Advanced Statistical Methods for Observational Studies

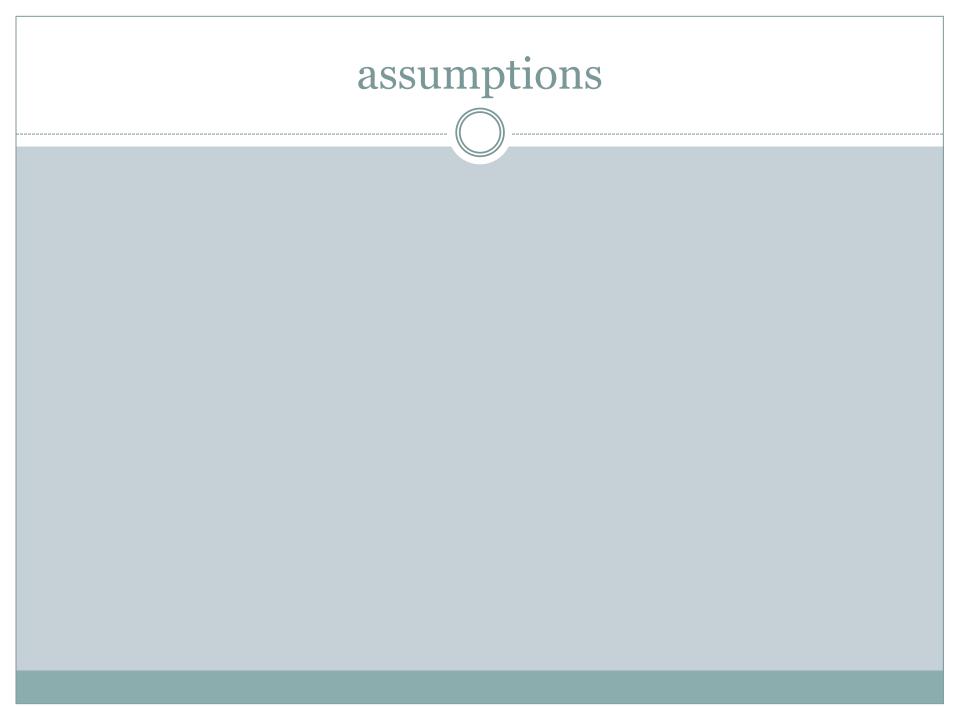
LECTURE 09

class management

- Problem Set is due Monday, June 1 by 5pm.
 - PDF it and send to Professor Baiocchi.
- If you're doing the class for three credits:
 - Create a slide deck, roughly 10 minutes worth of material.
 - Do a recording of you presenting it.
 - Send the slide deck and recording to Professor Baiocchi.
 - O Due Friday, June 12 by 5pm.

propensity score methods

THE ACHILLES HEEL



No unobserved confounders

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- Possibly even exacerbates the problem in the tails

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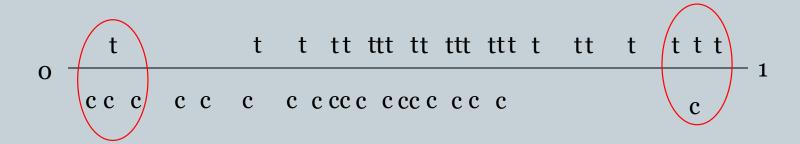
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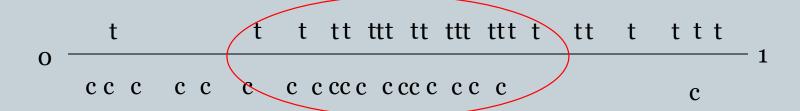
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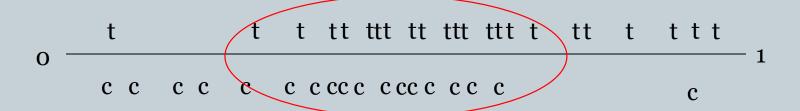


- No unobserved confounders
- Possibly even exacerbates the problem in the tails



inverse-probability weighting

- The tails are often up-weighted heavily.
- The standard errors greatly impacted by these weights.
- These tails are the most problematic for strongly ignorable treatment assignment.



<u>lecture 04</u>

naïve model: assumption one

• <u>Strongly Ignorable Treatment Assignment</u>: Those that look alike (in our data set) are alike

$$\pi_i = \Pr(Z_i = 1 | r_{Ti}, r_{Ci}, \mathbf{x}_i, u_i) = \Pr(Z_i = 1 | \mathbf{x}_i)$$

and

$$0 < \pi_i < 1$$
 for all $i = 1, 2, ..., n$

- If two subjects have the same propensity score, then their values of **x** may be different.
- By SITA, if these two subjects have the same e(x) then the differences in their x are not predictive of treatment assignment (i.e., $x \perp Z|e(x)$).
- Therefore the mismatches in **x** will be due to chance and will tend to balance. (more details)

• A version of SITA is used in regression, IPW, pscore matching... basically all methods that don't explicitly have a measurement of randomness.

real world randomness



(MAYBE)







Outcome





Outcome











2%

















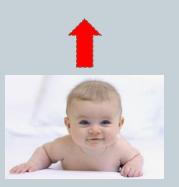




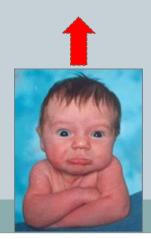


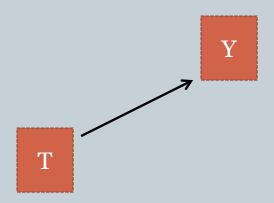


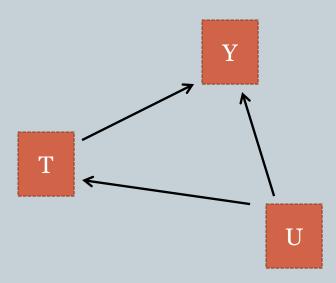


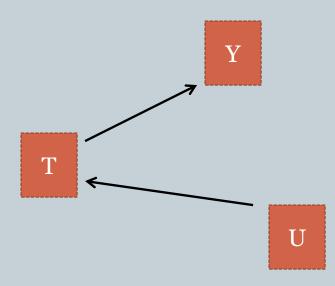


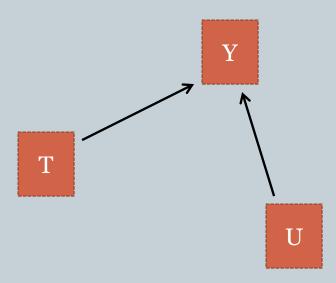


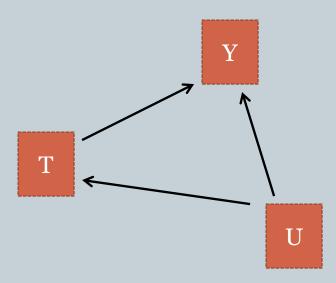


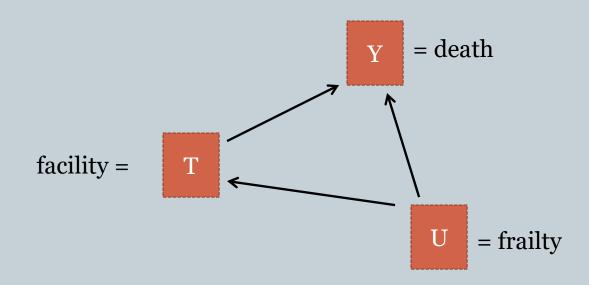




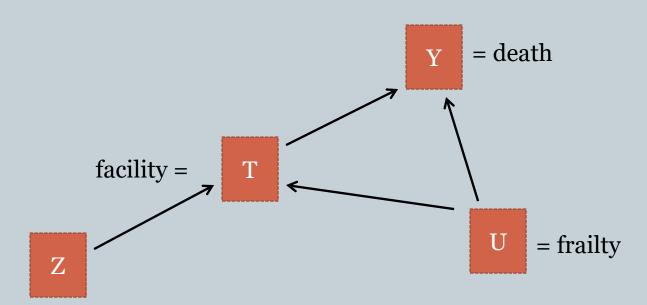




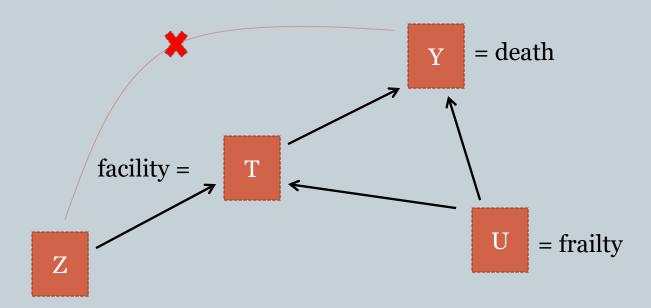




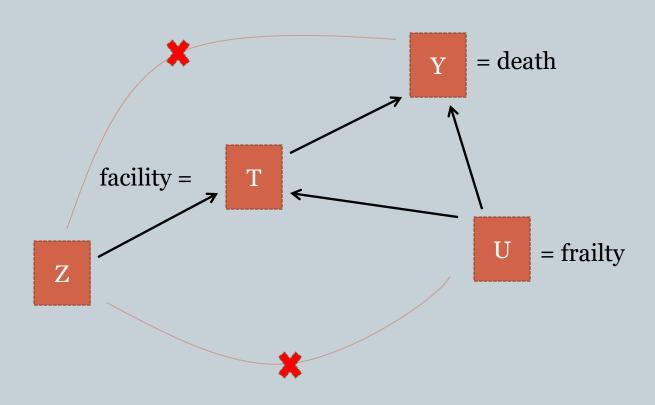
IV techniques – the idea



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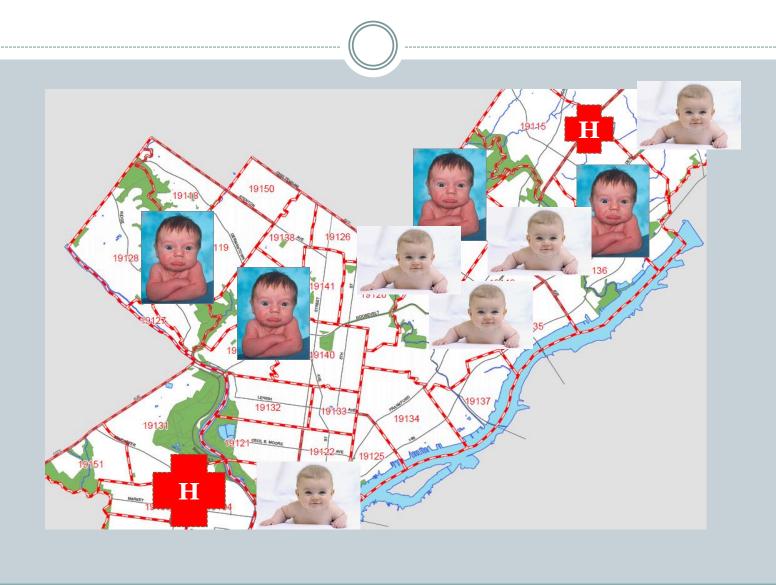


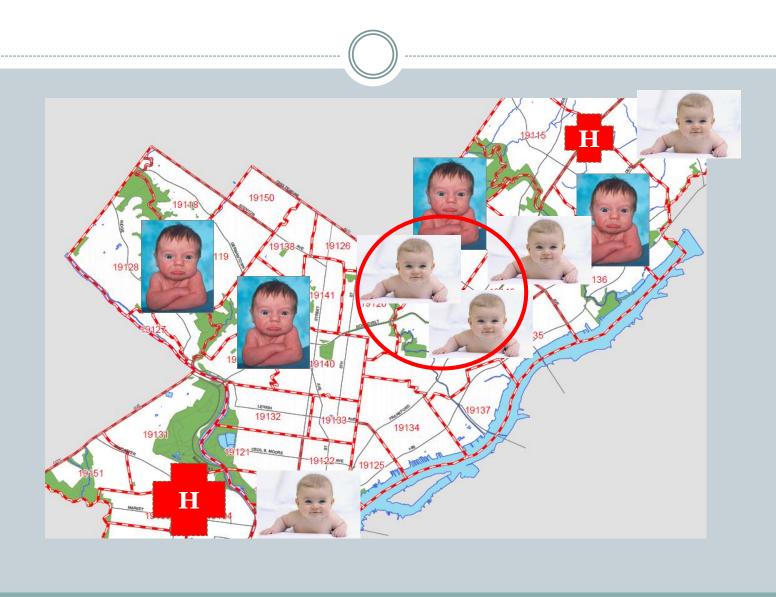
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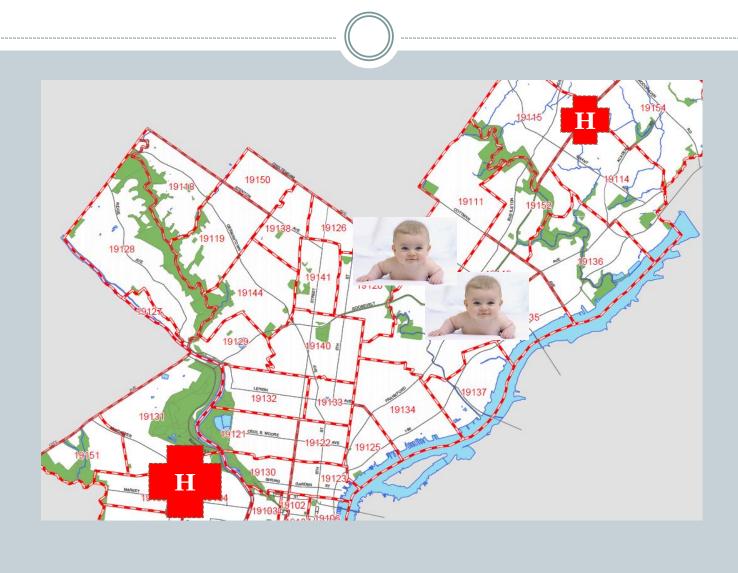


