Sensitivity Analysis for Unobserved Confounding

Trang Quynh Nguyen
(special thanks to Elizabeth Stuart)

Johns Hopkins Bloomberg School of Public Health, Department of Mental Health
trang.nguyen@jhu.edu

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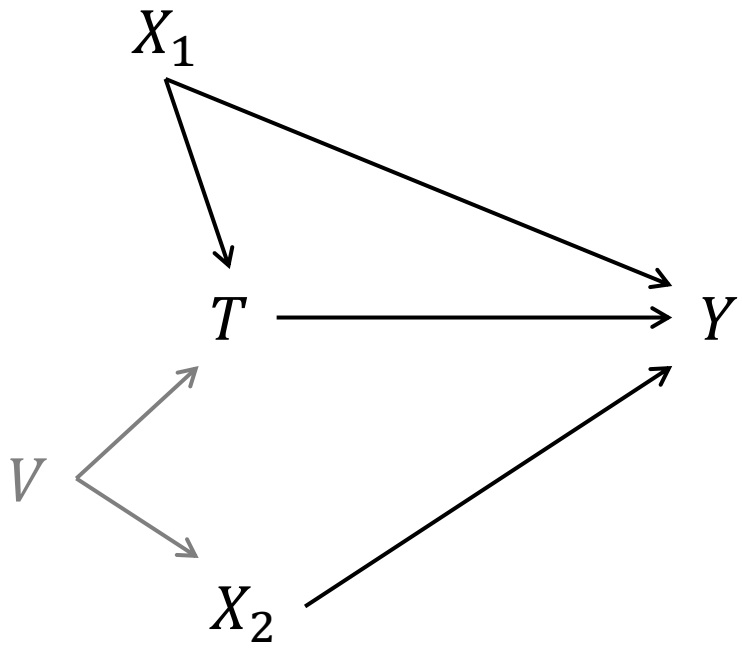
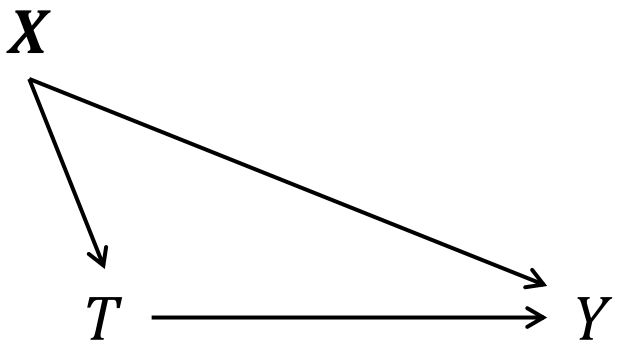
Confounding

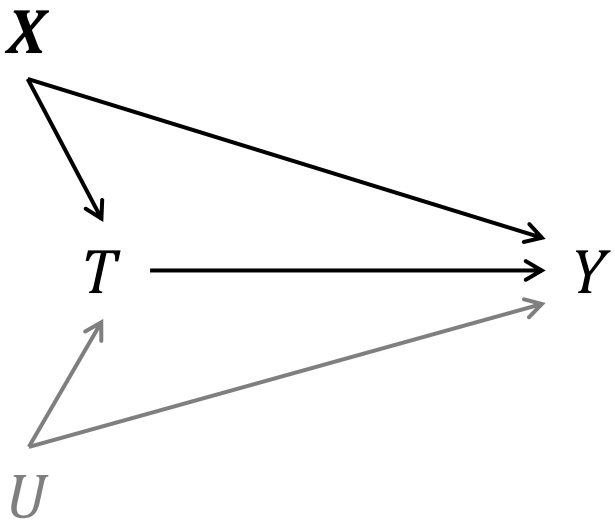


Adjustment for Observed Confounding



- Adjust for X via multiple regression or propensity score methods
- Assumption: No unobserved confounders (no "hidden" bias)

Unobserved Confounding



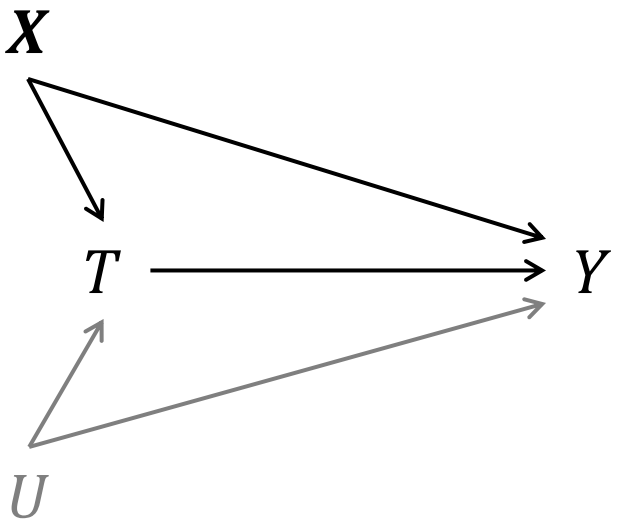
Unobserved Confounding in Pharmacoepidemiology

Table 1. Clinical, behavioral, and socioeconomic factors often not measured in pharmacoepidemiologic database studies and that may cause residual confounding

	Examples of drug—disease outcome associations possibly affected by residual confounding in epidemiologic database studies			
Potential confounders often unmeasured in pharmacoepidemiologic database studies	Anti-TNFα therapy and lymphoma in patients with rheumatoid arthritis	Statins and fractures	Cox-2 inhibitors and myocardial infarction	NSAIDs and short-term mortality
Body mass index		X	X	X
Over-the-counter aspirin use,			X	
Smoking		X	X	X
Frailty		X	X	X
Functional impairment		X		
Cognitive impairment		X		
Educational attainment		X	X	X
Income status		X	X	X
Laboratory values, for example, EBV antibody titer, lipid level, CRP level	X		X	
Results of invasive and non-invasive exams, for example, bone mineral density measure (DXA), ECG,		X	X	
Disease-specific severity markers	X			

Sebastian Schneeweiss. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiology & Drug Safety 2006 May. 15(5):291-303

Sensitivity Analysis for an Unobserved Confounder



Goal of a formal sensitivity analysis (Rosenbaum 1995, about Cornfield):

"replacing

a general qualitative statement that applies in all observational studies

by a quantitative statement that is specific to what is observed in a particular study"

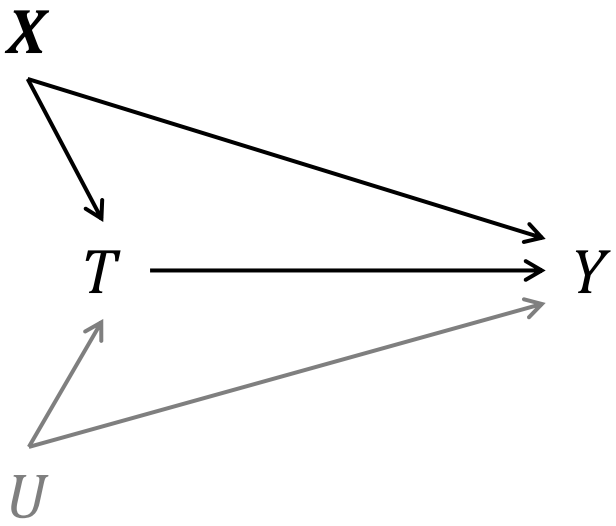
"instead of saying

that an association between treatment and outcome does not imply causation, that hidden biases can explain observed associations,

they say that

to explain the association seen in a particular study, one would need a hidden bias of a particular magnitude."

Sensitivity Analysis for an Unobserved Confounder



Questions:

- Consider a certain (range of) U, assess and correct bias
  - what is the bias of the TY effect?
  - what would the true TY effect be? (point & interval)

- Characterize U that nullifies the effect
  - with what U would the TY effect become stat. nonsig. or zero?
  - Could there be such a U?

Main message

- Many flavors
- Depends on specific situation (data, main analysis)
- Depends on question asked

Caveat: Only several methods will be covered to get you started. Far from exhaustive.

Methods covered

- Cornfield et al. (1959) smoking and lung cancer sensitivity analysis
- Rosenbaum's approach
  - Sensitivity analysis for subclasses (Rosenbaum & Rubin 1983)
  - Sensitivity analysis for match pairs (Rosenbaum 1987; Gastwirth, Krieger, Rosenbaum 1998)
- 2x2 tables and a binary U (Greenland 1996; Harding 2003)
- VanderWeele & Arah's (2011) bias formulas for general Y, T, U
- Sensitivity analysis w/out assumptions/E-value (Ding & VanderWeele 2016, VanderWeele & Ding 2017)
- Regression-based methods
  - Simple linear system & omitted variable bias (Harding 2009)
  - Complex non-linear systems (Lin, Psaty & Kronmal 1998)

Original example: Smoking and Lung Cancer

- R. A. Fisher (1958) thought that the observed relationship between smoking and lung cancer was due to some unobserved genetic factor that made people more susceptible to both.

- Cornfield et al. (1959) analysis apparently changed his mind: that genetic factor would have to be more strongly related to smoking and to lung cancer than anything already observed.

Fisher RA. Cigarettes, cancer and statistics. *Centennial Rev Arts and Sciences*. 2:151, Michigan State University, 1958.

Cornfield, J., Haenszel, W., Hammond, E. C., Lilienfeld, A. M., Shimkin, M. B., & Wynder, E. L. (1959). Smoking and lung cancer: Recent evidence and a discussion of some questions. *Journal of the National Cancer Institute*, *22*:173–203.

