Sensitivity Analysis for an Unobserved Confounder

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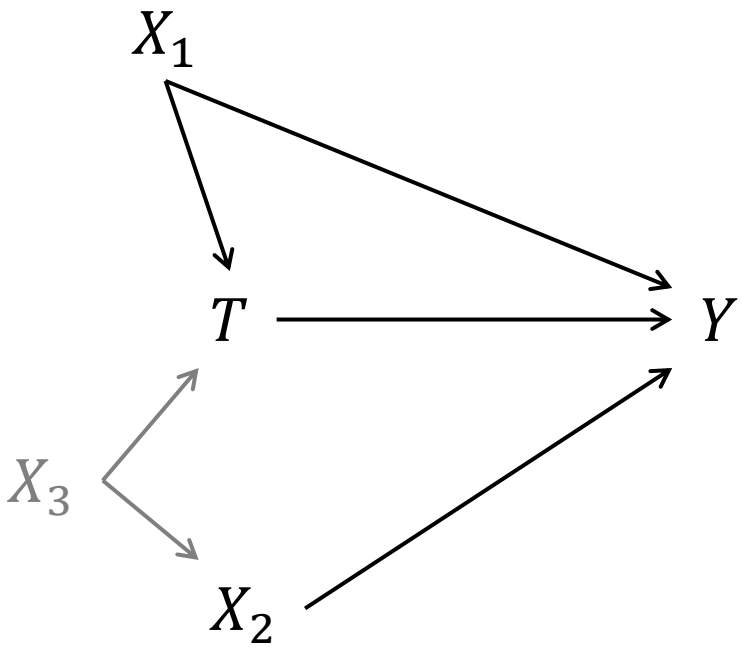
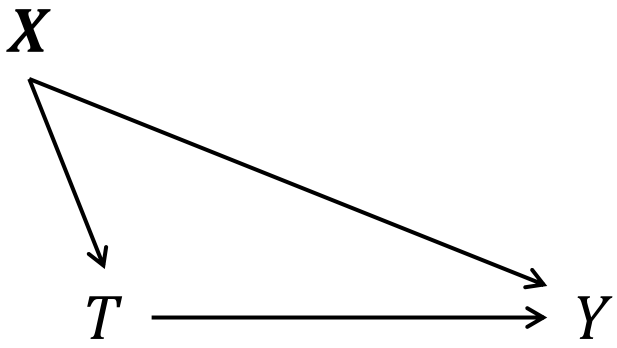
Confounding

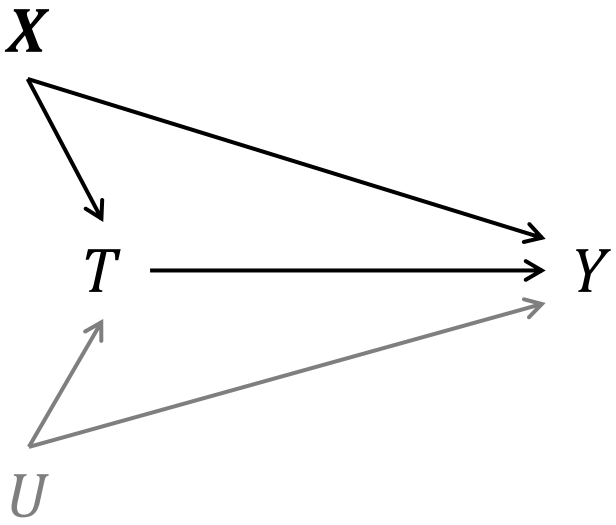


Adjustment for Observed Confounding

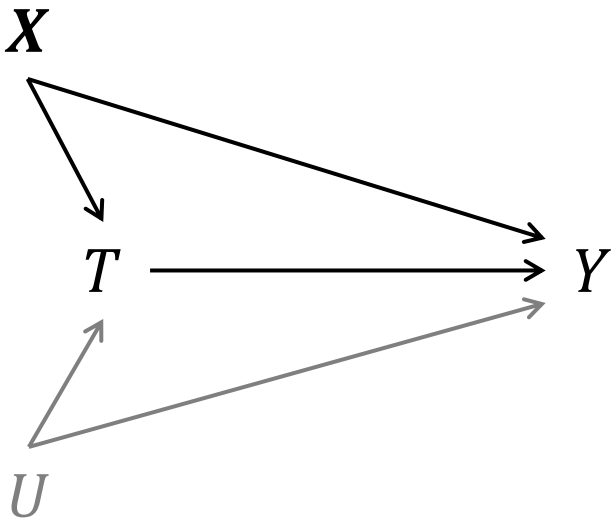


- Adjust for observed confounders $\boldsymbol{X}$ via multiple regression (non-causal analysis) or propensity score methods (causal analysis)
- Assumption: No unobserved confounders (no "hidden" bias")

Unobserved Confounding



Sensitivity Analysis for an Unobserved Confounder



Questions:

- How much would a certain (range of) U bias the TY effect?
- flip: What would the true TY effect be?
  - corrected point estimate (and confidence interval?)