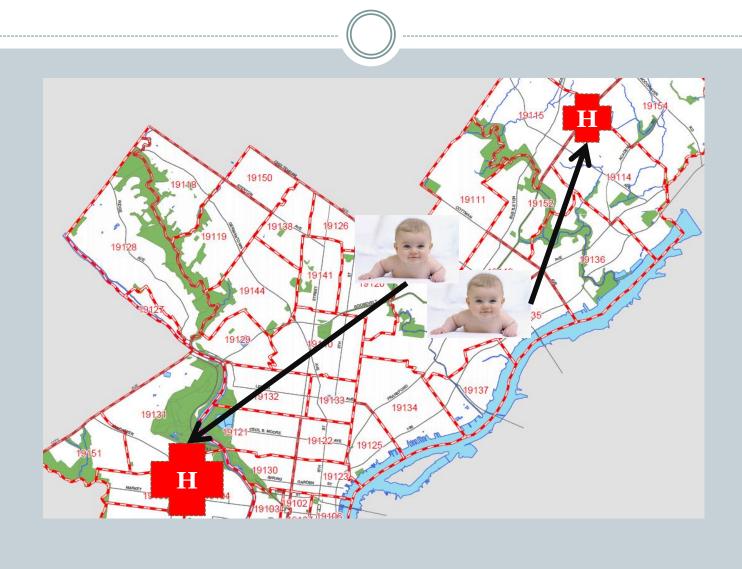
revised design

NEAR-FAR MATCHING

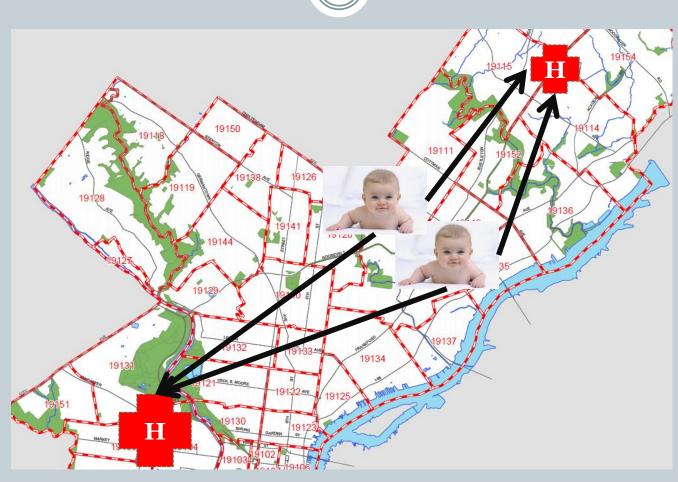




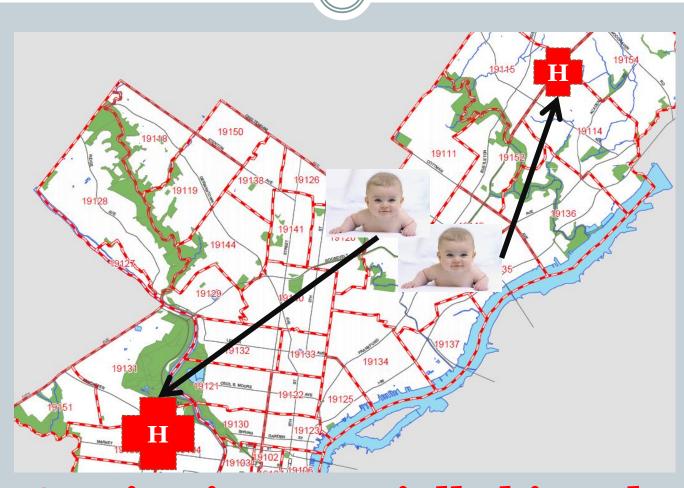






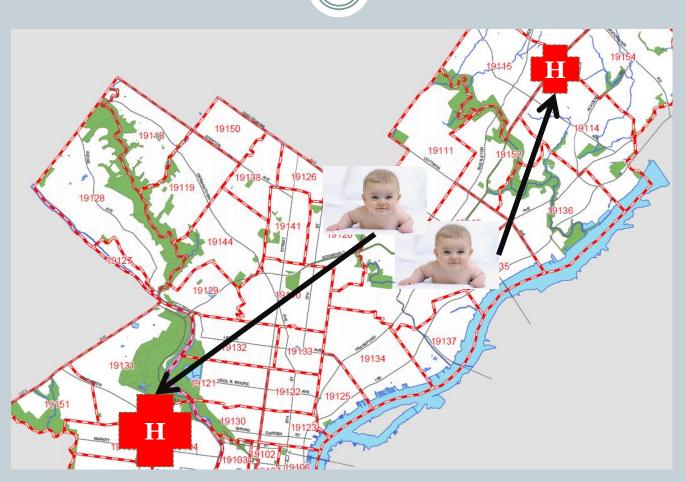


Sorting is potentially biased!

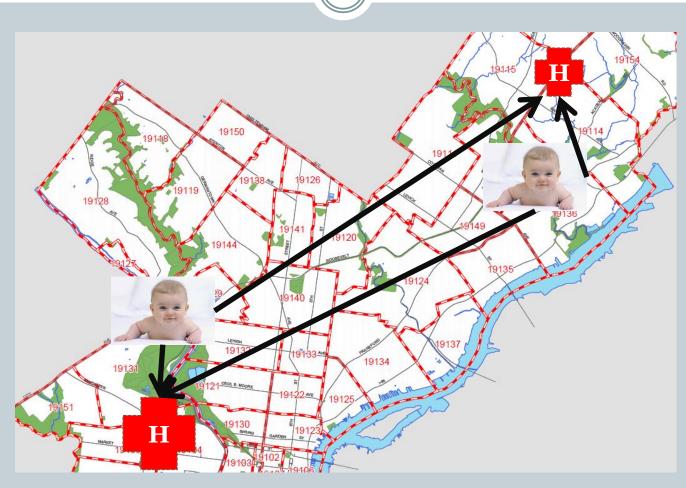


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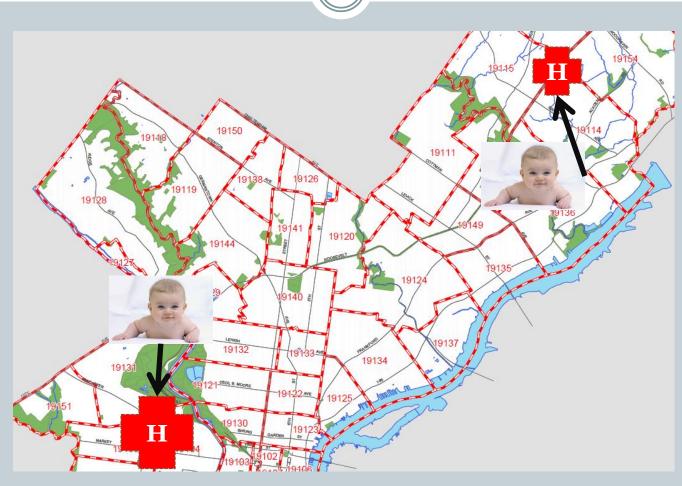
Bhattacharya and Vogt (2007) – <u>Do Instrumental Variables Belong in Propensity Scores?</u>



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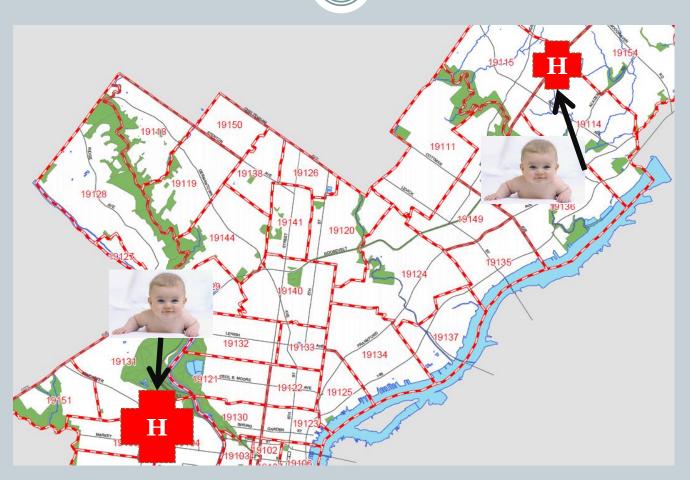


Sorting largely due to the randomness!

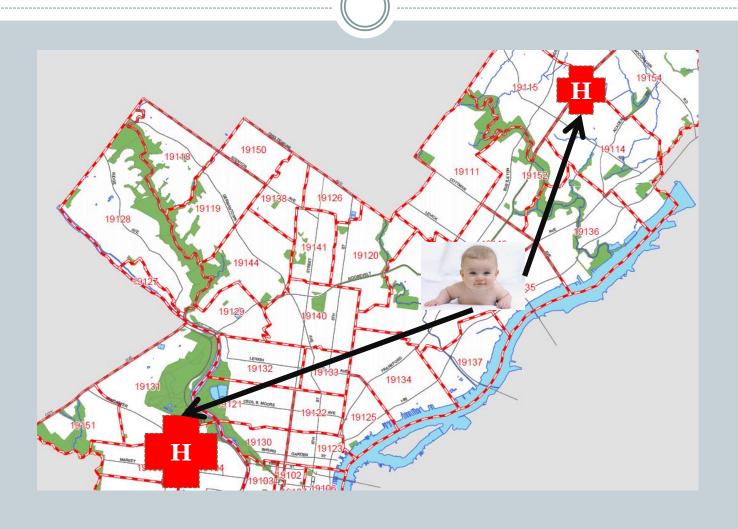


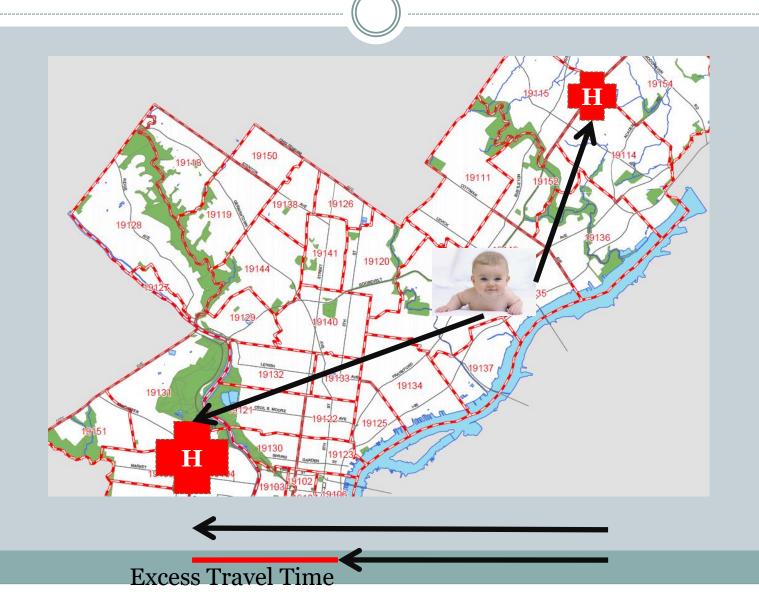
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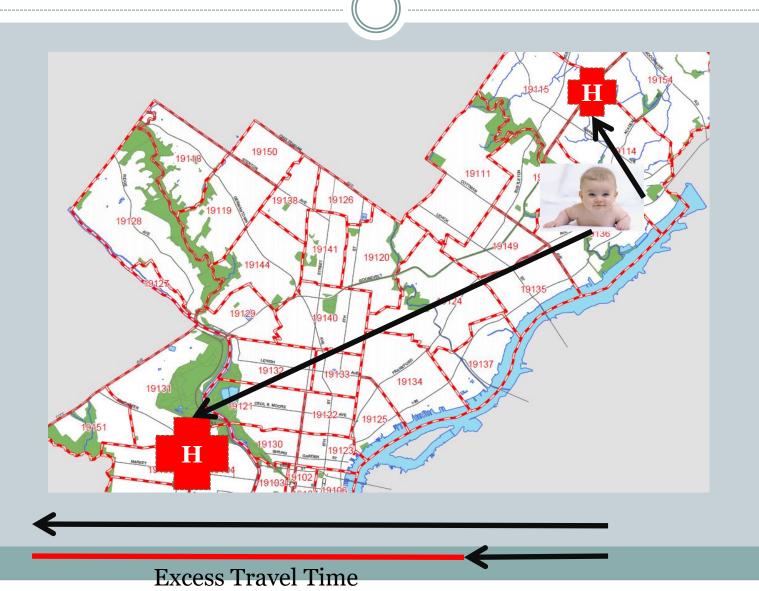
Baiocchi, Small, Lorch and Rosenbaum (2010) – <u>Building a Stronger Instrument in an Observational Study</u>