"if cigarette smokers have 9 times the risk of nonsmokers for developing lung cancer,

and this is not because cigarette smoke is a causal agent, but only because cigarette smokers produce hormone X,

then the proportion of hormone X-producers among cigarette smokers must be at least 9 times greater than that of nonsmokers.

If the relative prevalence of hormone X-producers is considerably less than ninefold, then hormone X cannot account for the magnitude of the apparent effect."

(Cornfield et al., 1959)

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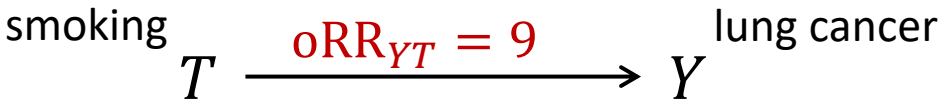

subscript $_{YT}$ means T predicting Y

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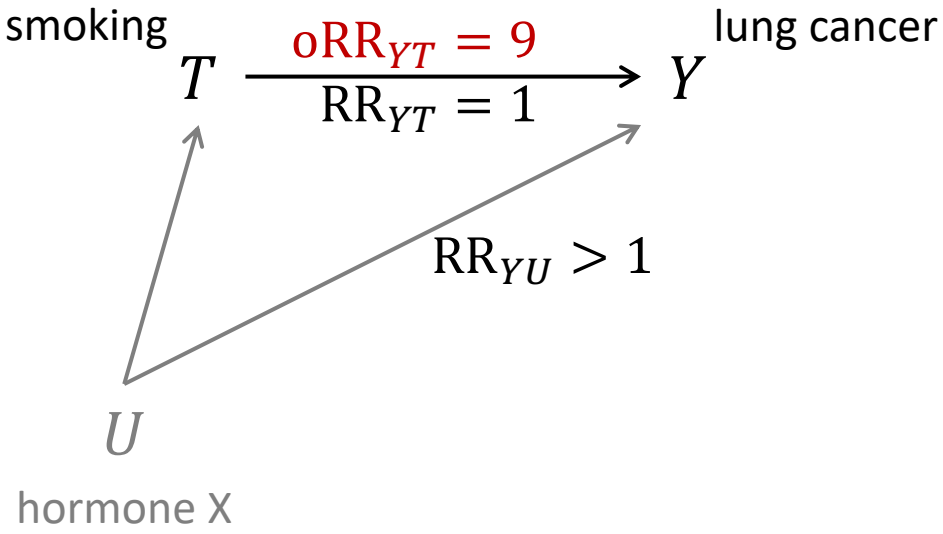

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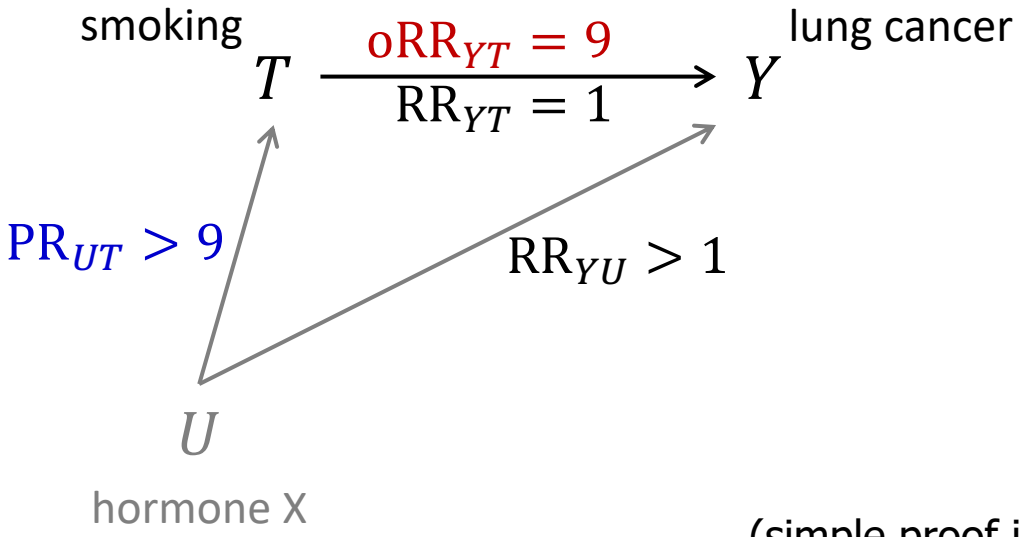

(simple proof in appendix A)

Cornfield et al. answered which of the following questions?

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Also, need methods that

accommodate both observed confounders and unobserved confounding!

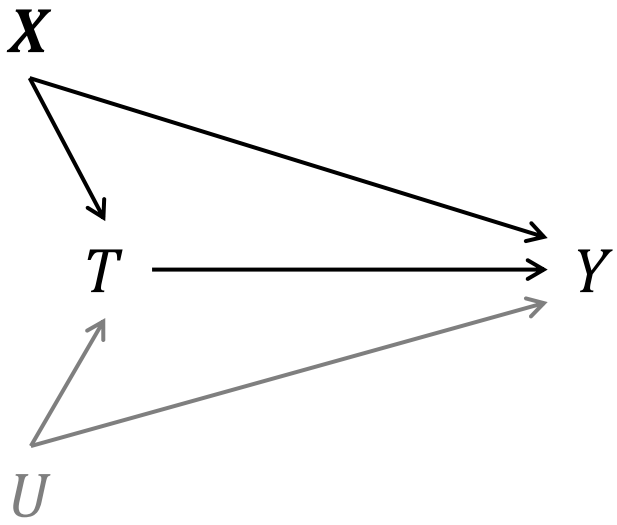
Treatment is unconfounded given observed $\boldsymbol{X}$ and unobserved U.

Rosenbaum's approach

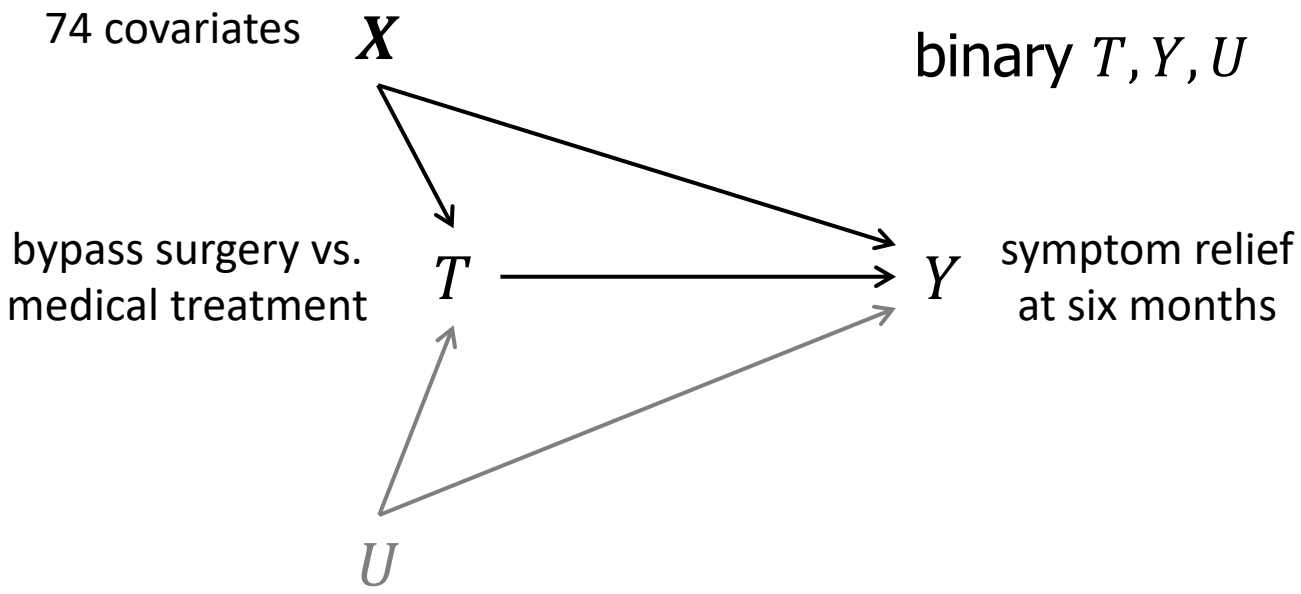
use propensity score methods to get balance on observed confounders $\boldsymbol{X}$

