <25	0.0004	2	1	50.0	0.000267	940	36	3.8	25.11
5 to <10	0	0	0	0	0.000066	313	6	1.9	
1 to <5	0	0	0	0	0.000027	251	8	3.2	
0 to <1	0	0	0	0	0.000007	62	1	1.6	
Overall	0.2521	212	34	16.0	0.0262	6057	327	5.4	3.35

* Propensity-stratum-specific-treatment–mortality odds ratio.
† Mean propensity score in percentile.

Kurth et al., AJE 2006

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Mortality in Patients with RA Treated Contrary to Predcition

Table 4. Quintile-Specific Mortality Rates

Quintile[a]	Exposed			Unexposed			Rate Ratio
	Deaths	Person-Years	Rate	Deaths	Person-Years	Rate	
1	36	1,819	19.8	16	1,762	9.1	2.18
2	52	4,168	12.5	5	285	17.6	0.71
3	57	4,704	12.1	2	141	14.2	0.85
4	66	5,080	13.0	2	63	31.9	0.41
5	93	5,467	17.0	2	28	71.5	0.24
Overall	304	21,237	14.3	27	2,279	11.8	1.21

[a] Quintile 1 is least likely to receive treatment; quintile 5 is most likely to receive treatment.
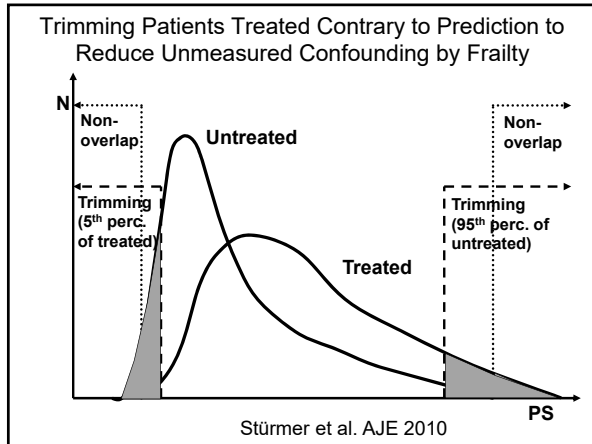
Lunt M et al., AJE 2009
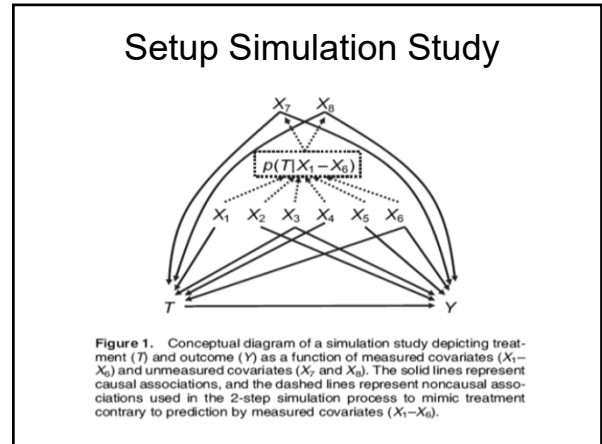
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High Mortality in Those Treated Contrary to Prediction

- Treatment withheld because of frailty?
- "Last resort" treatment because of infaust prognosis?
- Assuming frailty leads to overriding of predicted treatment decision
- Unmeasured confounding "concentrated" in the tails of the PS distribution
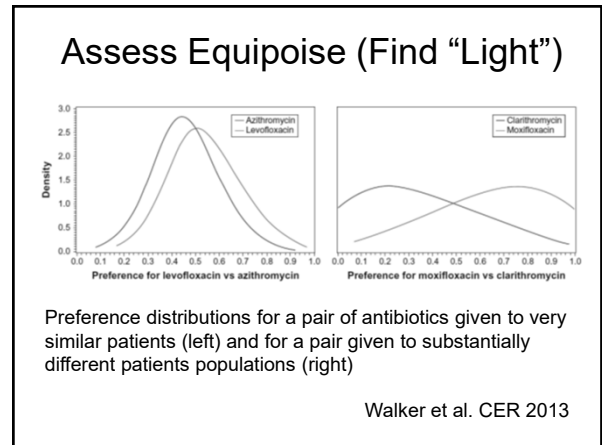- Where there is least "equipoise"

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Slide 7

Trimming Patients Treated Contrary to Prediction to Reduce Unmeasured Confounding by Frailty

Stürmer et al. AJE 2010

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Slide 8

Setup Simulation Study

Figure 1. Conceptual diagram of a simulation study depicting treatment (T) and outcome (Y) as a function of measured covariates (X_1–X_6) and unmeasured covariates (X_7 and X_8). The solid lines represent causal associations, and the dashed lines represent noncausal associations used in the 2-step simulation process to mimic treatment contrary to prediction by measured covariates (X_1–X_6).