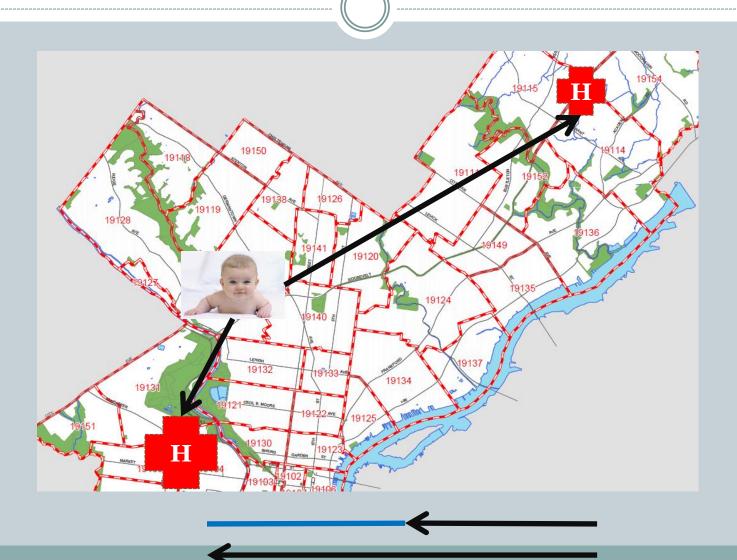


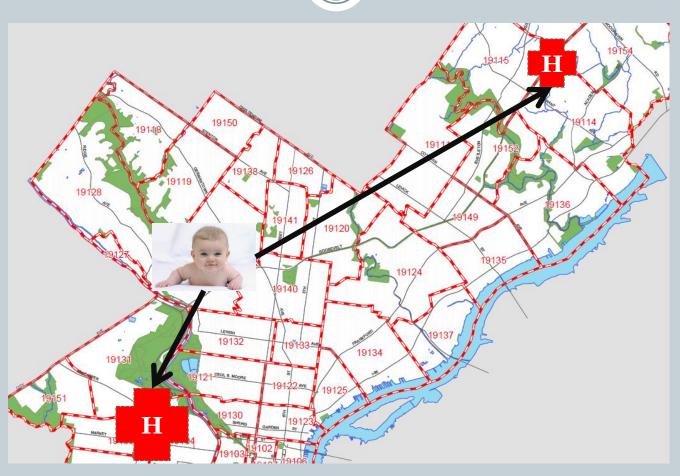
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McClellan, McNeil & Newhouse; "**Does more intensive treatment of acute myocardial infarction reduce mortality?**" *JAMA*. 272(11): 859-66, September 1994

instrumental variables

NEAR-FAR MATCHING

design-based IVs: a quick sketch

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• Use the idea of "block design" / "pair matching" to control **observed** variation.

design-based IVs: a quick sketch

 Use the idea of "block design" / "pair matching" to control <u>observed</u> variation.

• Use the idea of instrumental variables/encouragement to control **unobserved** variation.

design-based IVs: 1st step

• Summarize discrepancies in subjects' covariates

We used Mahalanobis distance

$$D_M(x_1, x_2) = \sqrt{(x_1 - x_2)' S^{-1}(x_1 - x_2)}$$

design-based IVs: 1st step

$$\mathbf{D}_{x} = \begin{pmatrix} d_{11} & d_{12} & d_{13} & \cdots & \cdots & d_{1n} \\ d_{21} & d_{22} & & & \vdots \\ d_{31} & & \ddots & & \vdots \\ \vdots & & & \ddots & \vdots \\ d_{n1} & \cdots & \cdots & \cdots & d_{nn} \end{pmatrix}$$

 d_{ij} = Mahalanobis distance between preemies i and j

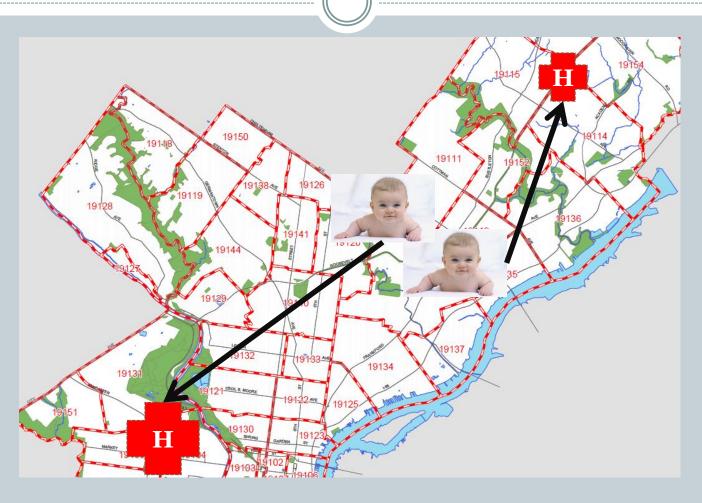
• Create a penalty for preemies with similar instrument values (e.g., calipers)

$$\mathbf{D}_{x} = \begin{pmatrix} d_{11} & d_{12} & d_{13} & \cdots & \cdots & d_{1n} \\ d_{21} & d_{22} & & & \vdots \\ d_{31} & & \ddots & & \vdots \\ \vdots & & & \ddots & \vdots \\ d_{n1} & \cdots & \cdots & \cdots & d_{nn} \end{pmatrix}$$

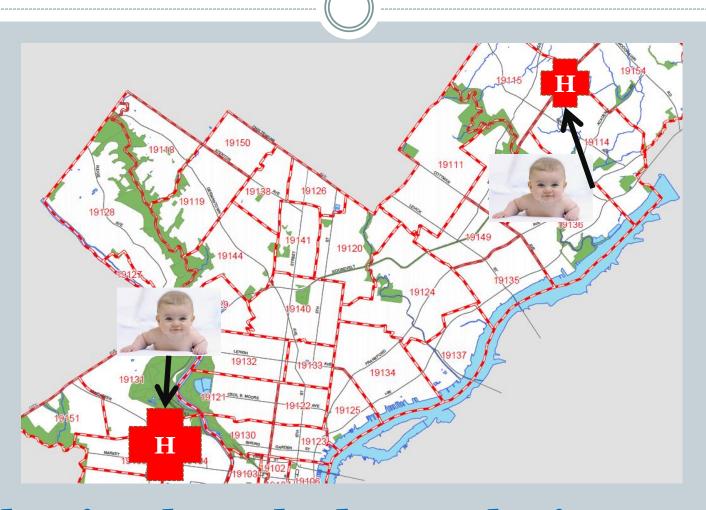
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$$C_{\mathbf{z}} = \begin{pmatrix} c_{11} & c_{12} & c_{13} & & c_{1n} \\ c_{21} & c_{22} & & & \vdots \\ c_{31} & & \ddots & & \vdots \\ \vdots & & & \ddots & \vdots \\ c_{n1} & \cdots & \cdots & \cdots & c_{nn} \end{pmatrix}$$



Selection is potentially biased!



Selection largely due to the instrument!

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design-based IVs: 2nd step

$$\mathbf{D}_{x} = \begin{pmatrix} d_{11} & d_{12} & d_{13} & \cdots & \cdots & d_{1n} \\ d_{21} & d_{22} & & & & \vdots \\ d_{31} & & \ddots & & & \vdots \\ \vdots & & & \ddots & & \vdots \\ d_{n1} & \cdots & \cdots & \cdots & \cdots & d_{nn} \end{pmatrix}$$

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Diff Covariates + Diff Encouragement = Discrepancy Matrix

$$\mathbf{D}_{x} = \begin{pmatrix} d_{11} & d_{12} & d_{13} & \cdots & \cdots & d_{1n} \\ d_{21} & d_{22} & & & & \vdots \\ d_{31} & & \ddots & & & \vdots \\ \vdots & & & \ddots & & \vdots \\ d_{n1} & \cdots & \cdots & \cdots & \cdots & d_{nn} \end{pmatrix}$$

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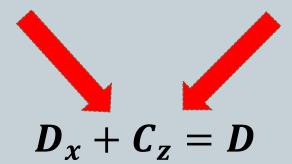




Diff Covariates + Diff Encouragement = Discrepancy Matrix (near) (far) (barrier to being paired)

$$\mathbf{D}_{x} = \begin{pmatrix} d_{11} & d_{12} & d_{13} & \cdots & \cdots & d_{1n} \\ d_{21} & d_{22} & & & & \vdots \\ d_{31} & & \ddots & & \vdots \\ \vdots & & & \ddots & \vdots \\ d_{n1} & \cdots & \cdots & \cdots & d_{nn} \end{pmatrix}$$

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design-based IVs: 3rd step

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 - As we force separation in the instrument, it will be more difficult to find preemies with similar covariates.

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 - As we force separation in the instrument, it will be more difficult to find preemies with similar covariates.
- Allow some subjects to be removed from the study design by matching to sinks.

design-based IVs: 3rd step

 Let k=number of sinks. Then augment the matrix like so:

$$\begin{pmatrix} D & \mathbf{0} \\ \mathbf{0}' & \infty \end{pmatrix}$$

 $D = n \times n$ discepancy matrix, after first two steps

 $\mathbf{0} = n \times k$ matrix, with all entries 0

 $\infty = k \times k$ matrix, with entries ∞

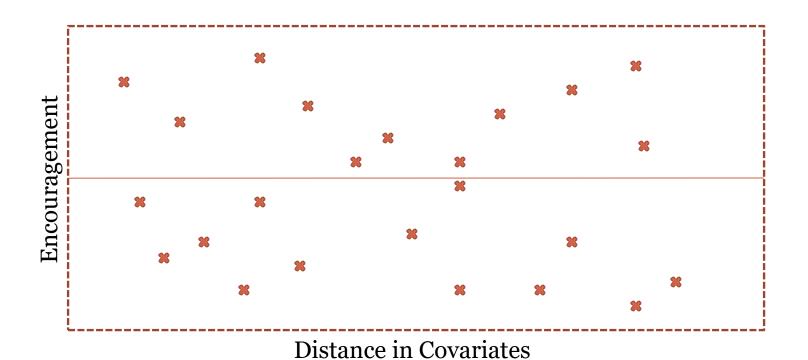
	Variable Type	High NICU	Low NICU	sd	∆/sd
Mortality	Outcome	2.26%	1.25%	13.33%	0.08
Difference in Travel Time	Instrument	4.57	19.00	17.18	-0.84
% attending high level NICU	Treatment	100.0%	0.0%	49.7%	2.01
Birth weight	D	2,454.07	2,693.24	739.27	-0.32
Gestational age	Preemie covariates	34.61	35.69	2.80	-0.39
GI	% of preemies with type of congenital disorders	0.9%	0.6%	8.7%	0.04
GU		0.9%	0.8%	9.0%	0.01
CNS		0.9%	0.4%	8.3%	0.05
Pulmonary		0.8%	0.7%	8.8%	0.01
Cardio		1.4%	0.7%	10.5%	0.06
Skeletal		0.7%	0.9%	9.0%	-0.02
Skin		0.0%	0.0%	0.0%	0.00
Chromosomes		0.4%	0.3%	6.3%	0.02
Other_Anomaly		0.8%	0.1%	7.0%	0.09
Gestational_DiabetesM		4.9%	4.3%	21.0%	0.03
Mother's education		3.76	3.58	1.19	0.16
Insurance - Fee for service	Mother covariates	24.0%	24.5%	42.8%	-0.01
Insurance - HMO		32.3%	27.8%	46.0%	0.10
Insurance - Government		23.5%	24.2%	42.6%	-0.02
Insurance - Other		16.8%	21.4%	39.1%	-0.12
Uninsured		2.2%	1.6%	13.7%	0.04
Prenatal care		2.51	2.37	1.30	0.11
Single birth (y/n)		79.0%	86.1%	38.3%	-0.18
Parity		2.08	2.09	1.31	-0.01
Mother's age		28.41	27.71	6.25	0.11
Median income		41,484.25	40,258.92	14,587.24	0.08
Median home value	Census level covariates	97,663.00	95,083.15	48,762.43	0.05
% completed high school		79.9%	80.0%	9.7%	-0.01
% completed college		22.2%	19.4%	13.1%	0.21
% renting		31.4%	27.9%	12.8%	0.28
% below poverty line		13.4%	11.8%	9.9%	0.16

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Gestational age		34.61	35.69	2.80	-0.39