and then

conduct sensitivity analysis on an unobserved confounder U



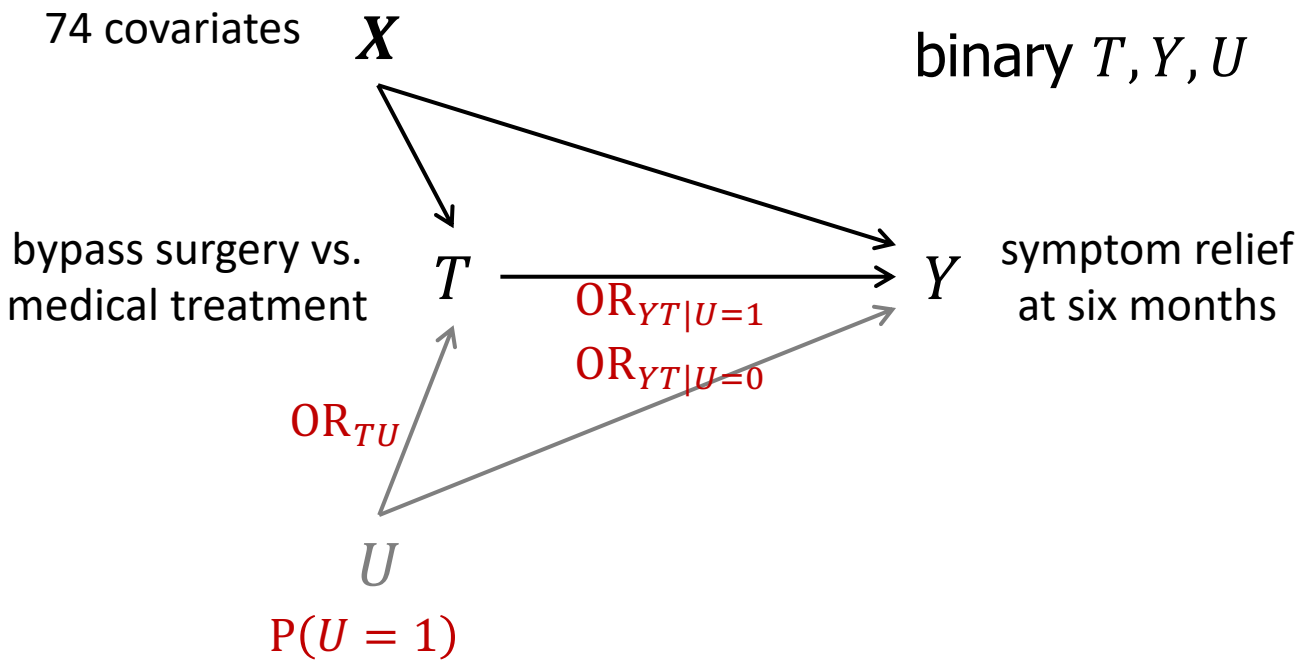
Rosenbaum & Rubin (1983) with subclassification



Usual analysis: propensity score subclassification to balance $\boldsymbol{X}$ and estimate the average treatment effect (ATE), $\mathrm{E}[Y_1] - \mathrm{E}[Y_0]$
(risk difference of symptom relief at six months)

Rosenbaum, P. R., & Rubin, D. B. (1983). Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. *Journal of the Royal Statistical Society*, *45*(2), 212–218

Rosenbaum & Rubin (1983) with subclassification



Sensitivity analysis:

- propensity score subclassification to balance $\boldsymbol{X}$
- within each subclass, sensitivity analysis on how U affects the ATE
- average over the subclasses

subclass-specific SA similar in spirit to SA for 2x2 table in Greenland (1996), Harding (2003) & Schneeweiss (2006)

Rosenbaum & Rubin's method answers which of the following questions?

Questions:

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  - with what U would the TY effect become stat. nonsig. or zero?
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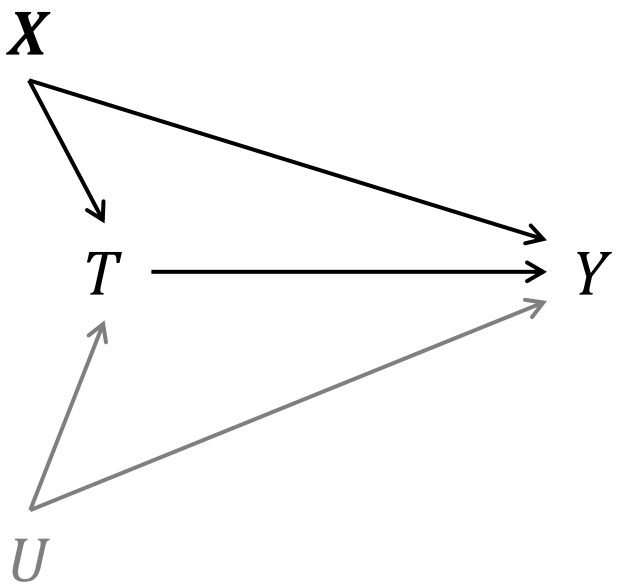
Rosenbaum & colleagues with matched pair data

Similar idea:

- Matching to balance $\boldsymbol{X}$ in each pair
- Find values of sensitivity parameters concerning an unobserved U where the true TY effect may be no longer statistically significant



Rosenbaum, P. R. (1987). Sensitivity analysis for certain permutational inferences in matched observational studies. *Biometrika*, *74*, 13–26.

Gastwirth, J. L., Krieger, A. M., & Rosenbaum, P. R. (1998). Dual and simultaneous sensitivity analysis for matched pairs. *Biometrika*, *85*(4), 907–920.

Starting point

If no unobserved confounding,

after matching on X,

the two individuals in a matched pair

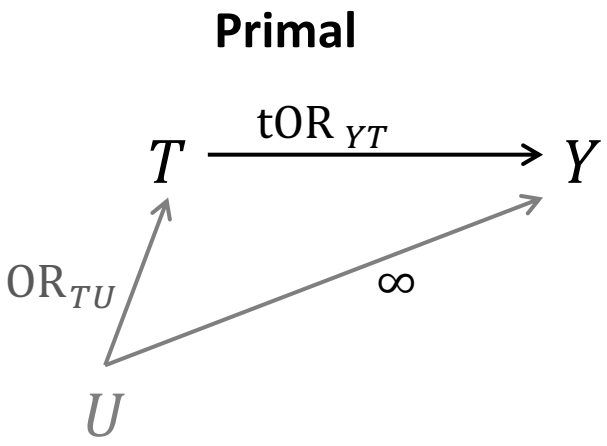
would have equal probability of treatment assignment

and equal odds of outcome for the same treatment

(ignorability/as if randomized)

Three methods for a binary Y: primal, dual and simultaneous

within a matched pair:



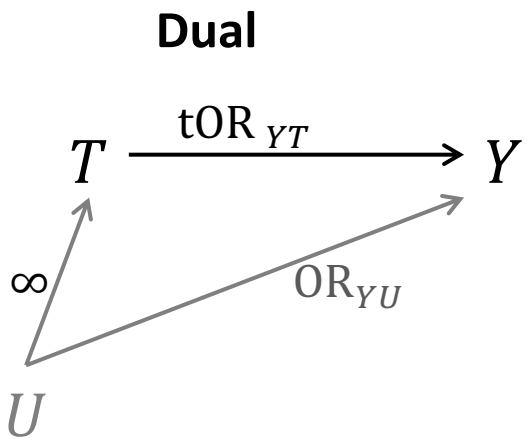
- Due to some unobserved U that is extremely predictive of the outcome, their odds of treatment assignment are different, $OR_{TU} \neq 1$
- Say the two odds are different by at most a factor of $\Gamma > 1$

$$\frac{1}{\Gamma} \leq \mathrm{OR}_{TU} \leq \Gamma$$

- Then tOR_{YT} is different from oOR_{YT}, and the true p-value for treatment effect is different from the observed p-value.
- What is the value of Γ where tOR_{YT} may become statistically non-sig?

Three methods for a binary Y: primal, dual and simultaneous

within a matched pair:



- Due to some unobserved U that is extremely correlated with treatment assignment, their odds of outcome are different, $OR_{YU} \neq 1$
- Say these two odds are different by at most a factor of $\Delta > 1$

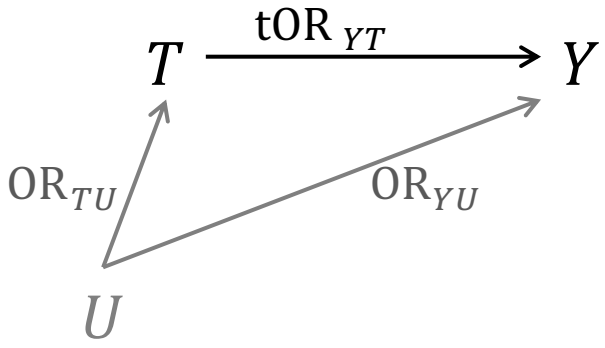
$$\frac{1}{\Delta} \leq \mathrm{OR}_{YU} \leq \Delta$$

- Then tOR_{YT} is different from oOR_{YT}, and the true p-value for treatment effect is different from the observed p-value.
- What is the value of Δ where tOR_{YT} may become statistically non-sig?

Three methods for a binary Y: primal, dual and simultaneous

Simultaneous

within a matched pair:



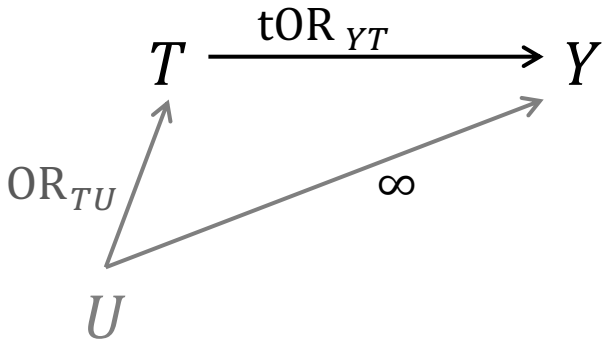
- Due to some unobserved U, their odds of treatment are different, $OR_{TU} \neq 1$, and their odds of outcome are different, $OR_{YU} \neq 1$
- Say these differences are bounded by factors of Γ and Δ (both > 1)

$$\frac{1}{\Gamma} \leq \mathrm{OR}_{TU} \leq \Gamma, \qquad \frac{1}{\Delta} \leq \mathrm{OR}_{YU} \leq \Delta$$

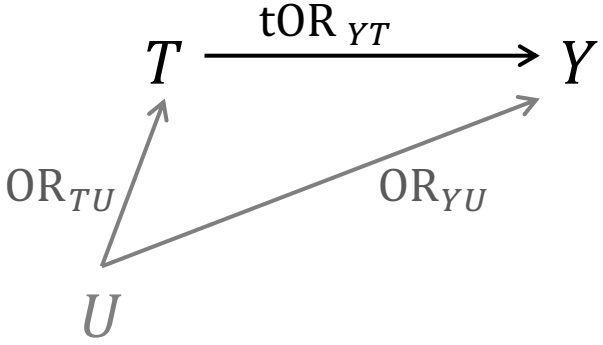
- Then tOR_{YT} is different from oOR_{YT}, and the true p-value for treatment effect is different from the observed p-value.
- What are the values of Γ and Δ where tOR_{YT} may be statistically non-sig?