- With what U does the TY effect go away?
  - statistically non-significant
  - zero point estimate
- related: Could there be a U that makes the TY effect go away?

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.

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.

"Thus, 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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smoking $T \xrightarrow{\text{oRR}_{YT} = 9} Y$ lung cancer

subscript $_{YT}$ means T predicting Y

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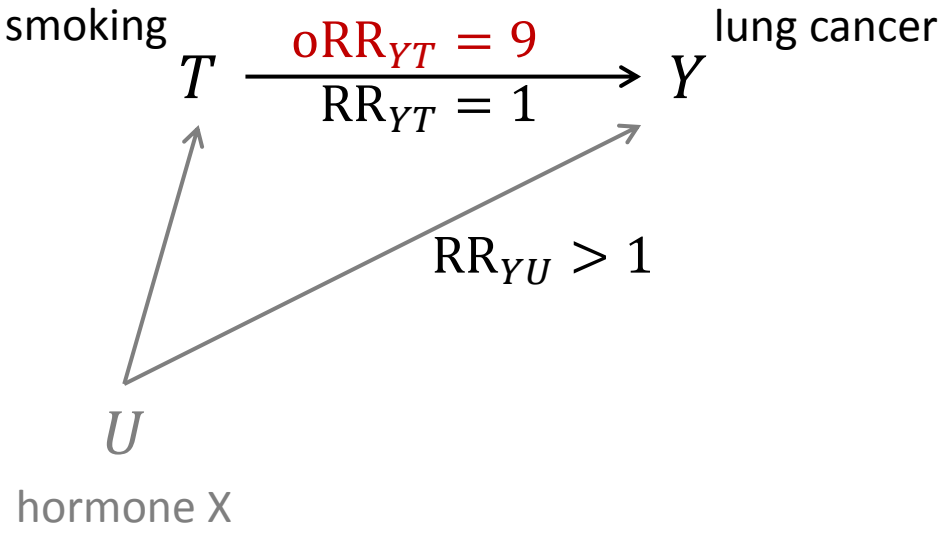

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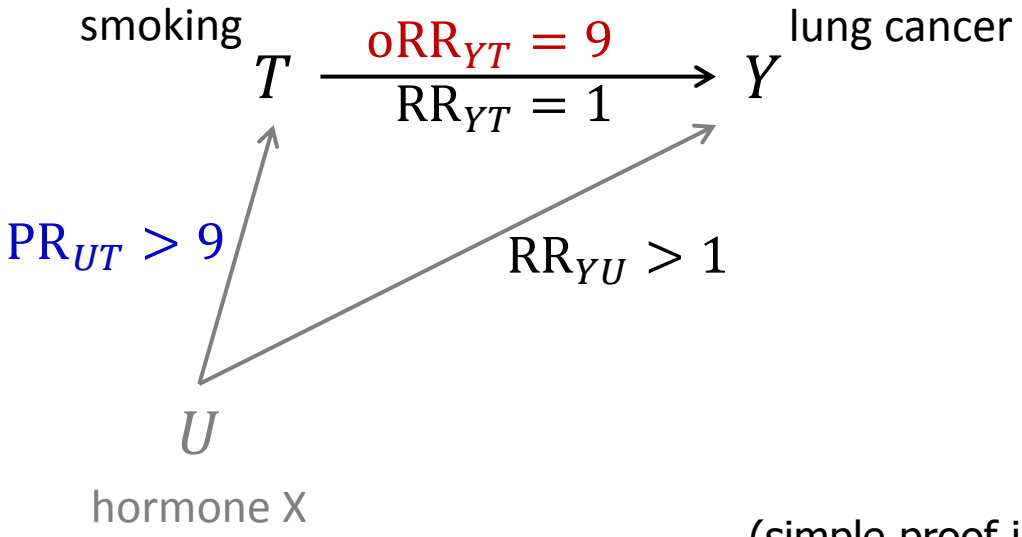

(simple proof in appendix A)

Cornfield et al. answered which of the following questions?

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Also, need methods that

accommodate both observed confounders and unobserved confounding!

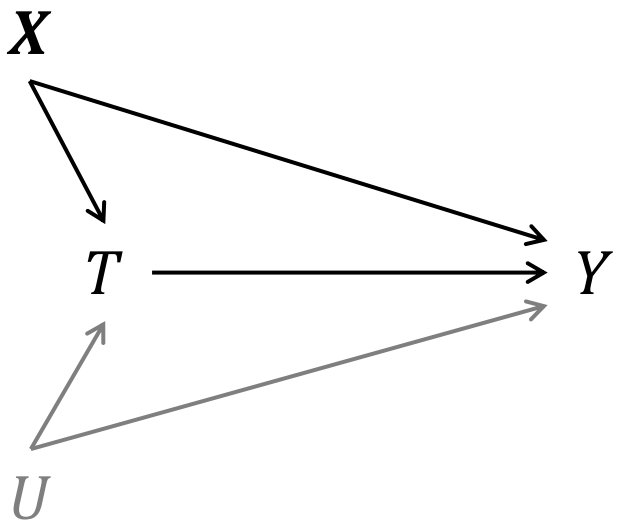
Treatment is not unconfounded given observed $\boldsymbol{X}$, but is unconfounded given observed $\boldsymbol{X}$ and unobserved U.