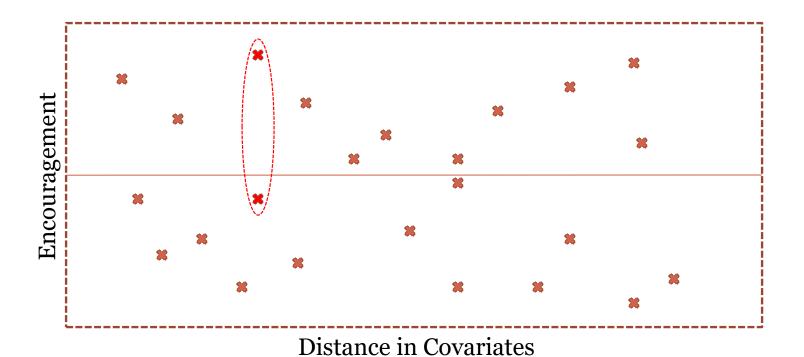
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	max(Δ/sd)
Mortality	1.93%	2.08%	1.47%	1.74%	0.05
Difference in Travel Time	(3.19)	1.12	10.15	35.35	2.24
% attending high level NICU	81.1%	69.8%	49.9%	21.6%	1.20
Birth weight	2,556.17	2,494.15	2,579.15	2,620.74	0.17
Gestational age	35.08	34.82	35.14	35.35	0.19

Matched Pairs 49,587	Variable Type	Encouraged Mean	Unencouraged Mean	sd	Δ/sd
Mortality	Outcome	1.54%	1.94%	12.86%	-0.03
Difference in Travel Time	Instrument	0.67	34.78	18.05	-1.89
% attending high level NICU	Treatment	68.6%	25.4%	49.7%	0.87
Birth weight	Preemie covariates	2,586.15	2,581.77	727.45	0.01
Gestational age		35.17	35.16	2.68	0.01