Three methods for a binary Y: primal, dual and simultaneous

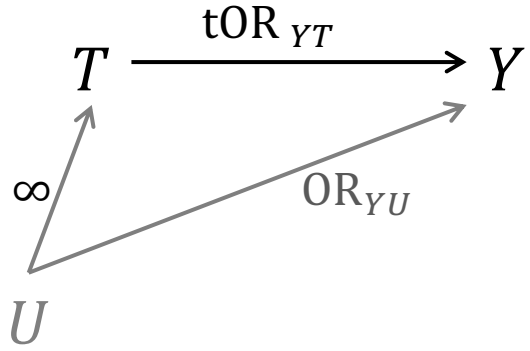
Primal



Simultaneous



Dual



$$\frac{1}{\Gamma} \leq \mathrm{OR}_{TU} \leq \Gamma$$

$$\frac{1}{\Delta} \leq \mathrm{OR}_{YU} \leq \Delta$$

$$\Gamma > 1, \Delta > 1$$

What are the values of Γ and/or Δ where tOR_{YT} is statistically non-sig?

using a modified McNemar's exact test for paired data

		$T=0$	
		$Y=1$	$Y=0$
$T=1$	$Y=1$	a	b
	$Y=0$	c	d

$b > c$

Liu, W., Kuramoto, S. J., & Stuart, E. A. (2013). An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prevention Science*, *14*(6), 570–80. doi:10.1007/s11121-012-0339-5

using a modified McNemar's exact test for paired data

		$T=0$: $Y=1$	$T=0$: $Y=0$
$T=1$	$Y=1$	a	b
	$Y=0$	c	d

$b > c$

Liu, Kuramoto & Stuart (2013) example:

		Mother death by accident		
		Child suicide hopspitalization	Child no suicide hospitalization	
Mother death by suicide	Child suicide hospitalization	7	**226**	233
	Child no suicide hospitalization	**121**	5246	5367
		128	5472	5600

Liu, W., Kuramoto, S. J., & Stuart, E. A. (2013). An introduction to sensitivity analysis for unobserved confounding in nonexperimental prevention research. *Prevention Science*, *14*(6), 570–80. doi:10.1007/s11121-012-0339-5

using a modified McNemar's exact test for paired data

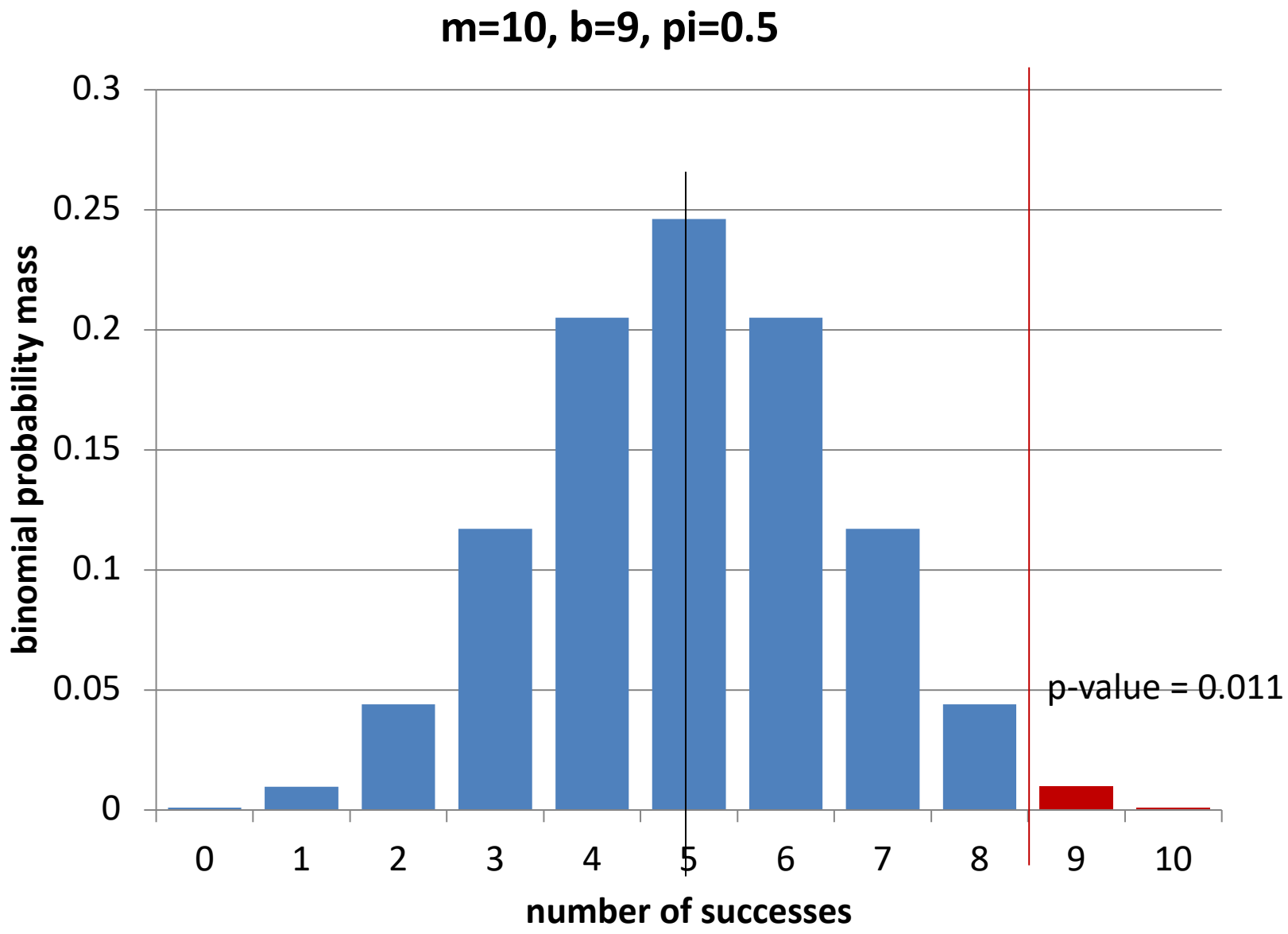
		$T=0$: $Y=1$	$T=0$: $Y=0$
$T=1$	$Y=1$	a	b [10]
	$Y=0$	c [01]	d

$b > c$

Original test:

- H0: for discordant pair, equal probability (0.5) of each type
- one-sided p-value = probability of observing b or more pairs of type [10] among $m = b + c$ discordant pairs

$$p = \sum_{i=b}^{m} \binom{m}{i} (0.5)^i (0.5)^{m-i}$$



Excel function `BINOM.DIST(b,m,pi,0)` (each column); or Stata function `bitest`, R function `binom.test`

using a modified McNemar's exact test for paired data

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$T=1$	$Y=1$	a	b [10]
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$$p = \sum_{i=b}^{m} \binom{m}{i} (0.5)^i (0.5)^{m-i}$$

Modified test:

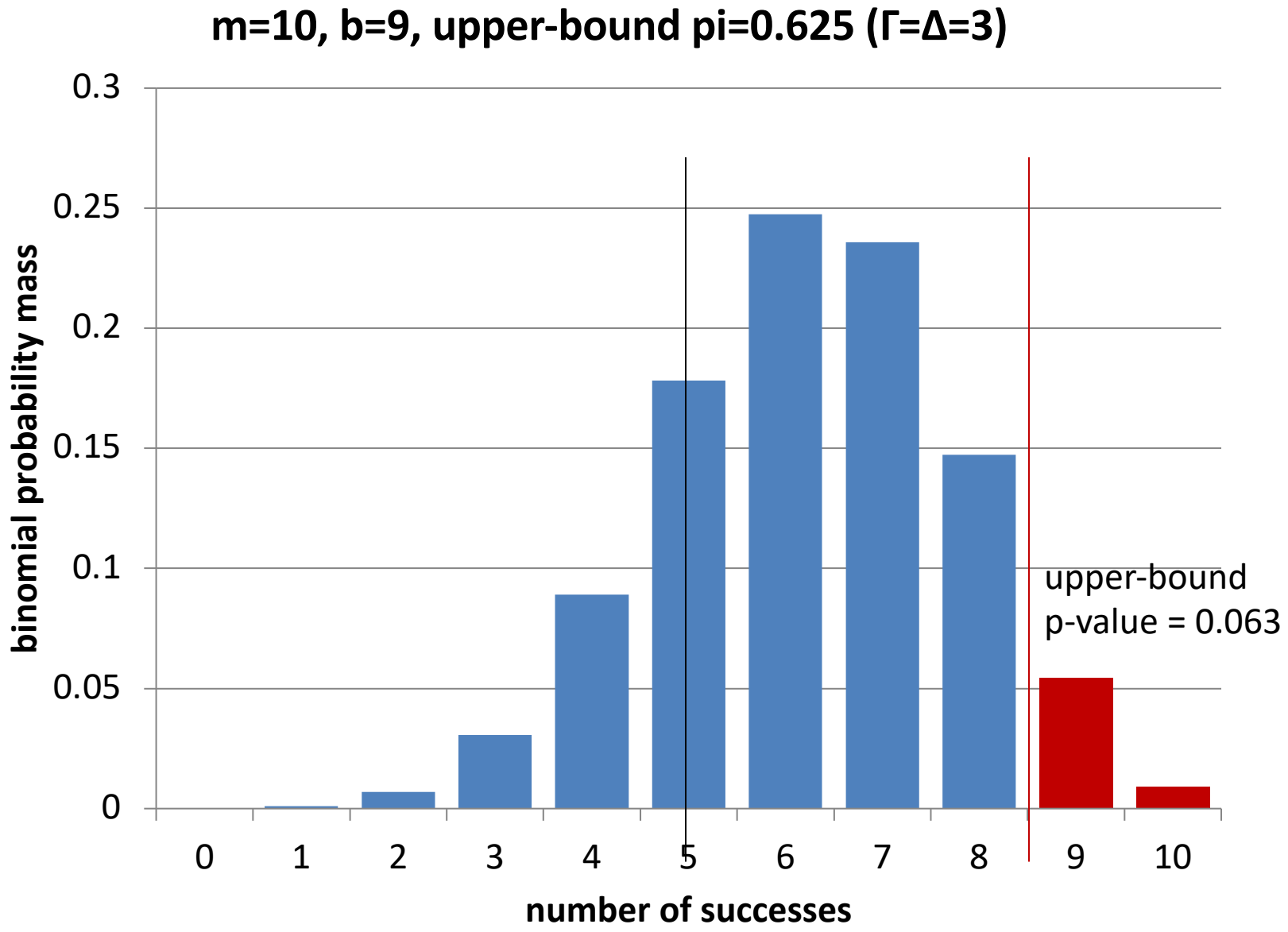
- H0: for discordant pairs, probability π of type [10], $(1-\pi)$ of type [01]