Rosenbaum's approach

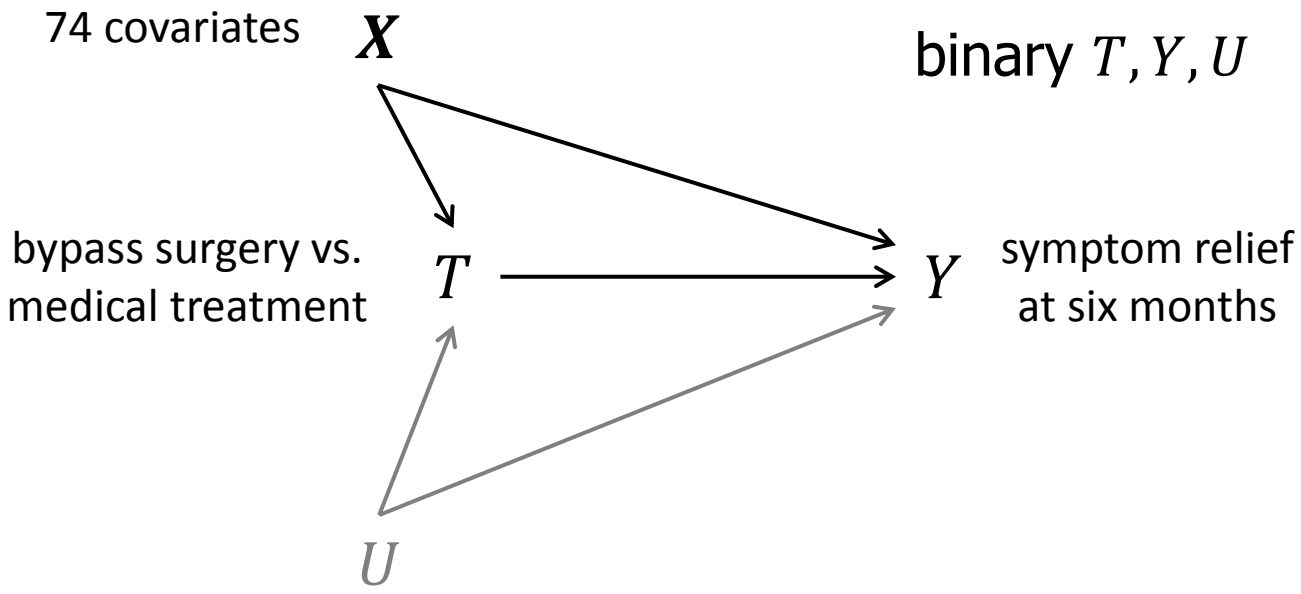
use propensity score methods to get balance on observed confounders $\boldsymbol{X}$

and then

conduct sensitivity analysis on an unobserved confounder U



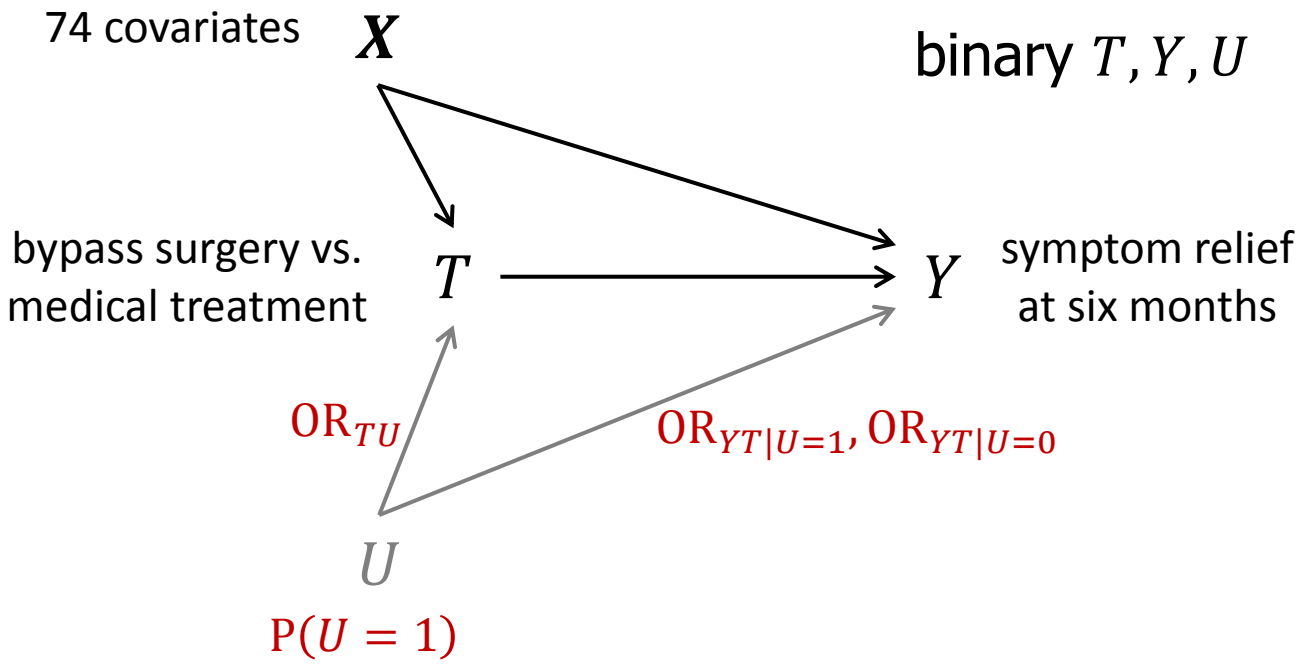
Rosenbaum & Rubin (1983) with subclassification