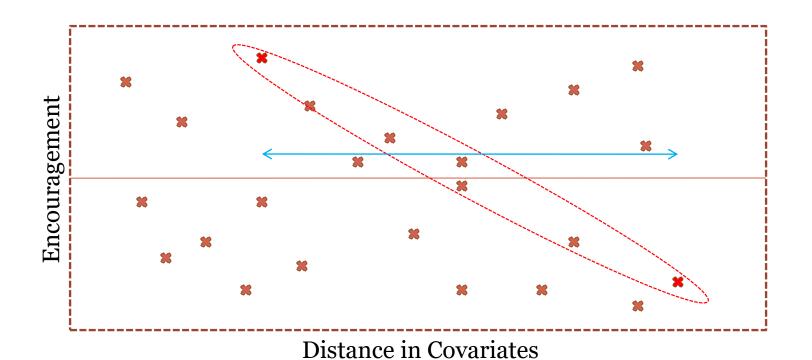
Our method – two criteria for matching



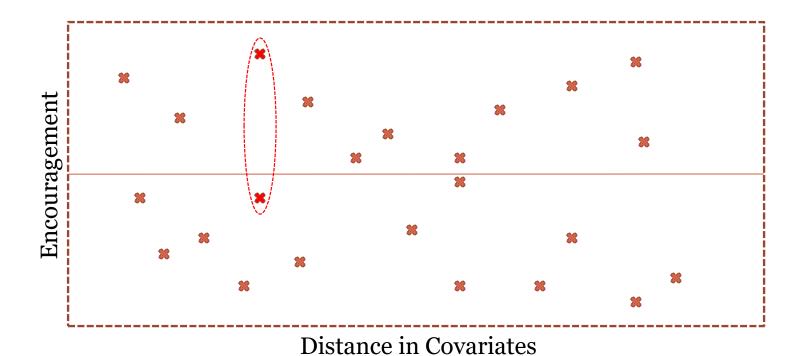
Our method – "near" in covariates



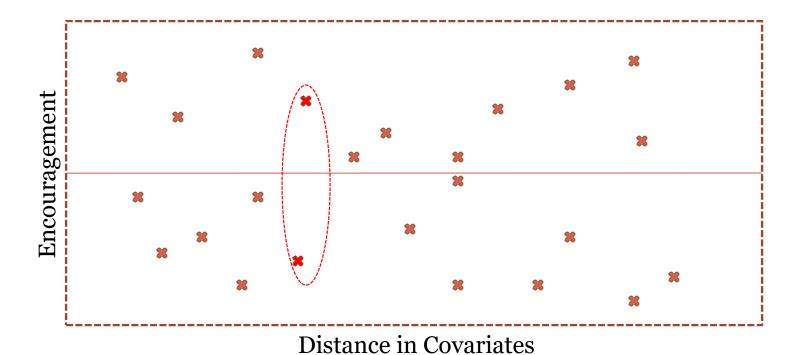
Our method – "far" in covariates

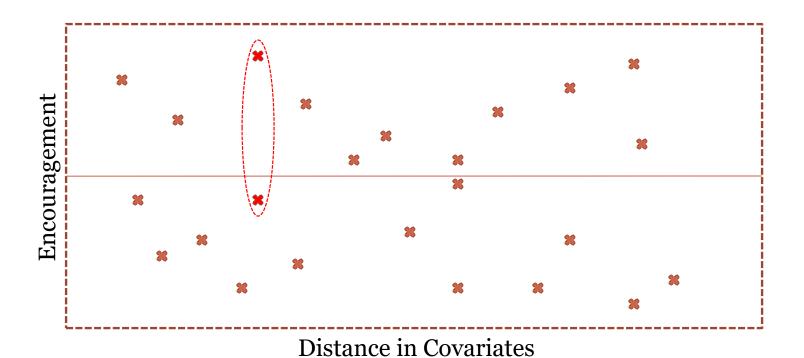


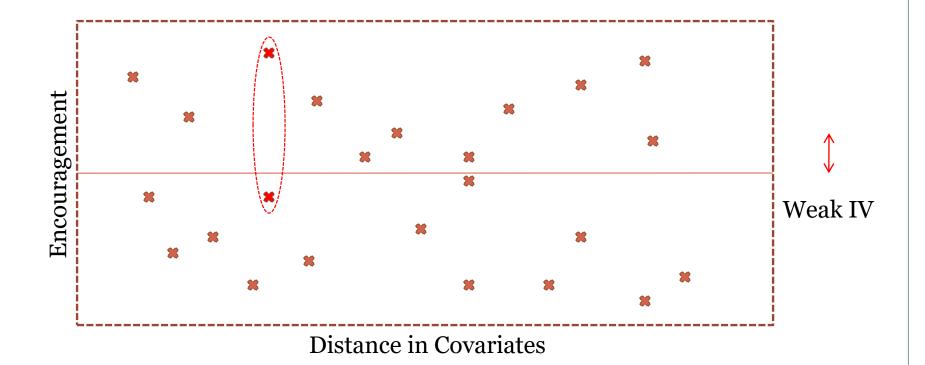
Our method – good pair

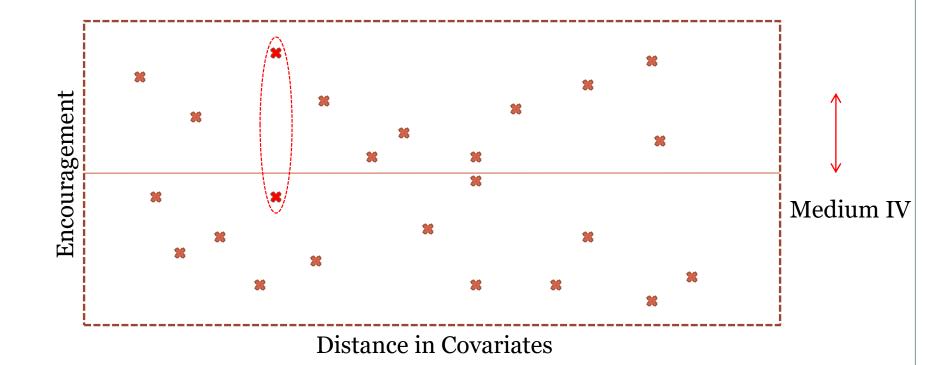


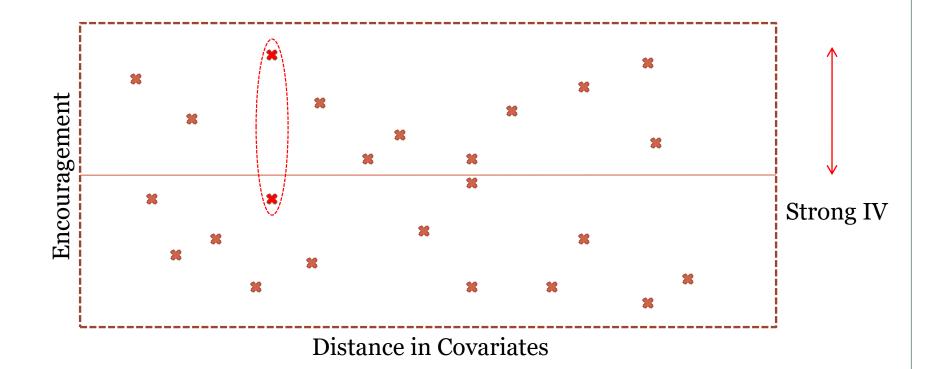
Our method – ok pair



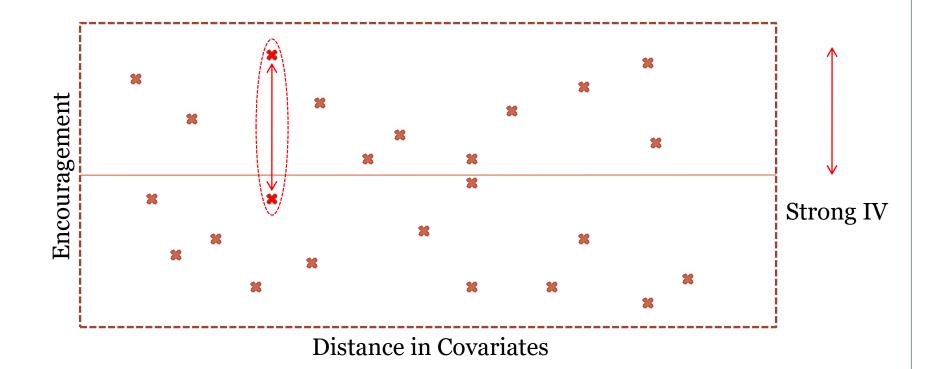


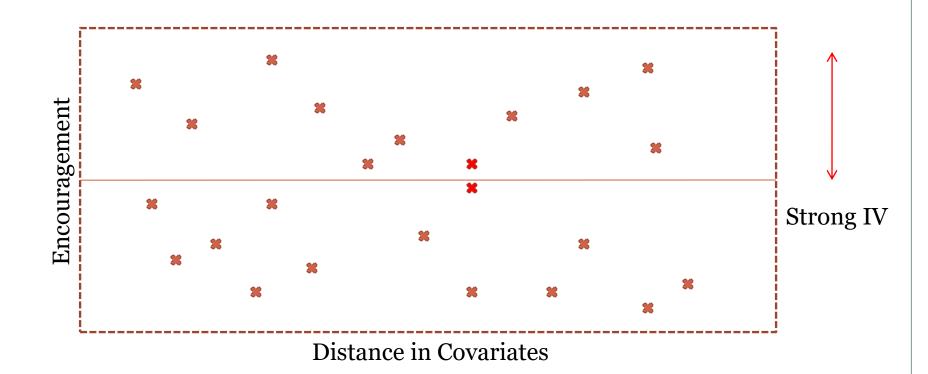


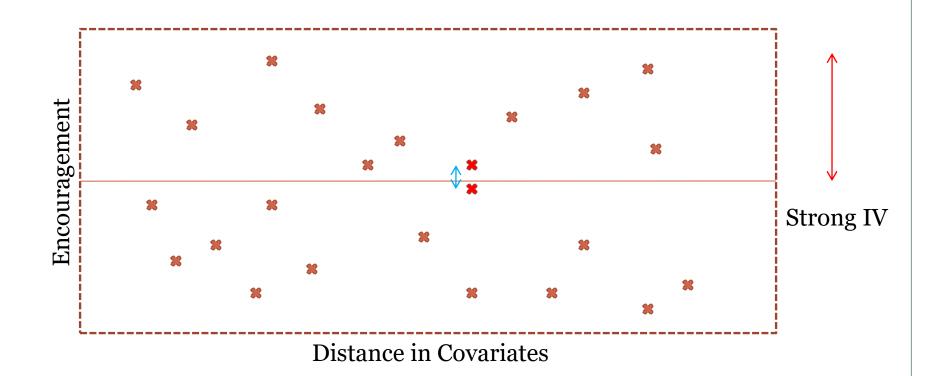


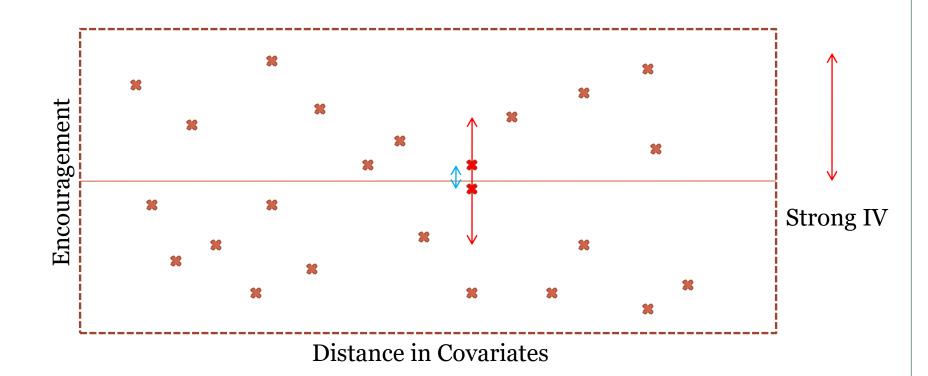


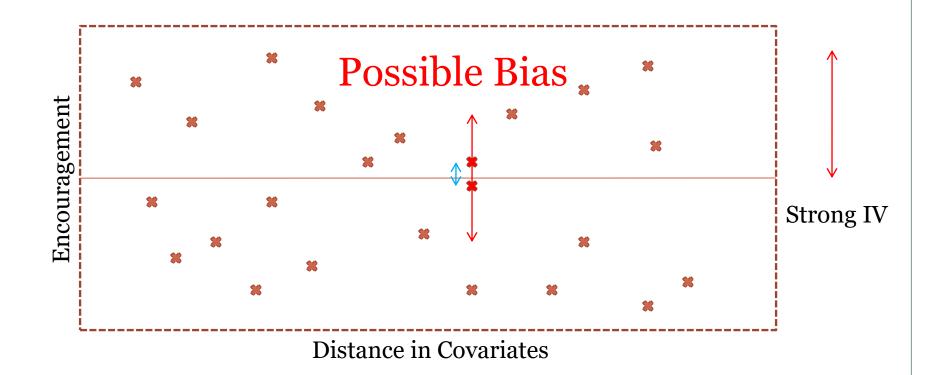
Our method – good pair

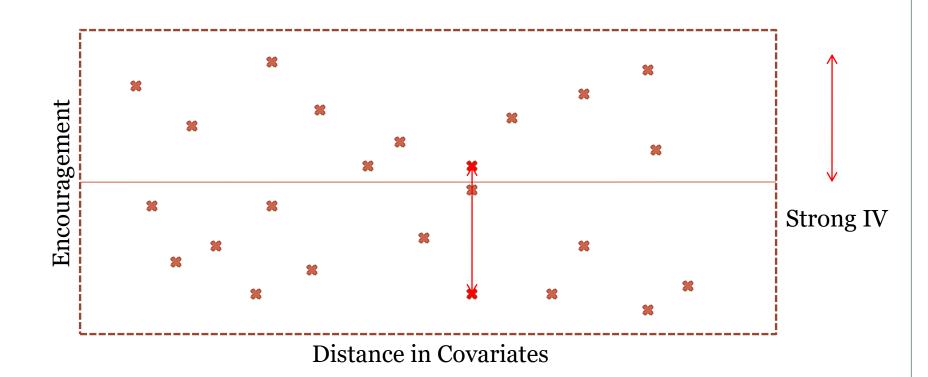


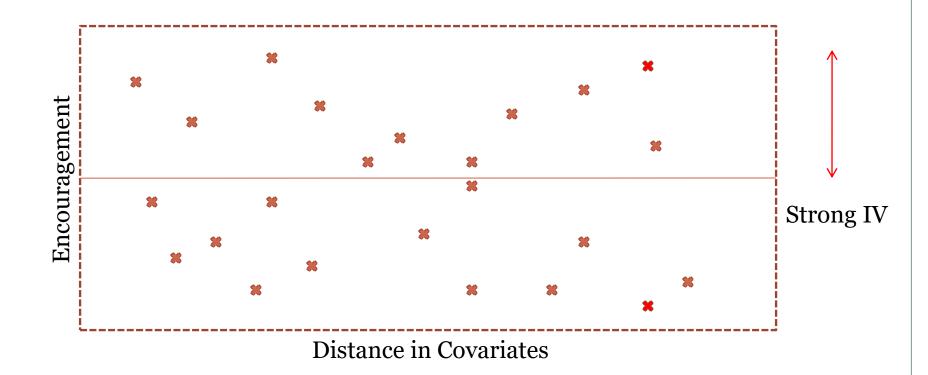


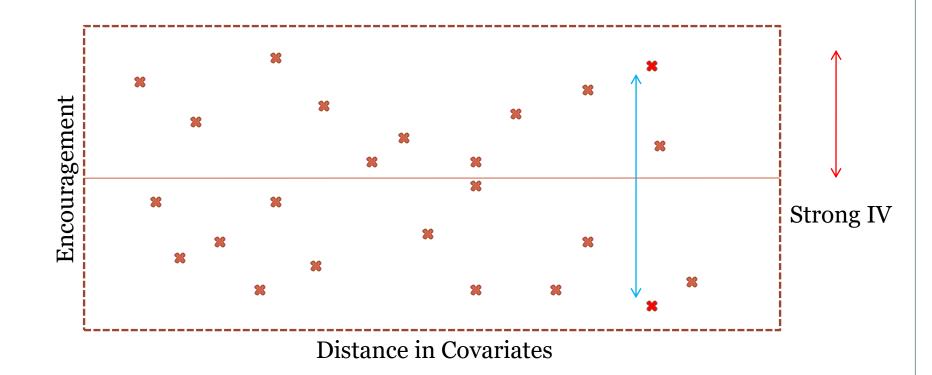


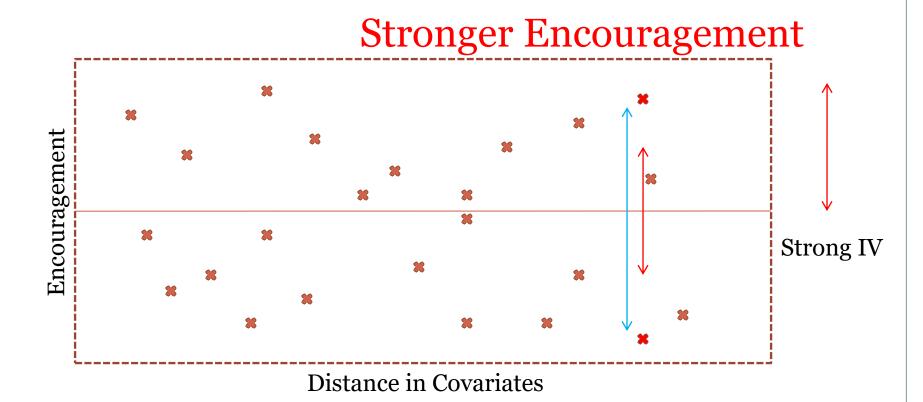




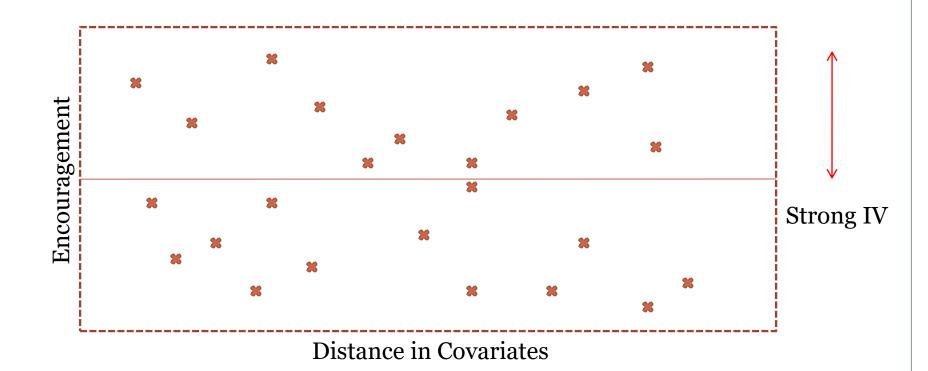




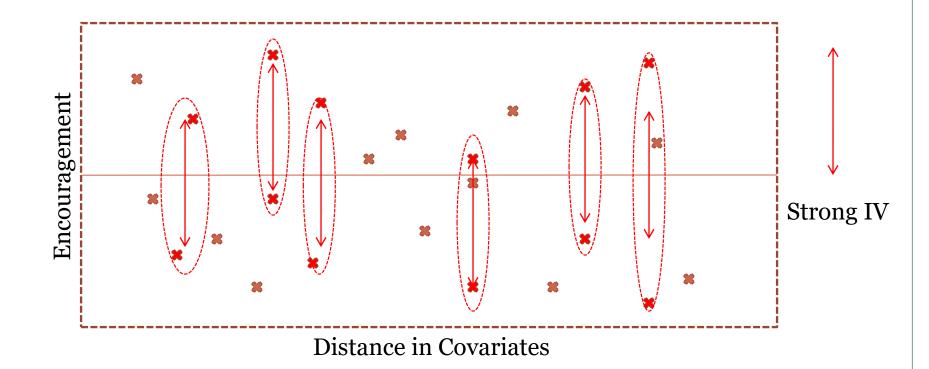




Find the experiment



Find the experiment



near-far matching

- Tutorial: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6207198/
- CRAN: https://cran.r-project.org/web/packages/nearfar/nearfar.pdf

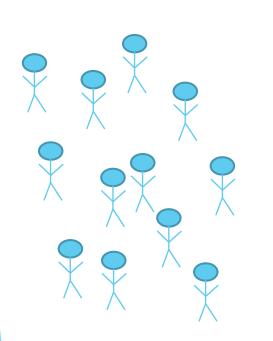
second IV example

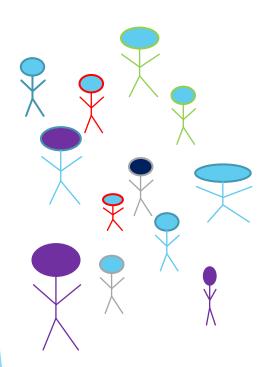
what is the impact of money-bail?

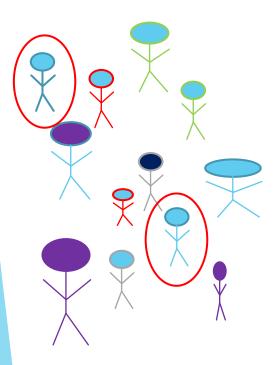
- This is a tough question because pre-trial detention is determined by variables that are also linked to probability of guilt (e.g., "looks guilty")
- One way to do this is by finding a "natural experiment"
 - ▶ Almost all decisions have some sort of haphazardness in them
- Location just over the border
- Judges before/after lunch
- We used judges' disposition:
 - ▶ Some judges are "strict" and some are "lenient"
 - ► Looked at historical records for a given judge, for a given charge, in a given location
- This is known as an "instrumental variable" study design