primal: $\frac{1}{1+\Gamma} \leq \pi \leq \frac{\Gamma}{1+\Gamma}$; dual: $\frac{1}{1+\Delta} \leq \pi \leq \frac{\Delta}{1+\Delta}$; simultaneous: $0.5 \leq \pi \leq \frac{\Gamma}{1+\Gamma} \cdot \frac{\Delta}{1+\Delta} + \frac{1}{1+\Gamma} \cdot \frac{1}{1+\Delta}$

- plugging in the bounds of π gives bounds of p-value:

$$p = \sum_{i=b}^{m} \binom{m}{i} \pi^i (1-\pi)^{m-i}$$

- which are the values of Γ and/or Δ where p-value upper-bound ≥ 0.05



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Application to Liu et al. (2013)

Upper-bound of one-sided p-value associated with Γ and Δ using Rosenbaum's simultaneous sensitivity analysis

Γ \ Δ	1.0	2.0	3.0	4.0	5.0	infinity
1.0	<.001	<.001	<.001	<.001	<.001	<.001
2.0	<.001	<.001	.006	.03	**.07**	**.75**
3.0	<.001	.006	**.17**	**.50**	**.75**	**1**
4.0	<.001	.03	**.50**	**.89**	**.98**	**1**
5.0	<.001	**.07**	**.75**	**.98**	**.99**	**1**
infinity	<.001	**.75**	**1**	**1**	**1**	**1**

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infinity	<.001	**.75**	**1**	**1**	**1**	**1**

.05

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2.0	<.001	<.001	.006	.03	.05	.07	.75
3.0	<.001	.006	.17	.50	.75	1
4.0	<.001	.03	.50	.89	.98	1
5.0	<.001	.07	.75	.98	.99	1
infinity	<.001	.05	.75	1	1	1

.05
.05
.05
.05

Rosenbaum's primal, dual and simultanenous methods answer which of the following questions?

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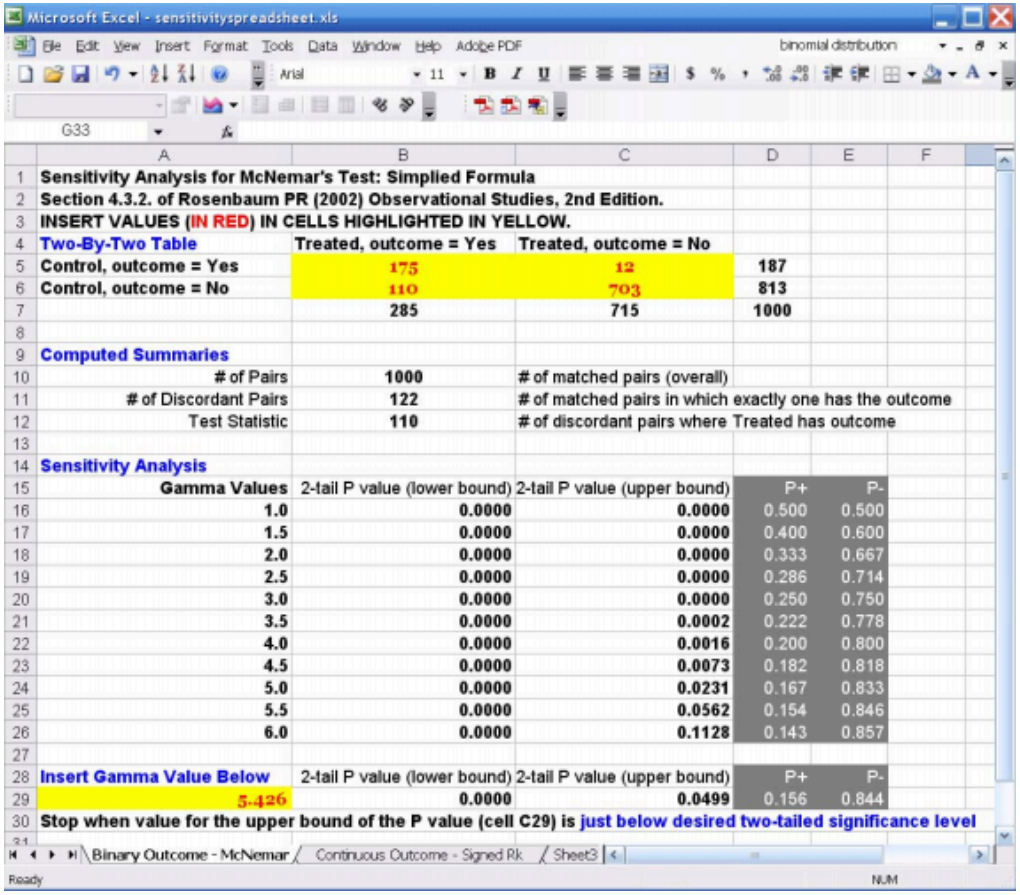
If due to unobserved confounding, between the treated and control units in matched pairs, the odds of treatment differ by a factor of up to 2.8 and the odds of outcome (net of treatment) also differ by a factor of up to 2.8, then the true treatment effect may be statistically non-sig.

Comments

- Brilliant idea!
- Only two (instead of four) sensitivity parameters
- Directly relevant when main analysis is matched analysis
  - In practice, matching might be done only to obtain balance, with analysis then ignoring that data are matched. Often regression is used to adjust for any remaining imbalance in (observed) confounders.
- Need to know the two numbers of discordant pairs
- Conservative because considers things at the edge:
  - When effect becomes non-sig, not when effect becomes zero
  - Upper-bound of p-value, not simply p-value
  - McNemar's exact test tends to be conservative for small m
- Can also be interpreted as sensitivity analysis for a binary U

Excel spreadsheet

Love TE (2008) Spreadsheet-based sensitivity analysis calculations for matched samples. Center for Health Care Research & Policy, Case Western Reserve University.
Available online at http://www.chrp.org/propensity



Microsoft Excel - sensitivityspreadsheet.xls

	A	B	C	D	E	F
1	Sensitivity Analysis for McNemar's Test: Simplied Formula					
2	Section 4.3.2. of Rosenbaum PR (2002) Observational Studies, 2nd Edition.					
3	INSERT VALUES (IN RED) IN CELLS HIGHLIGHTED IN YELLOW.					
4	Two-By-Two Table	Treated, outcome = Yes	Treated, outcome = No			
5	Control, outcome = Yes	175	12	187		
6	Control, outcome = No	110	703	813		
7		285	715	1000		
8						
9	Computed Summaries					
10	# of Pairs	1000	# of matched pairs (overall)			
11	# of Discordant Pairs	122	# of matched pairs in which exactly one has the outcome			
12	Test Statistic	110	# of discordant pairs where Treated has outcome			
13						
14	Sensitivity Analysis					
15	Gamma Values	2-tail P value (lower bound)	2-tail P value (upper bound)	P+	P-	
16	1.0	0.0000	0.0000	0.500	0.500	
17	1.5	0.0000	0.0000	0.400	0.600	
18	2.0	0.0000	0.0000	0.333	0.667	
19	2.5	0.0000	0.0000	0.286	0.714	
20	3.0	0.0000	0.0000	0.250	0.750	
21	3.5	0.0000	0.0002	0.222	0.778	
22	4.0	0.0000	0.0016	0.200	0.800	
23	4.5	0.0000	0.0073	0.182	0.818	
24	5.0	0.0000	0.0231	0.167	0.833	
25	5.5	0.0000	0.0562	0.154	0.846	
26	6.0	0.0000	0.1128	0.143	0.857	
27						
28	Insert Gamma Value Below	2-tail P value (lower bound)	2-tail P value (upper bound)	P+	P-	
29	5.426	0.0000	0.0499	0.156	0.844	
30	Stop when value for the upper bound of the P value (cell C29) is just below desired two-tailed significance level					

Binary Outcome - McNemar | Continuous Outcome - Signed Rk | Sheet3

Ready NUM

Other methods in this genre

- Matched data, continuous outcome: use a modified Wilcoxon signed rank test (Rosenbaum 1987)
- Sensitivity analysis in the context of matching with multiple controls (Gastwirth, Krieger & Rosenbaum 2000)
- Sensitivity analysis in the context of propensity score weighting (McCaffrey et al. 2004; Ridgeway 2006)

Gastwirth, J. L., Krieger, a M., & Rosenbaum, P. R. (2000). Asymptotic Separability in Sensitivity Analysis. *Journal of the Royal Statistical Society*, *62*, 545–555.