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) & Schneewise (2006)

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

- How much would a certain (range of) U bias the TY effect?
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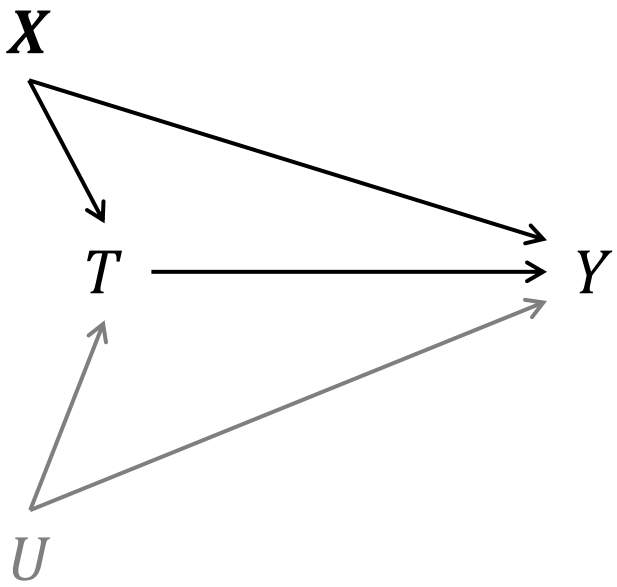
Rosenbaum & colleagues with matched pair data

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 not statistically significant



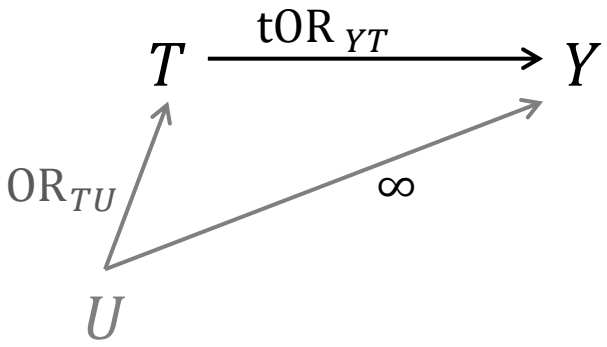
Rosenbaum, P. R. (1987). Sensitivity analysis for certain permutational inferences in matched observational studies. *Biometrika*, *74*, 13–26.

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

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

Primal

within a matched pair:



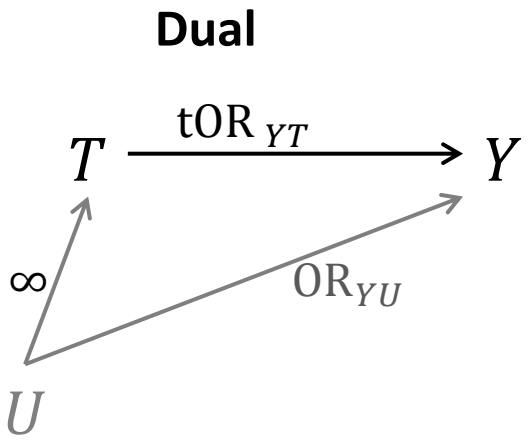
- If no unobserved confounding, the two individuals in a matched pair would have equal probability of treatment assignment
- Due to confounding by some unobserved U that is extremely predictive of the outcome, their odds of treatment assignment are different, $OR_{TU} \neq 1$
- Say they are different by at most a factor of $\Gamma > 1$

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

- Given Γ, true p-value for the YT effect is different from observed p-value.
- What are the values of Γ where tOR_{YT} may become statistically non-sig?