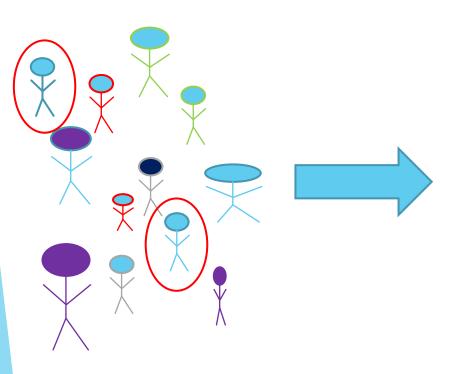


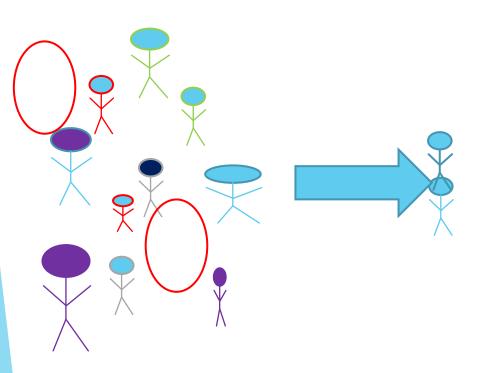


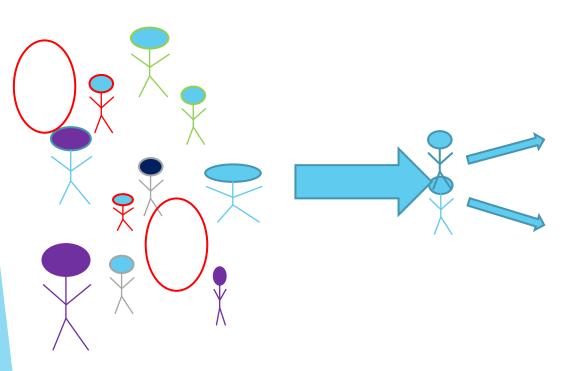


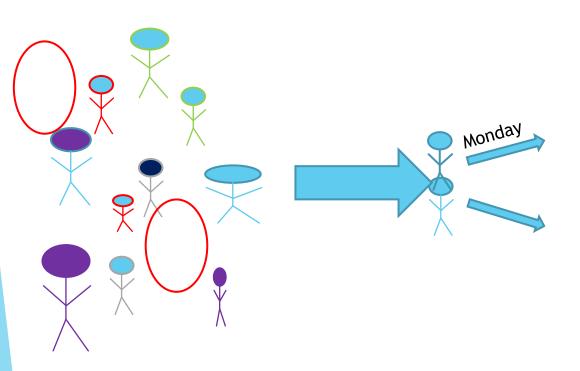


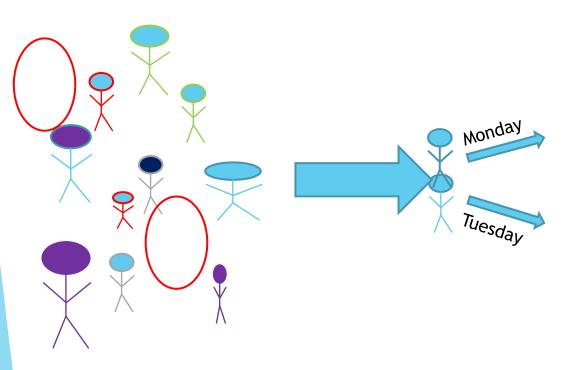


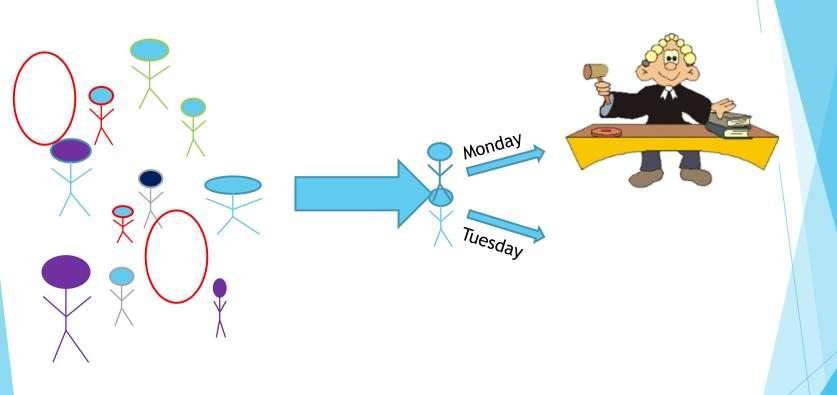


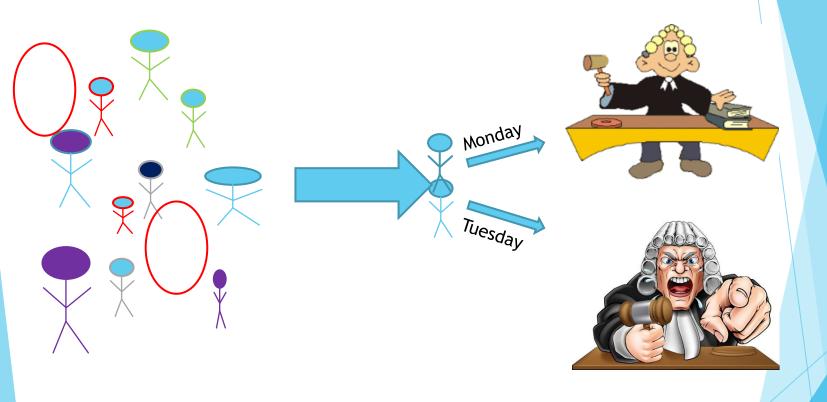


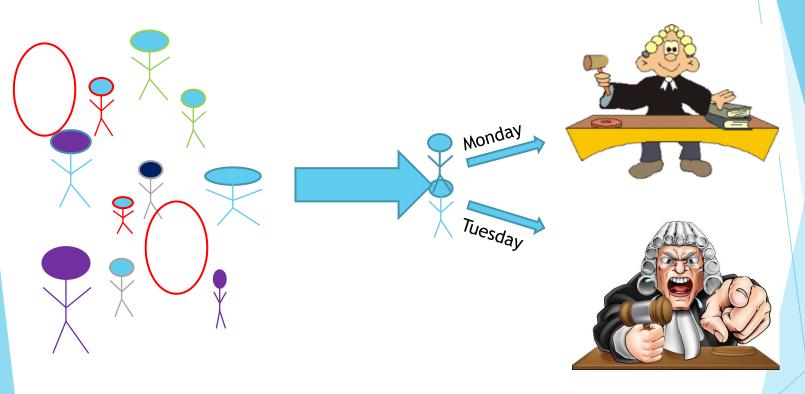




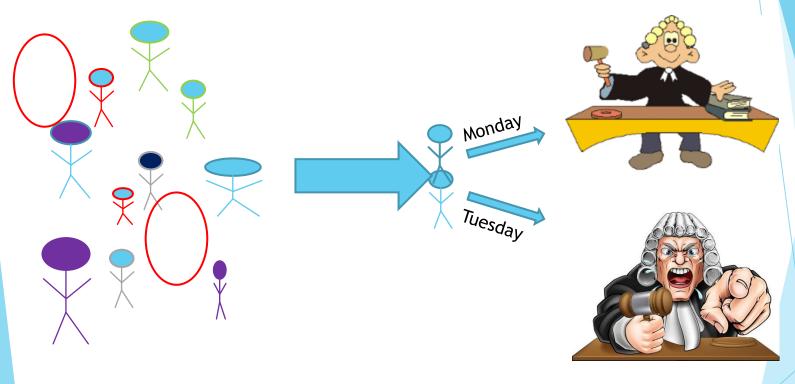








"near" in all the observed covariates.



"near" in all the observed covariates.

"far" in the assignment.

▶ The judge plays an important role in the assignment to bail.

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- ▶ The judge's decision only PARTLY reflects the issues with the accused.

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 - Stacks come in in some order?
- To be challenges, these patterns need to contain information about the accused that isn't in your data set. (That is, conditionally random on the observed covariates.)



	No Bail n=62826	Bail n=14057	Abs St Dif
Guilty	0.33	0.73	1.04
Bail Set	0.00	1.00	2.04
IV	0.01	-0.02	0.22
Age	31.93	35.94	0.32
White	0.29	0.28	0.02
Black	0.48	0.61	0.26
Non-Hispanic	0.63	0.66	0.08
Male	0.79	0.90	0.30
Prior Records 2014	0.38	1.36	0.70
Weekly Income	67.41	63.94	0.02
Any Income	0.15	0.14	0.02
Reported Employer	0.21	0.21	0.00
Reported Phone Number	0.18	0.19	0.04
Reported Address	0.89	0.93	0.12

Table 3: Table of pre-match standardized differences.

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Table 3: Table of pre-match standardized differences.

post-matching

post-matching

	Strict n=28367	Lenient n=28367	Abs St Dif
Guilty	0.41	0.40	0.03
Bail Set	0.21	0.16	0.12
IV	-0.07	0.07	1.18
Age	32.69	32.71	0.00
White	0.28	0.28	0.00
Black	0.52	0.52	0.00
Non-Hispanic	0.65	0.65	0.00
Male	0.81	0.81	0.00
Prior Records 2014	0.54	0.53	0.00
Weekly Income	53.00	52.75	0.00
Any Income	0.12	0.12	0.00
Reported Employer	0.17	0.17	0.00
Reported Phone Number	0.15	0.15	0.00
Reported Address	0.91	0.91	0.00

Table 5: Table of post-match standardized differences. Summary of data analyzed.

assessing the IV

	mean (sd)	Q.1	Q.2	Q.3	Q.4
Age	$32.61\ (12.53)$	33.74	31.32	31.75	33.59
Black	0.5	0.53	0.51	0.49	0.49
White	0.29	0.29	0.27	0.28	0.3
Non-Hispanic	0.63	0.65	0.63	0.62	0.63
Male	0.81	0.81	0.83	0.8	0.78
Reported Employer	0.21	0.24	0.22	0.2	0.2
Reported Phone Number	0.18	0.2	0.17	0.17	0.19
Reported Address	0.9	0.9	0.9	0.89	0.89
Weekly Income	$66.32\ (222.63)$	78.27	64.04	61.27	61.55
Any Income	0.15	0.16	0.15	0.14	0.14
Prior Records 2014	0.56 (1.39)	0.68	0.48	0.47	0.59

Table 4: Summary of Covariates by IV Quartile

	No Bail n=62826	Bail n=14057	Abs St Dif
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Table 3: Table of pre-match standardized differences.

third IV example

acute aortic dissection

acute aortic dissection

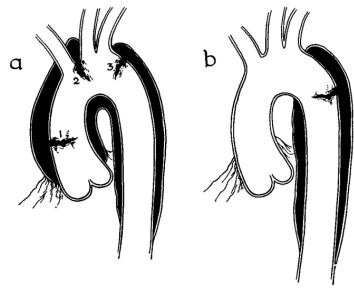


FIG. 3. Classification of aortic dissections. In type A the ascending aorta is dissected (a). The intimal tear has always been at position 1, but it can occur at positions 2 or 3 (see text). In type B dissection the dissection is limited to the descending aorta (b), and the intimal tear is usually within 2 to 5 cm. of the left subclavian artery.

aortic dissection

It's a particularly scary situation:

- Incidence is 4-7 per 100,000
- Mortality for untreated acute type A
 - First 24hrs = 25%
 - First 48hrs = 40%
- Upon diagnosis patients are rushed to operating room.
- Operative mortality in the range of 19-28%











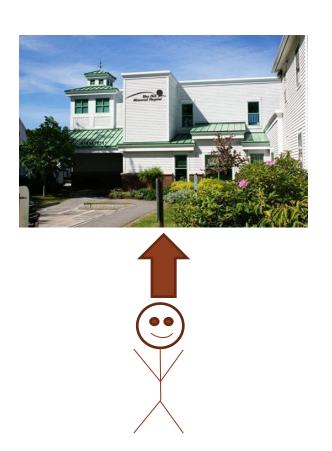
















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35%



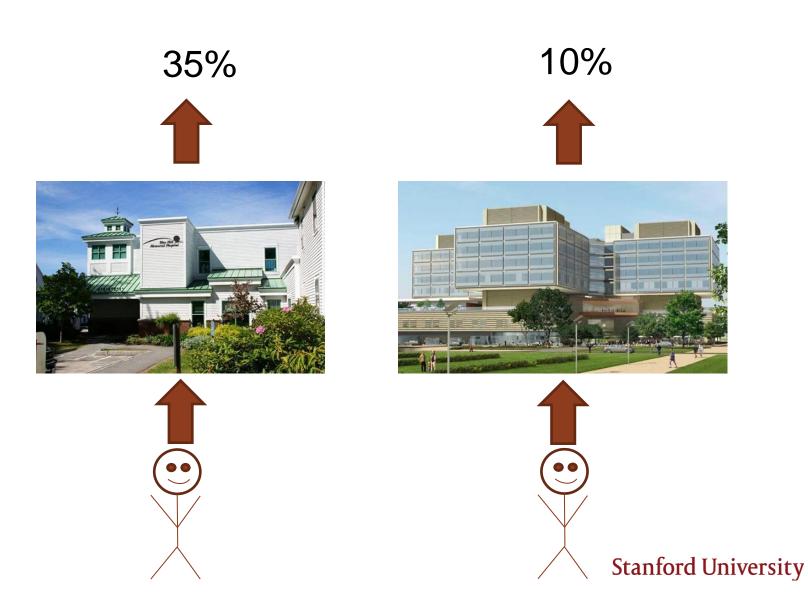


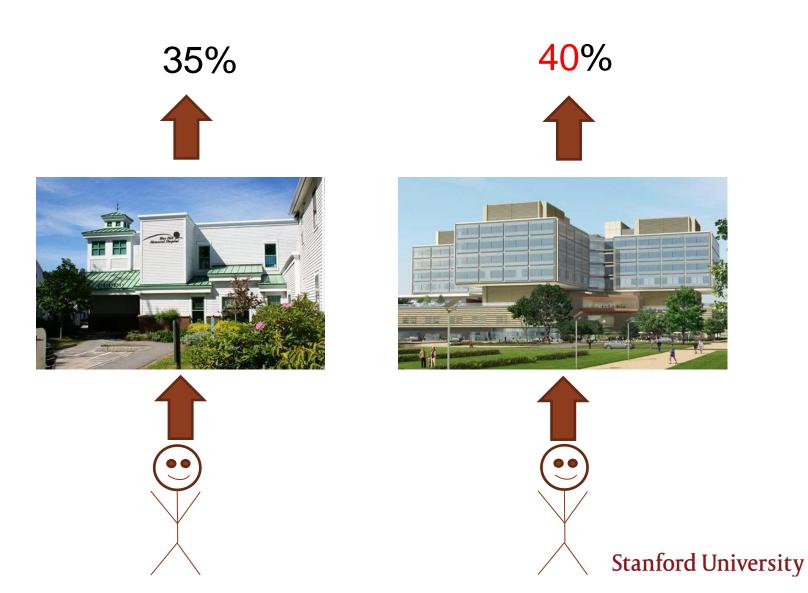


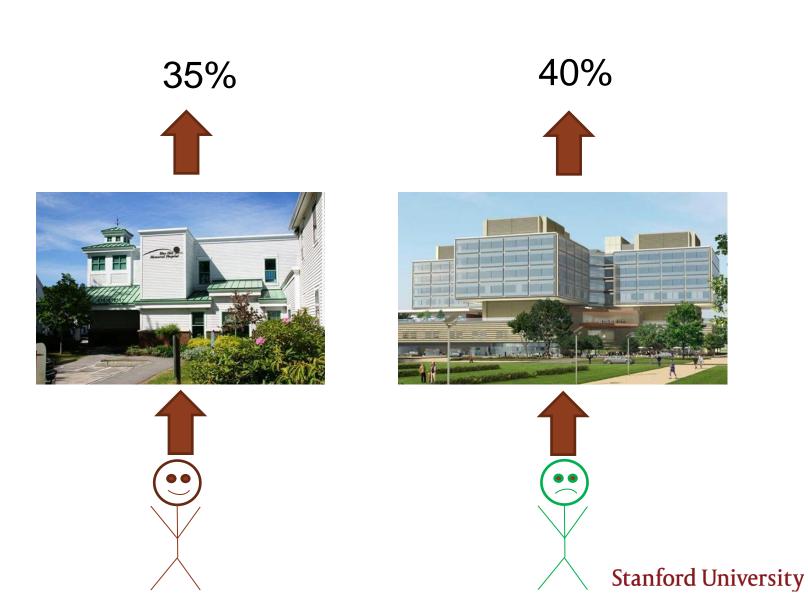




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high-quality causal inference

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Randomized controlled trials are (currently) the best way to generate data for causal inference.

high-quality causal inference

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What's special about RCTs?











































Coin flip?



