McCaffrey, D. F., Ridgeway, G., & Morral, A. (2004). Propensity score estimation with boosted regression for evaluating causal effects in observational studies. *Psychological Methods*, *9*(4), 403–425. Retrieved from http://psycnet.apa.org/journals/met/9/4/403/

Ridgeway, G. (2006). Assessing the effect of race bias in post-traffic stop outcomes using propensity scores. *Journal of Quantitative Criminology*, *22*(1), 1029. Retrieved from http://www.jstor.org/stable/23367478

Methods covered

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- Rosenbaum's approach
  - Sensitivity analysis for subclasses (Rosenbaum & Rubin 1983)
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  - Simple linear system & omitted variable bias (Harding 2009)
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Greenland's (1996) and Harding's (2003) methods

- Data as 2x2 table, either case-control or cohort

	$Y = 1$ (child suicide hospitalization)	$Y = 0$ (child no suicide hospitalization)
$T = 1$ (mother suicide)	A	B
$T = 0$ (mother accident)	C	D

Greenland, S. (1996). Basic methods for sensitivity analysis of biases. *International Journal of Epidemiology*, *25*(6), 1107–1116. doi:10.1093/ije/25.6.1107

Harding, D. J. (2003). Counterfactual Models of Neighborhood Effects: The Effect of Neighborhood Poverty on Dropping Out and Teenage Pregnancy. *American Journal of Sociology*, *109*(3), 676–719. doi:10.1086/379217

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- For specified plausible binary unobserved U, unpack into two tables

$U = 1$

	$Y = 1$	$Y = 0$
$T = 1$	a_1	b_1
$T = 0$	c_1	d_1

$U = 0$

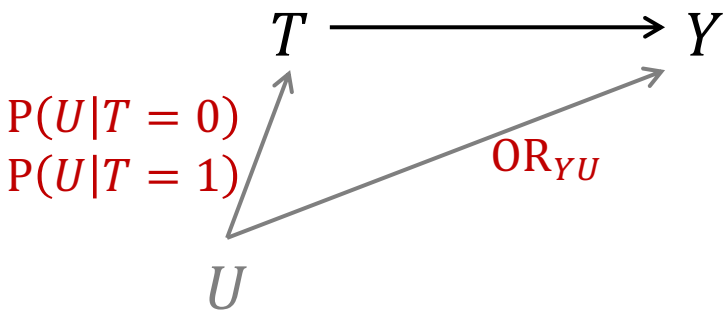
	$Y = 1$	$Y = 0$
$T = 1$	a_0	b_0
$T = 0$	c_0	d_0

$$a_1 + a_2 = A; \quad b_1 + b_2 = B; \quad c_1 + c_2 = C; \quad d_1 + d_2 = D$$

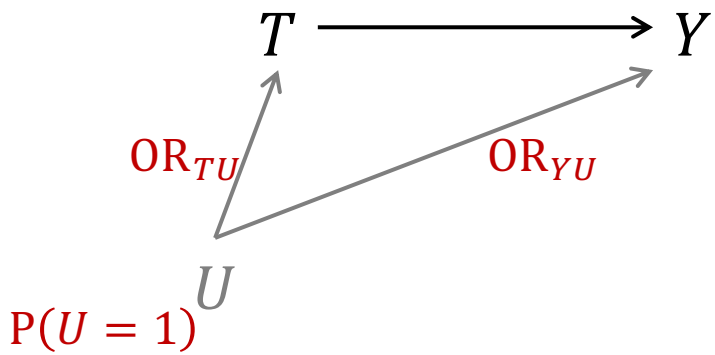
- and conduct analysis using the two tables or a constructed dataset with T, Y, U to obtain $OR_{YT|U}$

How to specify a plausible range of U?
3 sensitivity parameters (4 if allow TU interaction):

Greenland



Harding



For details on table cells calculation, see Liu et al., which does an excellent job of explaining it for the case without TU interaction.

Greenland's and Harding's methods can answer which of the following questions?

Questions:

- Consider a certain (range of) U, assess and correct bias
  - what is the bias of the TY effect?
  - what would the true TY effect be? (point & interval)

- Characterize U that nullifies the effect
  - with what U would the TY effect become stat. nonsig. or zero?
  - Could there be such a U?

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- Easy to understand
- Relatively easy to implement
- Corrected point estimate and confidence interval! ☺

- How to deal with observed confounders $\boldsymbol{X}$?

  Balance $\boldsymbol{X}$ using propensity score methods and then conduct sensitivity analysis for $\boldsymbol{X}$-balanced samples (or subsamples)
  - Suclassification and then sensitivity analysis within subclasses (Rosenbaum & Rubin 1983)
  - Matching (or weighting) and then use the matched/weighted sample as an $\boldsymbol{X}$-balanced sample (ignoring matched) for sensitivity analysis (Harding 2003; Liu et al. 2013)

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VanderWeele & Arah's (2011) general bias formulas

Very general!

For simplicity, let U be binary, and consider ATE on the additive scale.

Vanderweele, T. J., & Arah, O. a. (2011). Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*, *22*(1), 42–52. doi:10.1097/EDE.0b013e3181f74493

VanderWeele & Arah's (2011) general bias formulas

- Each individual has a potential outcome under treatment, Y_1, and a potential outcome under control, Y_0.
- Treatment effect is: $\mathrm{ATE} = \mathrm{E}[Y_1] - \mathrm{E}[Y_0]$

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$$\mathrm{ATE} = \sum_{\boldsymbol{x}} \sum_{u} \{\mathrm{E}[Y|T = 1, \boldsymbol{x}, u] - \mathrm{E}[Y|T = 0, \boldsymbol{x}, u]\}\mathrm{P}(\mathbf{u}, \boldsymbol{x}) .$$

Vanderweele, T. J., & Arah, O. a. (2011). Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*, *22*(1), 42–52. doi:10.1097/EDE.0b013e3181f74493

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$$\mathrm{ATE} = \sum_{\boldsymbol{x}} \sum_{u} \{\mathrm{E}[Y|T=1,\boldsymbol{x},u] - \mathrm{E}[Y|T=0,\boldsymbol{x},u]\}\mathrm{P}(u|\boldsymbol{x})\mathrm{P}(\boldsymbol{x})\,.$$

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- Adjusting for $\boldsymbol{X}$ but not U gives

$$\sum_{\boldsymbol{x}} \{\mathrm{E}[Y|T=1,\boldsymbol{x}] - \mathrm{E}[Y|T=0,\boldsymbol{x}]\}\mathrm{P}(\boldsymbol{x})\,.$$

- Bias is the difference between these two quantities.

General formula:

$$\text{bias} = \sum_{\boldsymbol{x}} \{\mathrm{E}[Y|T=1,U=1,\boldsymbol{x}] - \mathrm{E}[Y|T=1,U=0,\boldsymbol{x}]\}[\mathrm{P}(U=1|T=1,\boldsymbol{x}) - \mathrm{P}(U=1|\boldsymbol{x})]\mathrm{P}(\boldsymbol{x}) - \sum_{\boldsymbol{x}} \{\mathrm{E}[Y|T=0,U=1,\boldsymbol{x}] - \mathrm{E}[Y|T=0,U=0,\boldsymbol{x}]\}[\mathrm{P}(U=1|T=0,\boldsymbol{x}) - \mathrm{P}(U=1|\boldsymbol{x})]\mathrm{P}(\boldsymbol{x})$$

General formula:

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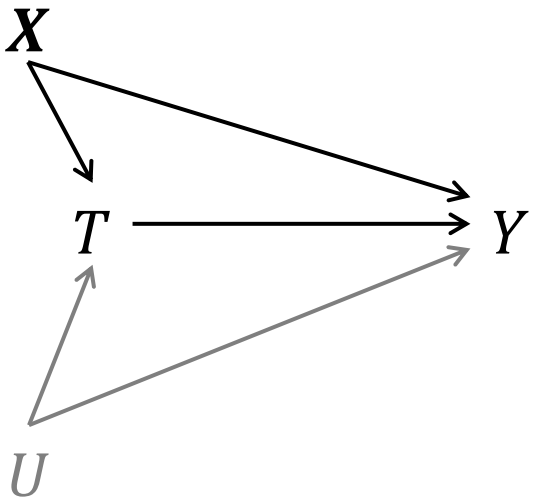
$$\sum_{x} \{\mathrm{E}[Y|T=0,U=1,\boldsymbol{x}] - \mathrm{E}[Y|T=0,U=0,\boldsymbol{x}]\}[\mathrm{P}(U=1|T=0,\boldsymbol{x}) - \mathrm{P}(U=1|\boldsymbol{x})]\mathrm{P}(\boldsymbol{x})$$

UY given T within $\boldsymbol{X}$ stratum

UT within $\boldsymbol{X}$ stratum

Strata could be strata of $\boldsymbol{X}$ (eg female & college)
or strata (subclasses) of propensity score.

Complicated, but simplifies in some cases.