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

within a matched pair:



- If no unobserved confounding, the two individuals in a matched pair would have equal odds of outcome (for the same treatment)
- Due to unobserved confounding by some U that is extremely correlated with treatment assignment, their odds of outcome are different, $OR_{YU} \neq 1$
- Say they are different by at most a factor of $\Delta > 1$

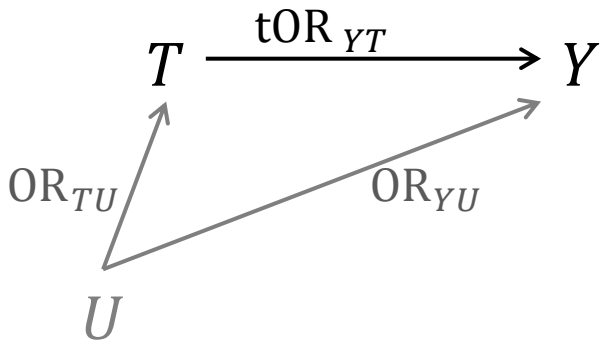
$$\frac{1}{\Delta} \leq \mathrm{OR}_{YU} \leq \Delta$$

- Given Δ, true p-value for the YT effect is different from observed p-value.
- What are the values of Δ where tOR_{YT} may become statistically non-sig?

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

Dual

within a matched pair:



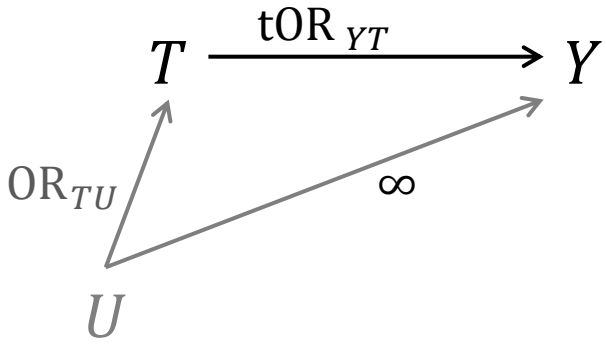
- If no unobserved confounding, the two individuals in a matched pair would have equal odds of treatment and equal odds of outcome (for the same treatment)
- Due to unobserved confounding by some U, their odds of treatment are different, $OR_{TU} \neq 1$, and their odds of outcome are different, $OR_{YU} \neq 1$
- Say these differences are bounded by factors of Γ and Δ (both > 1)

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

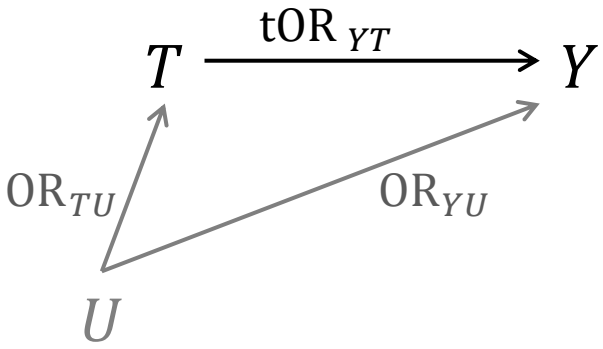
- Given Γ and Δ, true p-value is different from observed p-value.
- What are the values of Γ and Δ where tOR_{YT} may be statistically non-sig?