Coin flips are a completely deterministic process.



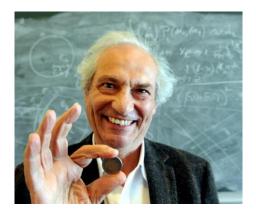












Persi Diaconis

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1.

2.

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 RCTs make use of assignment mechanisms which are determined by a noninformative process

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What's special about RCTs?

1. RCTs make use of assignment mechanisms which are determined by a noninformative process (technically: conditionally orthogonal).

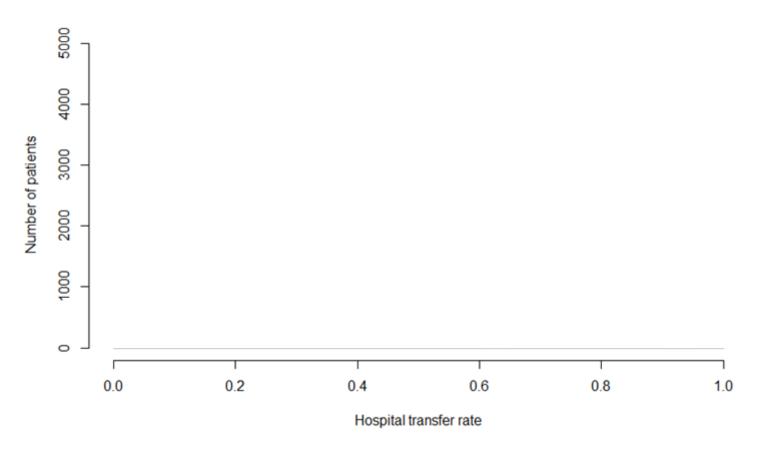
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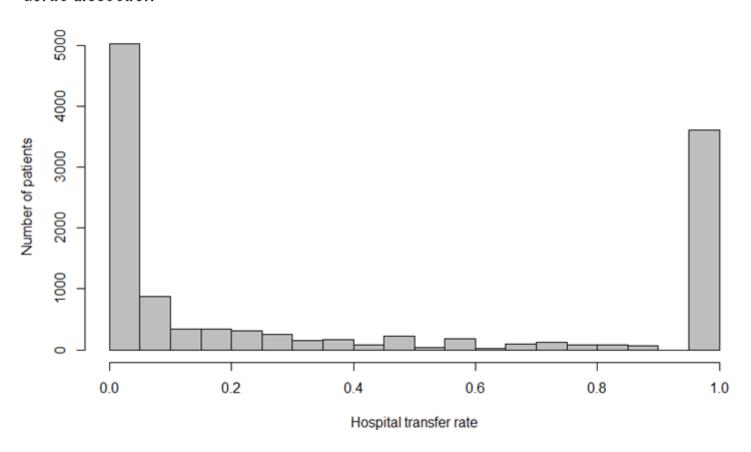
What's special about RCTs?

- 1. RCTs make use of assignment mechanisms which are determined by a noninformative process (technically: conditionally orthogonal).
- 2. Imposing control over "nuisance" variation.

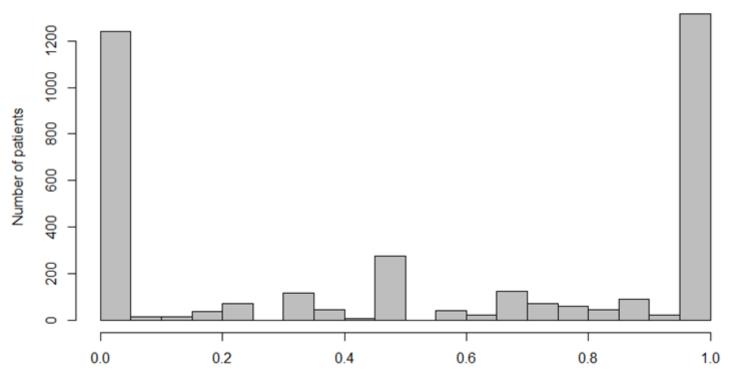
B Distribution of patients presenting to hospitals with varying transfer rates for acute type A aortic dissection



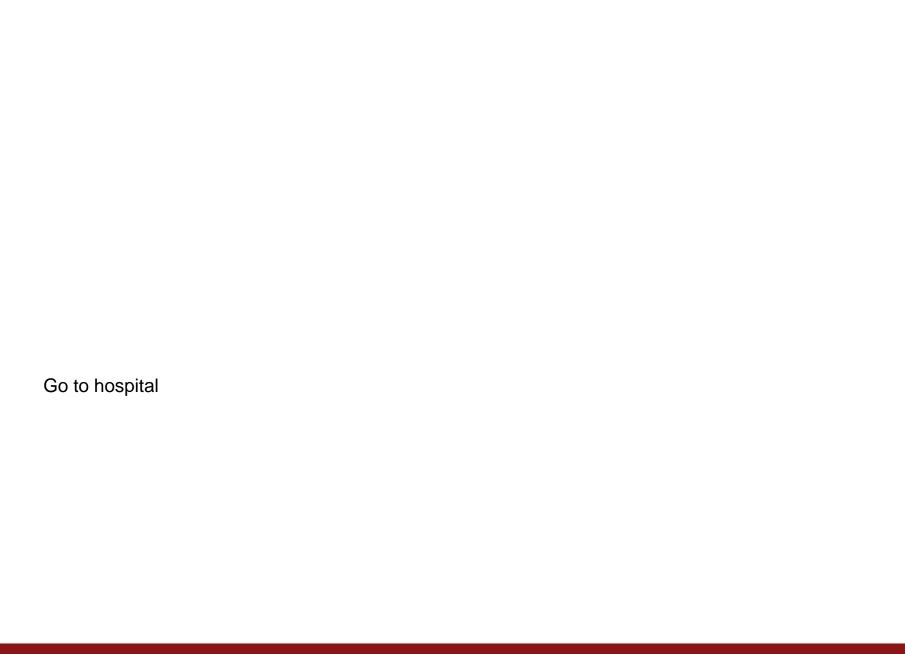
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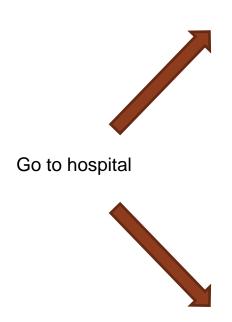


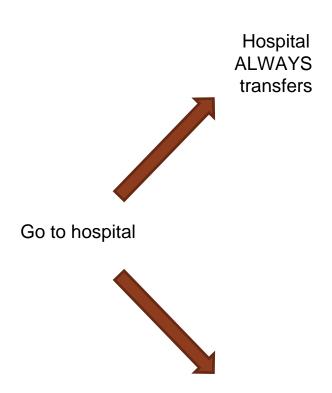
D Distribution of patients presenting to hospitals with varying transfer rates to high-volume centers among hospitals that always transferred patients with acute type A aortic dissection

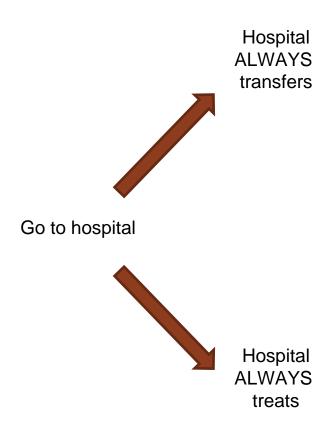


Hospital transfer rate to high-volume vs. low-volume

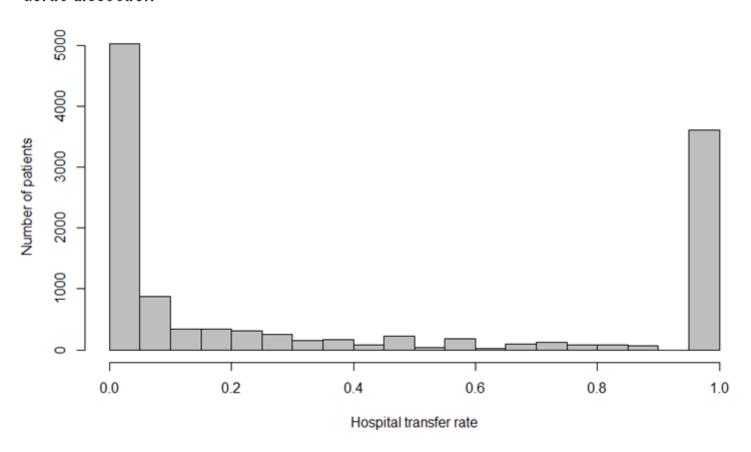


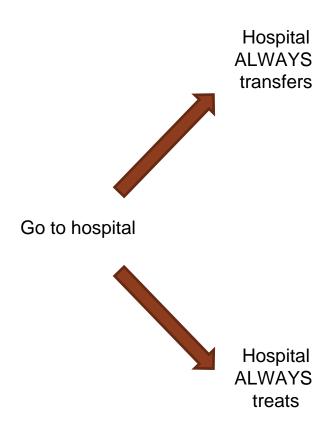


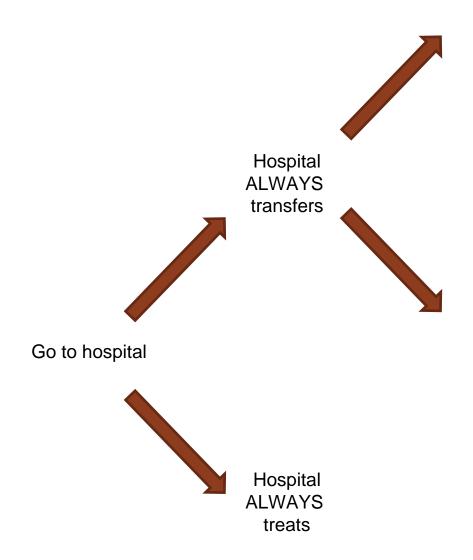


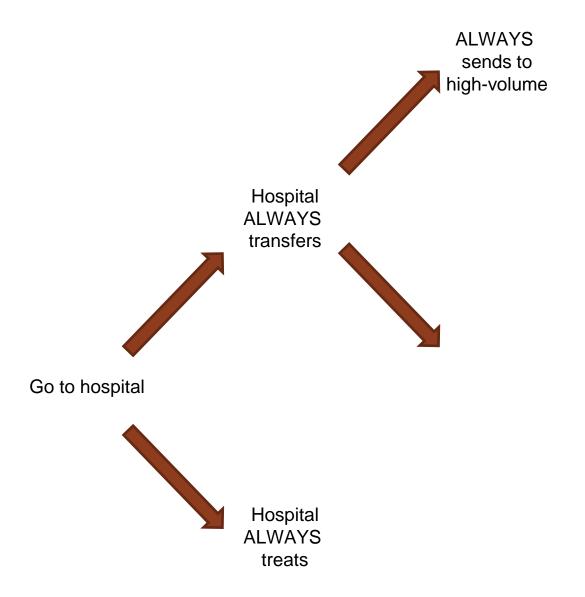


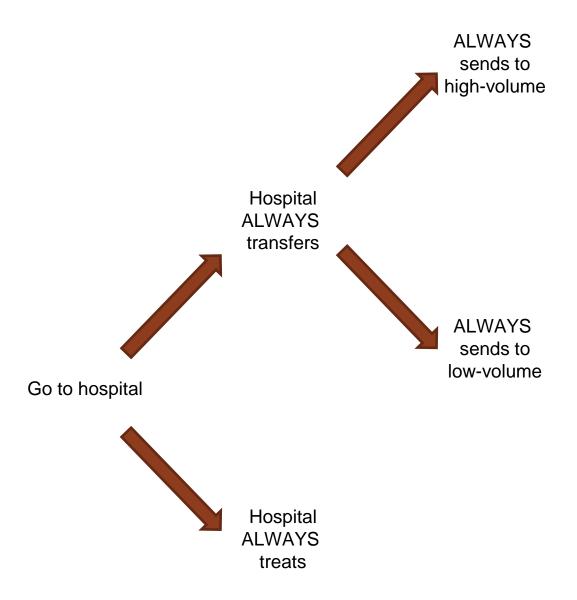
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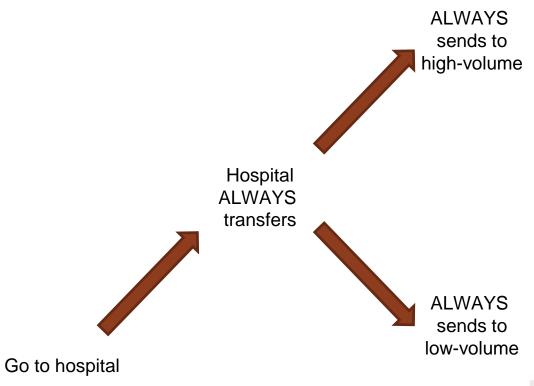