If simplification 1: within $\boldsymbol{X}$ stratum, no UT interaction

$$\text{bias} = \sum_{\boldsymbol{x}} \{\mathrm{E}[Y|U=1,T,\boldsymbol{x}] - \mathrm{E}[Y|U=0,T,\boldsymbol{x}]\}[\mathrm{P}(U=1|T=1,\boldsymbol{x}) - \mathrm{P}(U=1|T=0,\boldsymbol{x})]\mathrm{P}(\boldsymbol{x})$$

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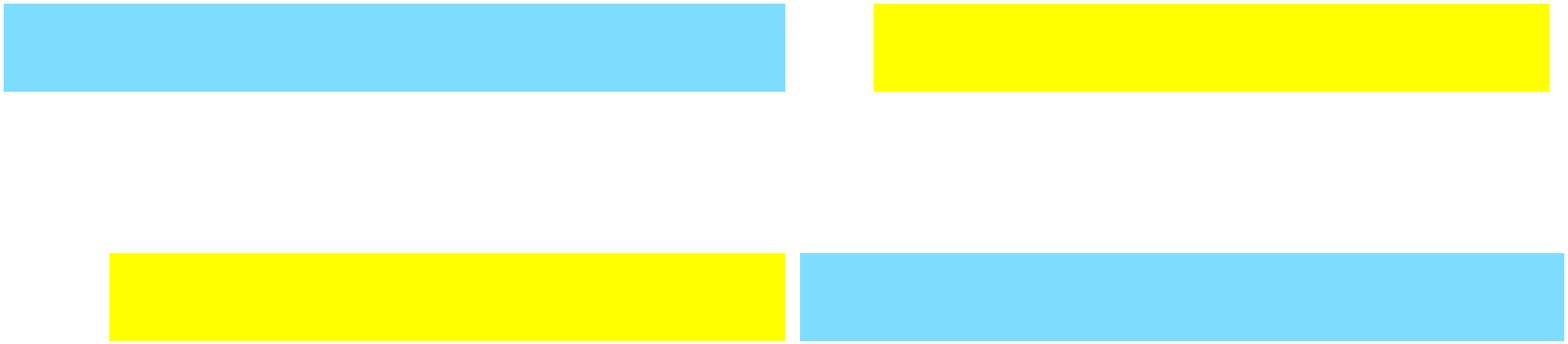
plus simplification 2: the UY relationship given T does not vary across $\boldsymbol{X}$ strata

$$\text{bias} = \{\mathrm{E}[Y|U=1,T,\boldsymbol{X}] - \mathrm{E}[Y|U=0,T,\boldsymbol{X}]\}\sum_{\boldsymbol{x}} [\mathrm{P}(U=1|T=1,\boldsymbol{x}) - \mathrm{P}(U=1|T=0,\boldsymbol{x})]\mathrm{P}(\boldsymbol{x})$$



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or plus simplification 3: the UT relationship does not vary across $\boldsymbol{X}$ strata

$$\text{bias} = [\mathrm{P}(U=1|T=1,\boldsymbol{X}) - \mathrm{P}(U=1|T=0,\boldsymbol{X})]\sum_{\boldsymbol{x}} \{\mathrm{E}[Y|U=1,T,\boldsymbol{x}] - \mathrm{E}[Y|U=0,T,\boldsymbol{x}]\}\mathrm{P}(\boldsymbol{x})$$

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or plus both simplifications 2 and 3

$$\text{bias} = \{\mathrm{E}[Y|U=1,T,\boldsymbol{X}] - \mathrm{E}[Y|U=0,T,\boldsymbol{X}]\}[\mathrm{P}(U=1|T=1,\boldsymbol{X}) - \mathrm{P}(U=1|T=0,\boldsymbol{X})]$$

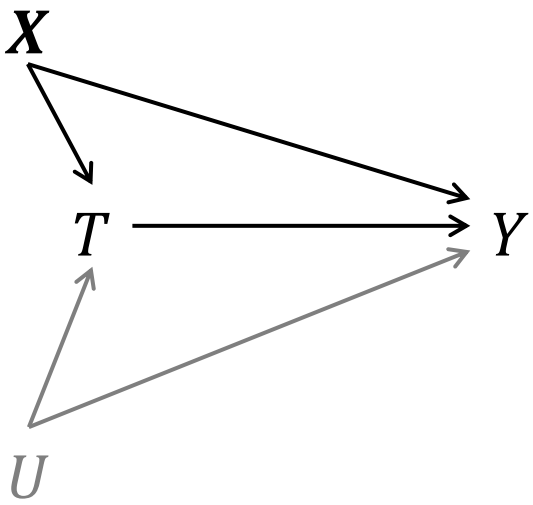
How does this translate to sensitivity parameters?

How does it relate to prior methods?

Consider the simplest formula, with all three simplifications,

$$\text{bias} = \{\mathrm{E}[Y|U=1,T,\boldsymbol{X}] - \mathrm{E}[Y|U=0,T,\boldsymbol{X}]\}[\mathrm{P}(U=1|T=1,\boldsymbol{X}) - \mathrm{P}(U=1|T=0,\boldsymbol{X})]$$

$\mathrm{RD}_{YU|T,\boldsymbol{X}}$ $\mathrm{PD}_{UT|\boldsymbol{X}}$



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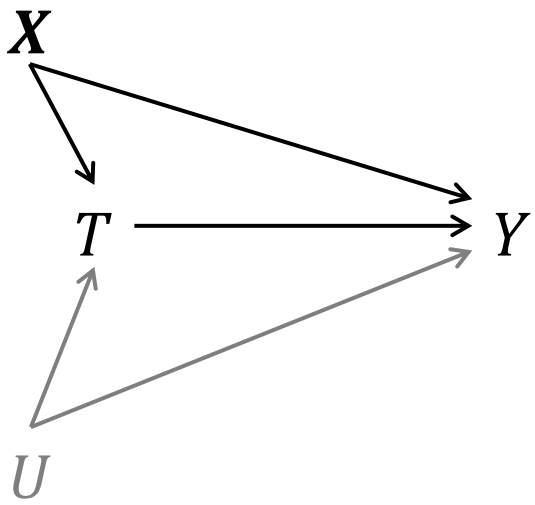

In the $\boldsymbol{X}$ stratum specific case (or no $\boldsymbol{X}$ case), alternatives to specifying $\mathrm{PD}_{UT|\boldsymbol{x}}$:

- To combine a relative measure of association

  $\mathrm{PR}_{UT|\boldsymbol{x}}$ or $\mathrm{RR}_{TU|\boldsymbol{x}}$ or $\mathrm{OR}_{TU|\boldsymbol{x}}$

  and a prevalence

  $\mathrm{P}(U=1|T=0,\boldsymbol{x})$ or $\mathrm{P}(U=1|\boldsymbol{x})$
- To specify two prevalences

  $\mathrm{P}(U=1|T=0,\boldsymbol{x})$ or $\mathrm{P}(U=1|T=1,\boldsymbol{x})$

With fewer simplications, more parameters!

Website for sensitivity analyses in similar spirit

https://jiangtammy.shinyapps.io/quantitative_bias_analysis/

Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York, NY: Springer New York; 2009. doi:10.1007/978-0-387-87959-8

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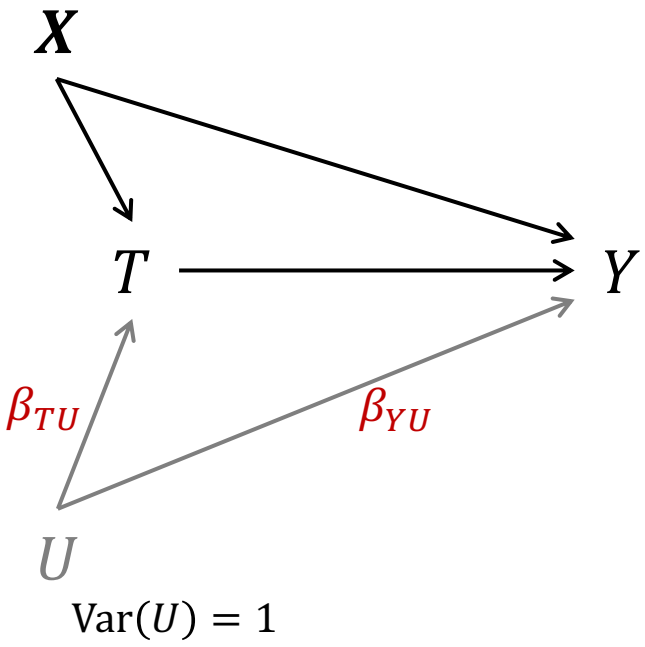
A regression-based approach: sensitivity analysis based on omitted variable bias (Harding 2009)



- T is binary (smoking) – my example, not Harding's.
- Y is binary or continuous (obesity/weight).
- U is continuous (depressive symptom severity), variance fixed at 1, independent of $\boldsymbol{X}$ (think $\boldsymbol{X}$ have been "regressed out" of U).
- Rely on linear models

$$\mathrm{E}[Y] = \alpha_Y + \beta_{YX}X + \beta_{YT}T + \beta_{YU}U$$
$$\mathrm{E}[T] = \alpha_T + \beta_{TX}X + \beta_{TU}U$$

- Need to standardize T, get bias $\beta_{TU}\beta_{YU}$

$$t\beta_{YT} = o\beta_{YT} - \beta_{TU}\beta_{YU}$$

Harding, D. J. (2009). Collateral Consequences of Violence in Disadvantaged Neighborhoods. *Social Forces*, *88*(2), 757–784. doi:10.1353/sof.0.0281

Comments:

- Would like to not standardize T

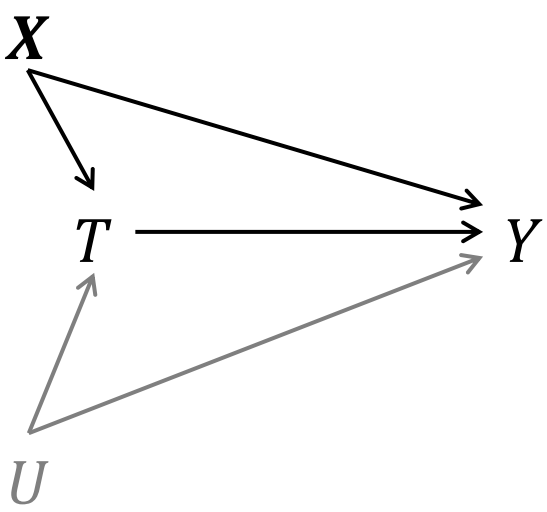
  Simple fix: Shift the representation of the UT relationship from β_{TU} (RD of treatment associated with one SD difference in U) to β_{UT} (the difference in mean U comparing $T = 1$ and $T = 0$). Then

  $$t\beta_{YT} = o\beta_{YT} - \beta_{UT}\beta_{YU}$$

  Note that this difference in means is not a causal effect (causation is assumed to be the opposite direction).