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

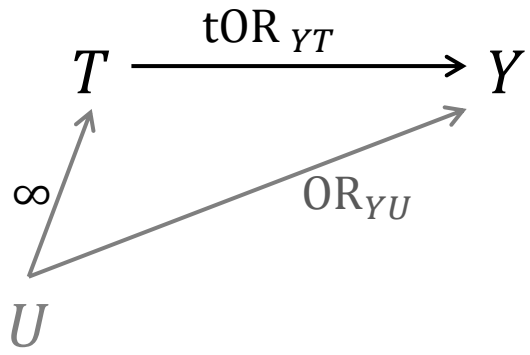
Primal



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

use a modified McNemar's exact binomial test for paired data

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

use a modified McNemar's exact binomial test for paired data

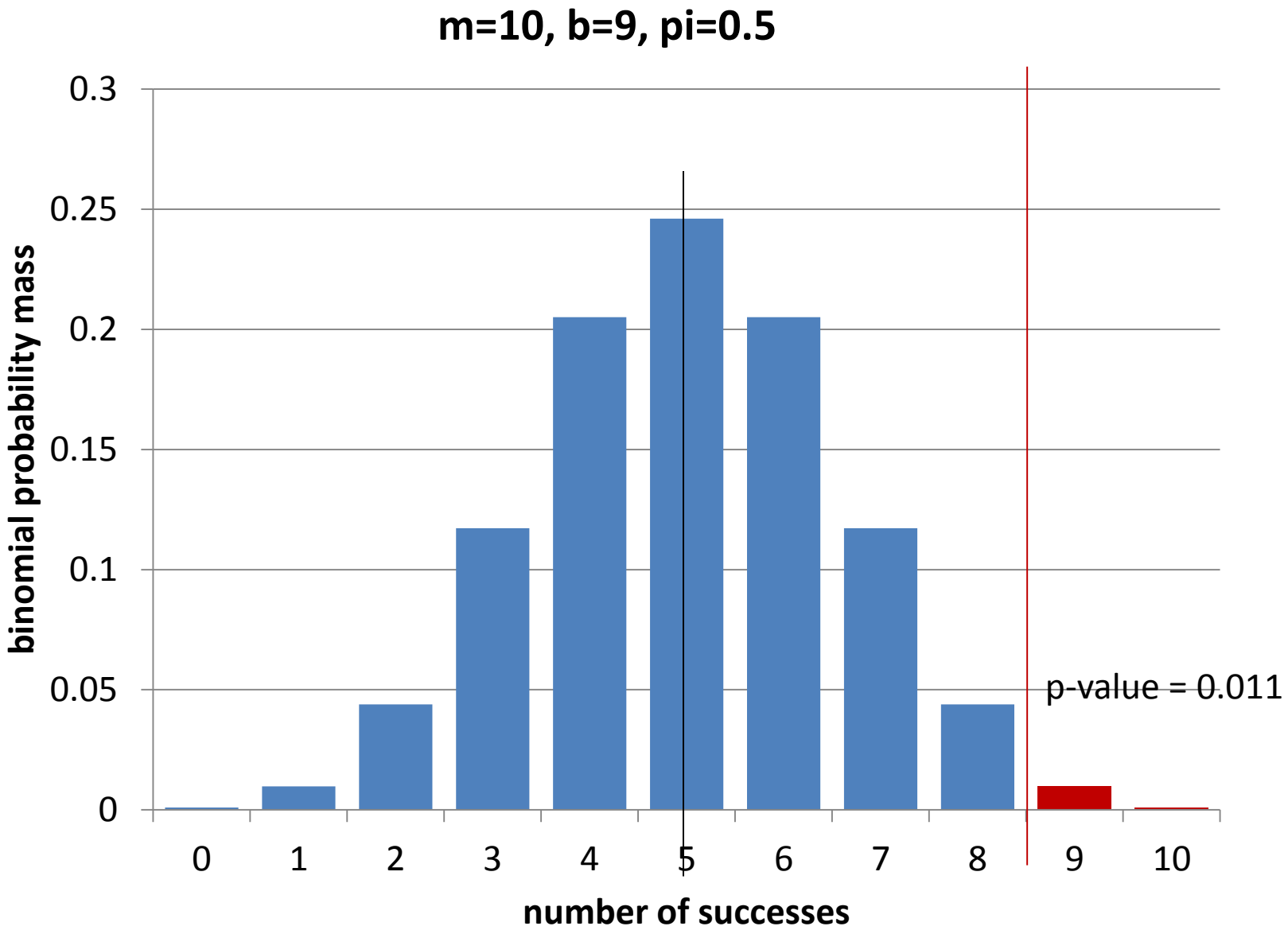
		$T=0$: $Y=1$	$T=0$: $Y=0$
$T=1$	$Y=1$	a	b [10]
	$Y=0$	c [01]	d

$b > c$

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`

use a modified McNemar's exact binomial test for paired data

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

$b > c$

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Modified test:

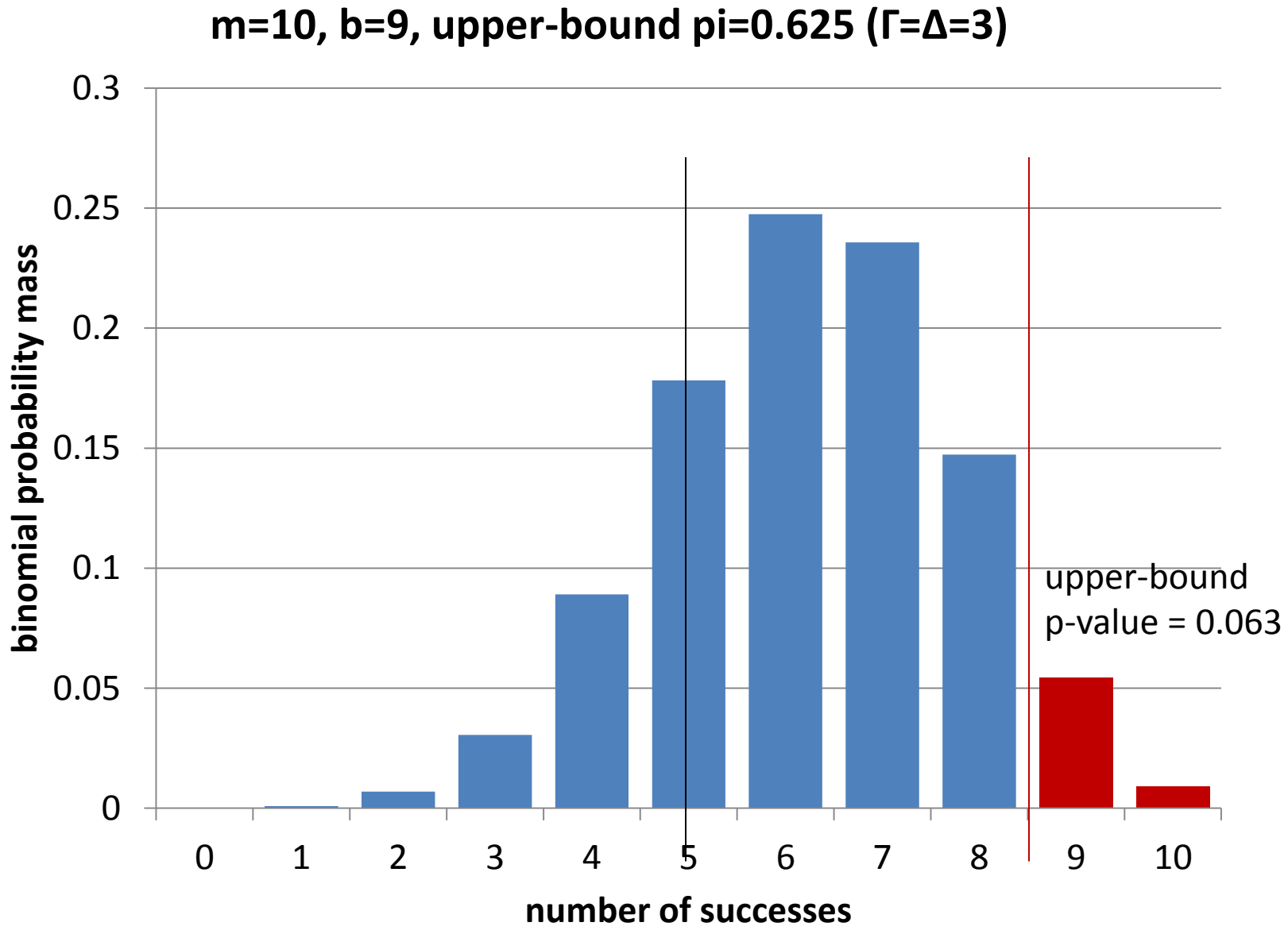
- H0: for discordant pairs, probability π of type [10], $(1-\pi)$ of type [01]