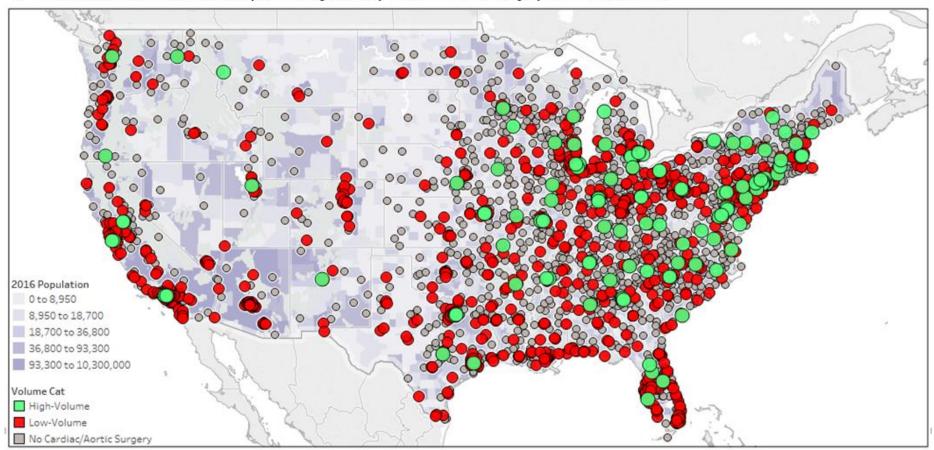




Hospital
ALWAYS
treats

	high	low
transfer		
stay		

A Distribution of United States Hospitals Categorized by Proximal Aortic Surgery Volume, 1999-2010



We have to think about the decision making process that goes into these decisions.

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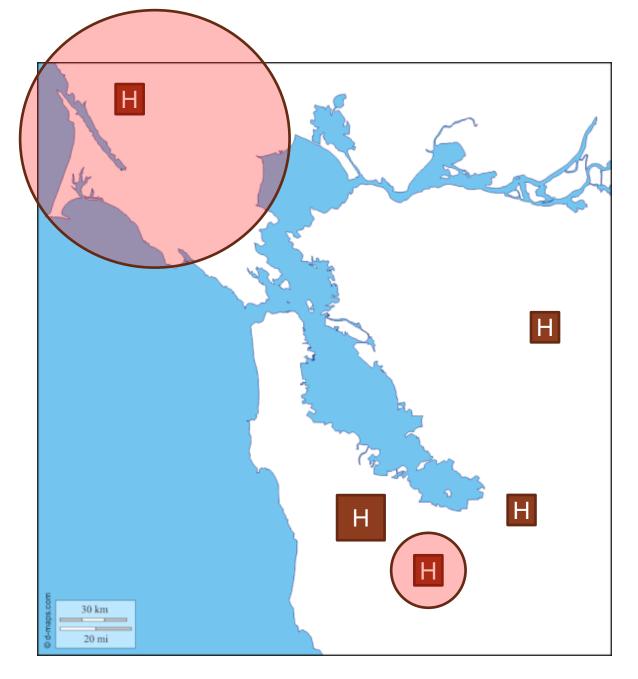
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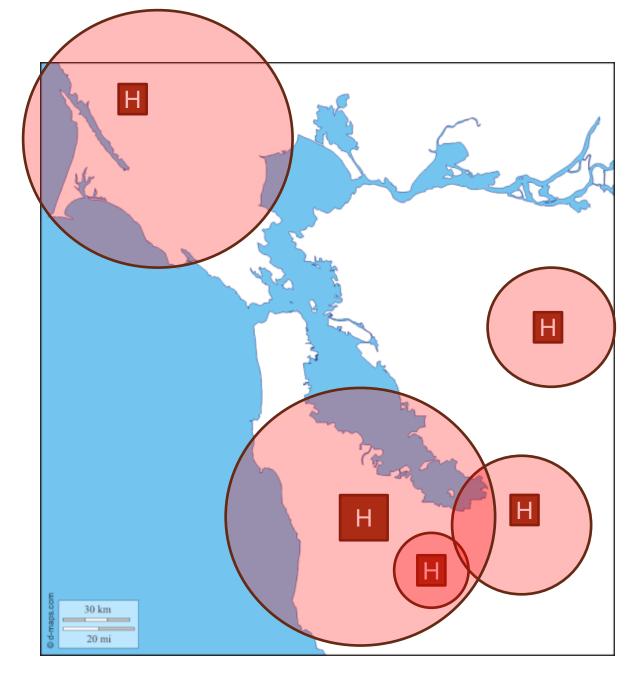
How did patients end up at the original hospital?



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NEMSIS data base: (nearly) all EMS transport records in the USA. 50% patient/family decision, 40% proximity

would regionalizing improve survival?

Table 2. Between-Group Differences in Operative Mortality and Overall Survival for Comparison of Transfer and Regionalization

Operative Mortality	Rerouted vs. Not Rerouted (reference)*						
Group Contrast Measure	Estimate	95% CI	P Value	Estimate	95% CI	P Value	
Absolute Risk Difference (%)	-0.62	-2.6 - 1.34	0.57	-7.5	-10.64.4	<0.001	
Odds Ratio	0.97	0.87 - 1.08	0.55	0.68	0.57 - 0.80	< 0.001	
Number Needed to Treat (no.)	-	-	-	14	9 - 23	-	
Overall Survival	Transferr	ed vs. Stayed (r	eference)	Rerouted vs. Not Rerouted (reference)			
Group Contrast Measure	Estimate	95% CI	P Value	Estimate	95% CI	P Value	
Hazard Ratio (PH model)	1.02	0.94 - 1.11	0.64	0.8	0.74 - 0.86	< 0.001	
Restricted Mean Survival Time		15 years			15 years		
Difference (days)	-44.9	-141.2 - 51.5	0.36	232.2	105.2 - 359.1	< 0.001	
Ratio	0.98	0.94 - 1.02	0.36	1.12	1.05 - 1.18	< 0.001	
Ratio of Restricted Mean Time Lost	1.02	0.98 - 1.05	0.36	0.93	0.89 - 0.97	< 0.001	

^{*}Gamma = 1.32 for this comparison. The gamma parameter estimates the amount of unmeasured bias necessary to render the finding null. For interpretation, sickest patients requiring rerouting (to regionalize care) would need to have a 33% increased odds of needing to be rerouted (despite matching) in order for the presented findings to be null.

CI, confidence interval; PH, proportional hazards

would regionalizing improve survival?

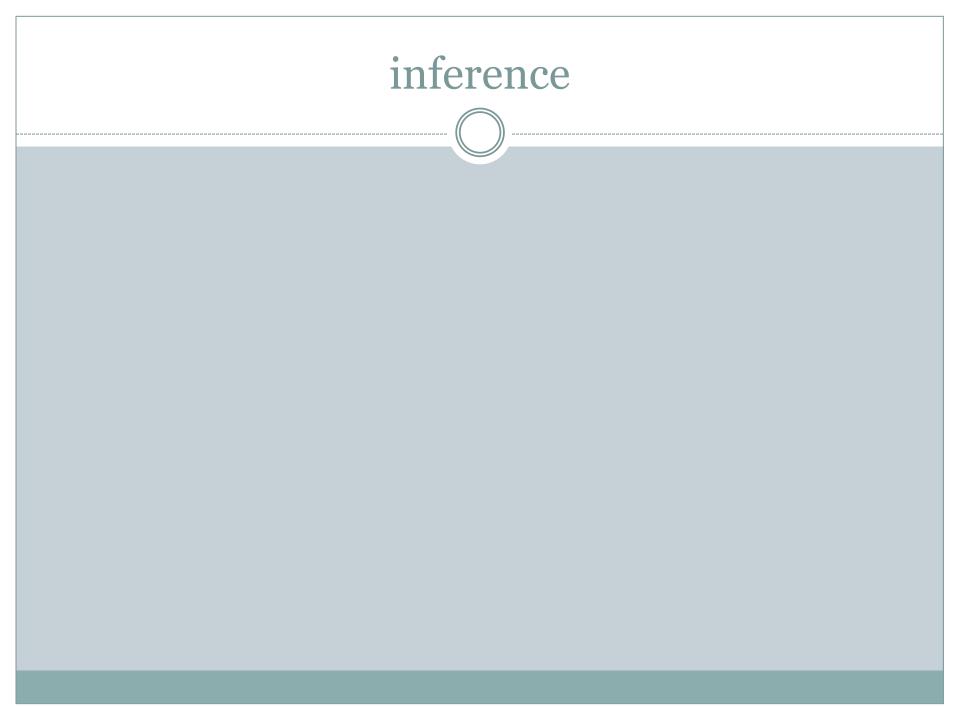
Table S7. Propensity Score Analsyis - Between-Group Differences in Operative Mortality and Overall Survival for Comparison of Transfer and Regionalization

Operative Mortality	Transferred vs. Stayed (reference)			High-Volume vs. Low-Volume (reference)*			Rerouted vs. Not Rerouted (reference)**			
Group Contrast Measure	Estimate	95% CI	P <u>Va</u> lue	Estimate	95% CI	P Value	Estimate	95% CI	P Value	
Absolute Risk Difference (%)	-1.7	-3.20.001	0.03	-6.1	-7.74.5	<0.001	-9.6	-11.47.8	<0.001	
Odds Ratio	0.9	0.82 - 0.99	0.03	0.73	0.67 - 0.79	< 0.001	0.6	0.54 - 0.67	< 0.001	
Number Needed to Treat (no.)	-	-	-	17	13 - 23	-	11	9 - 13	-	
Overall Survival	Transferred vs. Stayed (reference)			High-Volume	vs. Low-Volume	(reference)*	Rerouted vs. Not Rerouted (reference)**			
Group Contrast Measure	Estimate	95% CI	P Value	Estimate	95% CI	P Value	Estimate	95% CI	P Value	
Hazard Ratio (PH model)	1.02	0.94 - 1.11	0.64	0.76	0.71 - 0.80	<0.001	0.8	0.74 - 0.86	< 0.001	
Restricted Mean Survival Time		15 years			15 years			15 years		
Difference (days)	-44.9	-141.2 - 51.5	0.36	300.6	206.4 - 394.7	< 0.001	232.2	105.2 - 359.1	< 0.001	
Ratio	0.98	0.94 - 1.02	0.36	1.15	1.10 - 1.20	<0.001	1.12	1.05 - 1.18	< 0.001	
Ratio of Restricted Mean Time Lost	1.02	0.98 - 1.05	0.36	0.9	0.88 - 0.93	< 0.001	0.93	0.89 - 0.97	< 0.001	

^{*} Gamma = 1.31

Using "all of the data."

^{**} Gamma = 1.44



• Historically: two-stage least squares

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Selection into the treatment:

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Usually looks like

$$d = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p + \beta_z z + \varepsilon_d$$

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- Generally speaking, 2sls is a "predictor substitution" method.... which have problems.
- Historically, the big problems came up when the outcomes (y) was not linear.
- Take-away: If the outcome is linear AND the treatment is EITHER linear or binary then two-stage least squares is the path of least resistance.

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- They perform quite well in many of the GLM setting –
 e.g., logistic.
- In the linear outcome/linear treatment case 2sls and RIMs are the same.
- Take-away: Probably best to opt for RIMs.

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• Use the Z as the randomizer.

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- Applied reference:
 - o Greevy, Silber, Cnaan, and Rosenbaum (2004) "Randomization inference with imperfect compliance in the ACE-inhibitor after anthracycline randomized trial."