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Results Simulation Study

	RR	MSE	Cov
True model	2.0	0.003	96%
Crude	2.9	0.131	0%
PS based on measured variables			
Trimming			
None	1.3	0.215	0%
1 – 99	1.5	0.084	5%
2.5 – 97.5	1.8	0.023	59%
5 – 95	2.0	0.008	93%

Results from PS matching (others similar)

Stürmer et al. AJE 2010

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Slide 10

Assess Equipoise (Find "Light")

Preference distributions for a pair of antibiotics given to very similar patients (left) and for a pair given to substantially different patients populations (right)

Walker et al. CER 2013

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Slide 11

Comparison of PS based Restrictions

C-Crump et al. 09
W=Walker et al. 13,
S=Stürmer et al. 10

L=excluded low
B=balanced
H=excluded high

Glynn RJ, Lunt M, Rothman KJ, Poole C, Schneeweiss S, Stürmer T. Propensity score trimming to balance confounders for observational comparative effectiveness research. Manuscript submitted
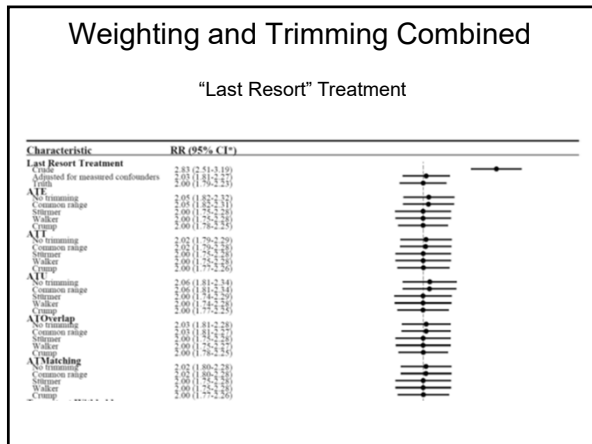
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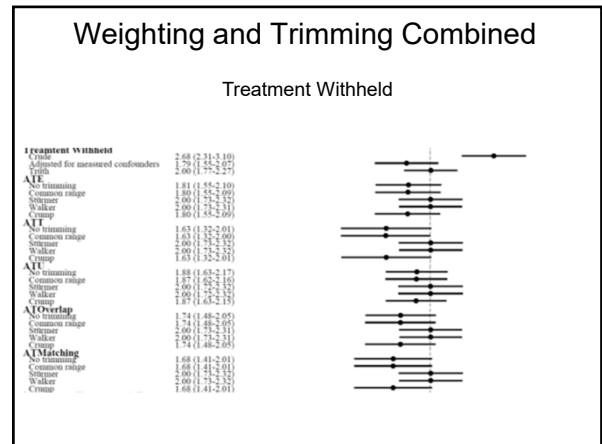
What About Matching or Overlap Weights?

Stürmer, Rothman, Ellis, Wyss, Conover, Lunt, Glynn. Comparison of Propensity Score (PS) Weighting and Trimming Strategies to Reduce Variance and Bias of Treatment Effect Estimates: a Simulation Study.[abstract] PDS 2018
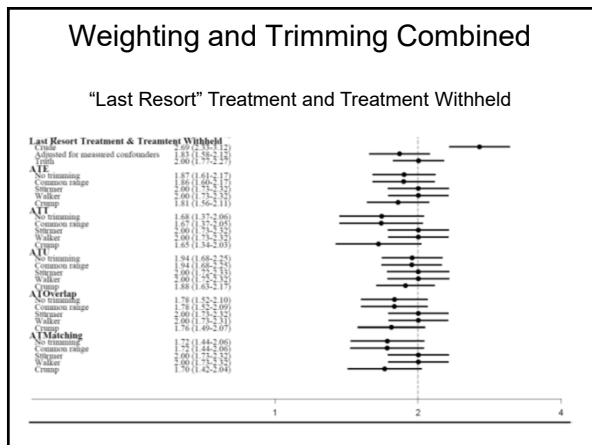
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Weighting and Trimming Combined

"Last Resort" Treatment

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Weighting and Trimming Combined

Treatment Withheld

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Weighting and Trimming Combined

"Last Resort" Treatment and Treatment Withheld

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Conclusions Populations With Equipoise

- Strong preference for one treatment akin to confounding by indication
- Treatment contrary to prediction more likely due to unmeasured factors than chance
- Restriction is a widely applied approach to control confounding in observational studies
- Focus on populations with better equipoise can help reduce unmeasured confounding
  - But change in estimate could be due to heterogeneity!
- Matching/overlap weights cannot replace trimming
- Estimation of treatment effects in appealing targets for causal inference moot if biased?
  - Or rather think of bias vs. true effect in target pop?

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