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



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

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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5.0	<.001	**.07**	**.75**	**.98**	**.99**	**1**
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	.75	1	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.

Other comments:

- Briliant idea!
- Only two 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 analysis is used to adjust for any remaining imbalance in (observed) confounders – double robustness.
- 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
- The question of one-sided or two-sided test

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

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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$T = 0$ (mother accident)	C	D

- 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

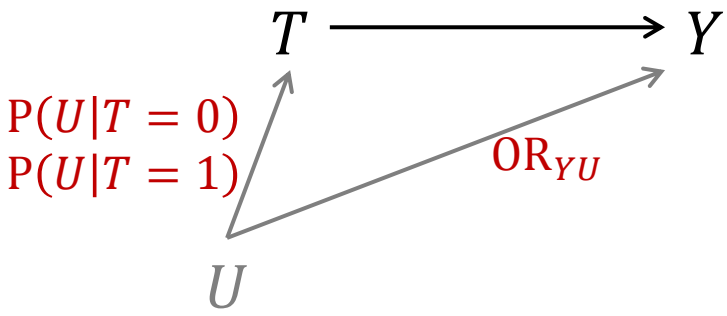
$$a_1 + a_2 = A;\ \ b_1 + b_2 = B;\ \ c_1 + c_2 = C;\ \ d_1 + d_2 = D$$

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

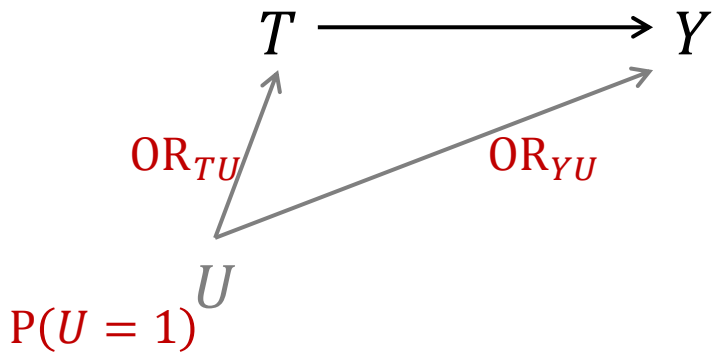
How to specify a plausible range of U?

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?

- How much would a certain (range of) U bias the TY effect?
- flip: What would the true TY effect be?
  - corrected point estimate (and confidence interval?)

- With what U does the TY effect go away?
  - statistically non-significant
  - zero point estimate
- related: Could there be a U that makes the TY effect go away?

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- related: Could there be a U that makes the TY effect go away?