- Need to be explicit about the assumptions of the linear system

More regression based: Lin, Psaty & Kronmal (1998)



Very interesting paper!

- T binary
- Y binary (log-linear or logistic) or survival time
- U binary or normal
- allowing TU interaction

Complicated equations are simplified based on the assumption that U and $\boldsymbol{X}$ are independent conditional on T, which is violated because T is a collider (Hernan & Robins 1999).

If no $\boldsymbol{X}$, reduce to simpler results.

VanderWeele & Arah note that this paper offers an alternative assumption that the conditional mean of U is additive in $\boldsymbol{X}$ and T which is helpful for deriving the bias.

Lin, D. Y., Psaty, B. M., & Kronmal, R. A. (1998). Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*, *54*(3), 948–963. doi:10.2307/2533848

Hernan, M. A., & Robins, J. M. (1999). Letter to the Editor: Assessing the sentivity of regression results to unmeasured confounders in observational studies. *Biometrics*, *55*, 1316–1317.

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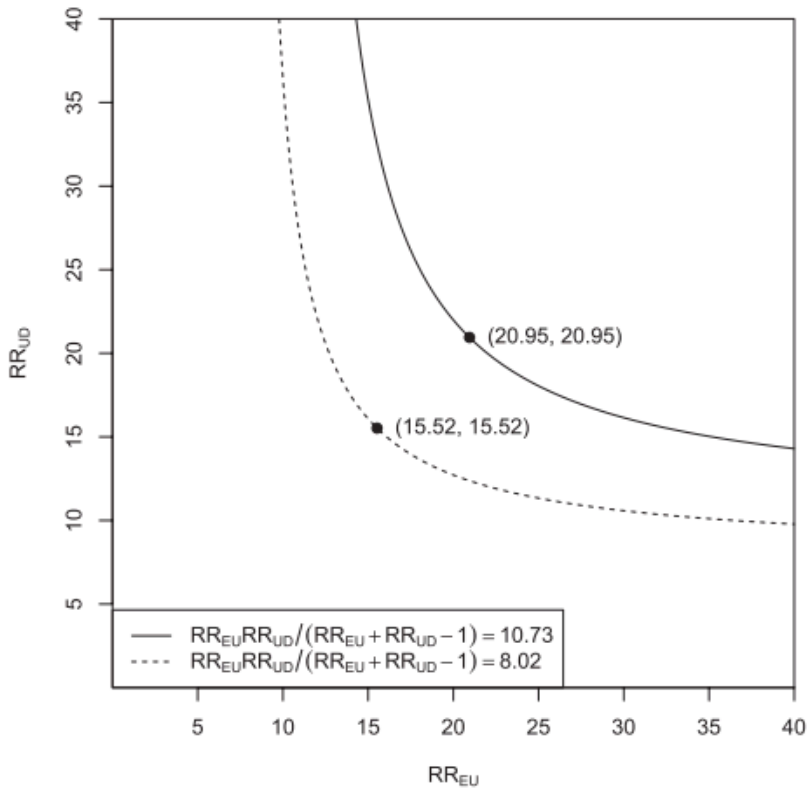
Ding and VanderWeele (2016)

$$\frac{oRR_{YT|X}}{tRR_{YT|X}} \geq \frac{\max\left(PR_{UT|X}\right)\max\left(RR_{YU|X}\right)}{\max\left(PR_{UT|X}\right)+\max\left(RR_{YU|X}\right)-1} = \frac{\beta_{UT}\beta_{YU}}{\beta_{UT}+\beta_{YU}-1}$$

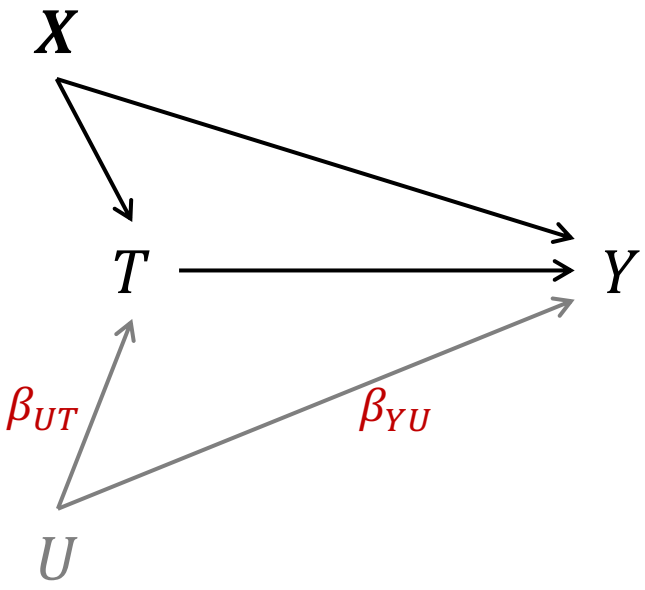
β_{YU}



β_{UT}

FIGURE. The areas above the two lines are the joint values of the exposure–confounder association RR_{EU} and the confounder–outcome association RR_{UD} that can would be required to explain away the effect estimate 10.73 and the lower confidence limit 8.02.

E-value for sensitivity analysis (VanderWeele and Ding 2017)



- T is binary (maternal breastfeeding)
- Y is binary (infant respiratory death)
- U is binary (maternal smoking status)

- Based on the bias factor

$$B = \frac{\beta_{UT}\beta_{YU}}{\beta_{UT} + \beta_{YU} - 1}$$

- E-value: the joint minimum strength of association on the *risk ratio scale* that an unmeasured confounder would need to have with the treatment and outcome (controlling for X) to explain away the observed risk ratio of β_{YT}

$$Evalue = \beta_{YT} + \sqrt{\beta_{YT} * (\beta_{YT} - 1)}$$

VanderWeele, T.J., Ding, P. (2017). Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017;167:268-274. doi:10.7326/M16-2607

Interpretation:

- "The observed risk ratio of β_{YT} could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of [insert E-value]-fold each, above and beyond the measured confounders, but weaker confounding could not do so."

- The higher the E-value, the stronger the unmeasured confounding associations must be to produce bias equal to the observed treatment-outcome association.

Notes:

- For RR <1, must take inverse of RR first, then apply the formula
- Good to also report E-value of confidence limit closest to the the null
- Paper summarizes calculations for other effect measures (e.g., OR, IRR)
- E-value not to be confused with P-value!

E-value calculator: https://www.evalue-calculator.com (covers a range of scenarios

Methods covered

- Cornfield et al. (1959) smoking and lung cancer sensitivity analysis
- Rosenbaum's approach
  - Sensitivity analysis for subclasses (Rosenbaum & Rubin 1983)
  - Sensitivity analysis for match pairs (Rosenbaum 1987; Gastwirth, Krieger, Rosenbaum 1998)
- 2x2 tables and a binary U (Greenland 1996; Harding 2003)
- VanderWeele & Arah's (2011) bias formulas for general Y, T, U
- Regression-based methods
  - Simple linear system & omitted variable bias (Harding 2009)
  - Complex non-linear systems (Lin, Psaty & Kronmal 1998)
- Sensitivity analysis w/out assumptions/E-value (Ding & VanderWeele 2016, VanderWeele & Ding 2017)

Other aproaches

- Simulation
  - Arah, O., Chiba, Y., & Greenland, S. (2008). Bias formulas for external adjustment and sensitivity analysis of unmeasured confounders. *Annals of Epidemiology*, *18*(8), 637–46. doi:10.1016/j.annepidem.2008.04.003
  - Steenland, K., & Greenland, S. (2004). Monte Carlo Sensitivity Analysis and Bayesian Analysis of Smoking as an Unmeasured Confounder in a Study of Silica and Lung Cancer. *American Journal of Epidemiology*, *160*(4), 384–392. doi:10.1093/aje/kwh211
- Bayesian methods
  - Steenland & Greenland (2004)
  - McCandless, L. C., Gustafson, P., & Levy, A. (2007). Bayesian sensitivity analysis for unmeasured confounding in observational studies. *Statistics in Medicine*, *26*, 2331–2347. doi:10.1002/sim
- Using external data to adjust results
  - Stürmer, T., Schneeweiss, S., Avorn, J., & Glynn, R. J. (2005). Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration. *American Journal of Epidemiology*, *162*(3), 279–89. doi:10.1093/aje/kwi192
- Design sensitivity
  - Zubizarreta, J. R., Cerdá, M., & Rosenbaum, P. R. (2013). Effect of the 2010 Chilean earthquake on posttraumatic stress: reducing sensitivity to unmeasured bias through study design. *Epidemiology*, *24*(1), 79–87. doi:10.1097/EDE.0b013e318277367e