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

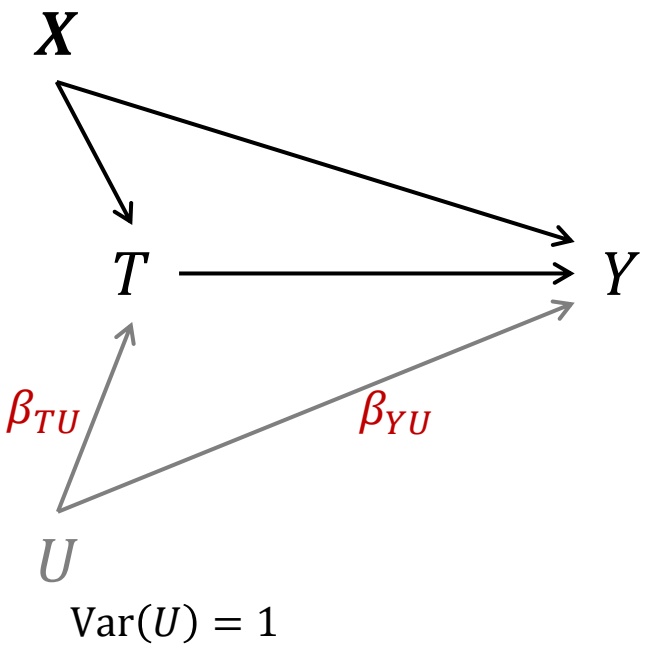
- How to deal with observed confounders $\boldsymbol{X}$?

  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)

Schneeweiss (2006)

- class critique

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

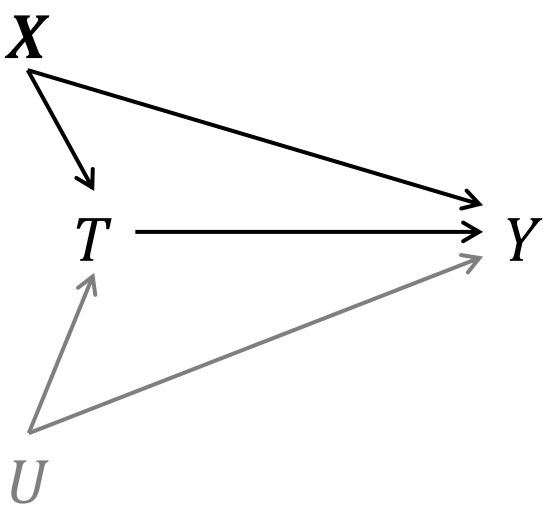
  Simple fix: Shift the representation of the UT relationship from β_{TU} (RD of treatment associated with one SD difference in U) to β_{UT} (the difference in mean U comparing $T = 1$ and $T = 0$). Then

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

  Note that this mean difference 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 an offers 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.

VanderWeele & Arah's (2011) general bias formulas

Very general!

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

- Each individual has a potential outcome under treatment Y_1 and a potential outcome under control Y_0.
- Treatment assignment is unconfounded (as good as random) given observed $\boldsymbol{X}$ and unobserved U.
- Treatment effect is: $\mathrm{ATE} = \mathrm{E}[Y_1] - \mathrm{E}[Y_0]$

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

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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- 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:

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

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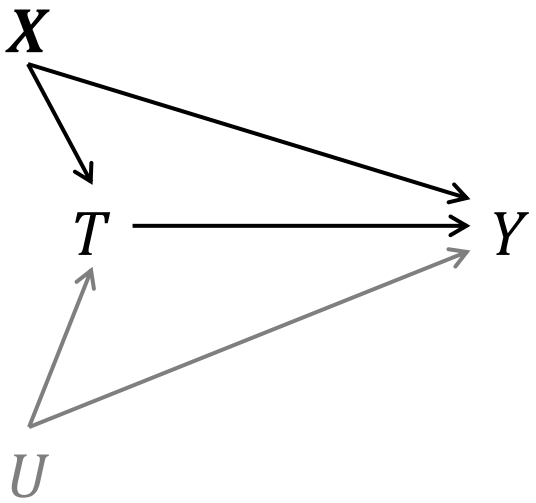
UY given T within $\boldsymbol{X}$ stratum

UT within $\boldsymbol{X}$ stratum

Complicated, but simplifies in some cases.



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

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

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

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

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

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

or plus both simplications 2 and 3

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

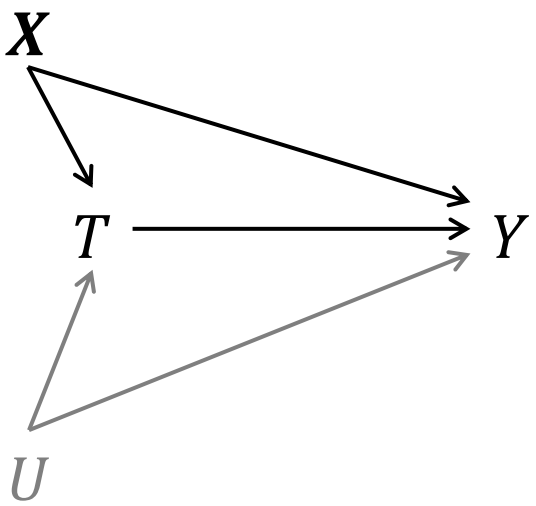
How does this translate to sensitivity parameters?

For example, with all three simplications,

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

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

With fewer simplications, more parameters.



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