

500 Slides Set 7

<https://thomaseLove.github.io/500/>

2021-03-18

Setup

```
library(knitr)
library(Matching)
library(rbounds)
library(janitor)
library(tidyverse)
```

Sensitivity Analysis for Matched Samples

The Role of Assumptions

Scenario	Analytic Goal	Role of Assumptions
Randomized Experiments	Testing H_0 : No effect	None
Randomized Experiments	Estimating effects, CIs	Minor
Observational Studies	Anything at all	Massive

- **All** observational studies are potentially affected by hidden bias.
 - Sensitivity analyses are needed in any such study.

Stability Analyses

- Are our conclusions mere artifacts of analytic decisions, or are they stable over analyses that differ in (apparently) innocuous ways?
- Examine a series of discrete decisions, hoping conclusions mostly don't change if the decision is changed.

Sensitivity Analyses

- How much do plausible changes in assumptions change conclusions?
- How much hidden bias would have to be present to alter the study's conclusions?

We want to assess the potential for **unmeasured** covariates to change our conclusions.

- To maximize trouble, the unmeasured covariate must be independent of the variables in our propensity model.
 - We missed a dimension of the problem, or our measure is terribly weak.
 - This is part of the motivation to be inclusive in building the PS model.

Idealized Standards for a Sensitivity Evaluation

- Logic, Theory and Empirical Evidence
- “It is unlikely that a non-huge hidden bias would substantially change our conclusions”
 - Measured and incorporated every major known factor that we could identify.
 - Effects on health outcomes were generally large, consistent with earlier work and clinically plausible.

An omitted variable is most likely to change our conclusions about the exposure if it is

- closely related to the outcome,
- seriously imbalanced by exposure,
- uncorrelated with the propensity score.

Does PS Matching Balance “Omitted” Covariates?

No.

- We fit¹ a published PS model to data from the RHC study, using 82 covariates.
- Then we obtained data on 17 other covariates, not included in the PS model.

Corr. with PS	Covariates	Balance Improved	Median Bias Reduction
Sig. ($p < .05$)	10	9 (90%)	45%
Not Sig.	7	2 (29%)	-36%

¹Love et al 2003 abstract

Sensitivity Analysis Approach

- When describing possible hidden bias, we refer to characteristics we did not observe, and therefore did not control for in PS.
- If our study was randomized, or somehow free of hidden bias, we would have strong evidence of a treatment effect.
- To explain away the observed effect, an unobserved covariate would need to increase the odds of exposure to treatment and the odds of outcome by at least a factor of Γ .

The Role of Sensitivity Analysis

- Cameron and Pauling (1976, 1978) concluded Vitamin C increased survival time of colon cancer patients.

The Role of Sensitivity Analysis

- Cameron and Pauling (1976, 1978) concluded Vitamin C increased survival time of colon cancer patients.
- The result was not sensitive to an unmeasured binary covariate which led to a 10-fold increase in odds of exposure to vitamin C and was a perfect predictor of the outcome².

²See Rosenbaum 2002, 2017

The Role of Sensitivity Analysis

- Cameron and Pauling (1976, 1978) concluded Vitamin C increased survival time of colon cancer patients.
- The result was not sensitive to an unmeasured binary covariate which led to a 10-fold increase in odds of exposure to vitamin C and was a perfect predictor of the outcome².
- Sensitivity analysis looks great, yet the findings were contradicted in a Mayo Clinic RCT.

²See Rosenbaum 2002, 2017

The Role of Sensitivity Analysis

- Cameron and Pauling (1976, 1978) concluded Vitamin C increased survival time of colon cancer patients.
- The result was not sensitive to an unmeasured binary covariate which led to a 10-fold increase in odds of exposure to vitamin C and was a perfect predictor of the outcome².
- Sensitivity analysis looks great, yet the findings were contradicted in a Mayo Clinic RCT.
- Conclusion: Sensitivity analyses cannot indicate what biases are present, it can only indicate the magnitude needed to alter the conclusion.

²See Rosenbaum 2002, 2017

Surgery vs. Medicine for Coronary Artery Disease

CAD: Surgery or Medicine

Coronary bypass surgery or medical/drug therapy for CAD³?

- 1,515 subjects
 - 590 surgical patients (39%), the rest medical
- PS included 74 observed covariates
 - Hemodynamic, Angiographic, Lab and Exercise Test Results
 - Patient histories, and demographics
- Stratified into PS quintiles, then combined estimates of $\Pr(\text{sustained improvement at 6 mo})$.

³See Rosenbaum and Rubin 1983, 1984

Surgery vs. Medicine Study: Results + Sensitivity

Substantial Improvement		Prob (SE)
	Medical	0.359 (0.042)
	Surgical	0.669 (0.059)

Conclusion: $\Pr(\text{improved} \mid \text{Surgery}) > \Pr(\text{improved} \mid \text{medicine})$

- A hypothetical unobserved binary covariate would have to **more than triple** the odds of surgery and **more than triple** the odds of improvement, before altering the conclusion⁴.

⁴See Rosenbaum and Rubin 1983, 1984

Goal of a Formal Sensitivity Analysis

To replace a general qualitative statement that applies in all observational studies. . .

“The association we observe between treatment and outcome does not imply causation.”

“Hidden biases can explain observed associations.”

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

“To explain the association seen in this particular study, one would need a hidden bias of this particular magnitude.”

Hidden Bias

- Two units (patients, subjects, whatever) with the same observed covariates have different chances of receiving the exposure.
- If the association is strong, the hidden bias needed to explain it would be large.
- If a study is free of hidden bias (one example: RCT), this means that any two units that appear similar in terms of their observed covariates actually have the same chance of assignment to exposure.

How would inferences about treatment effects be altered by hidden biases of various magnitudes? - How large would these differences have to be to alter the qualitative conclusions of the study?

The Design Sensitivity Parameter Γ

Γ measures degree of departure from a study that is free of hidden bias. A sensitivity analysis will consider possible values of Γ and show how the inference might change.

- Γ describes the odds ratio comparing the odds of being selected for treatment for two units who are similar on all observed covariates.
 - If $\Gamma = 1$, this means that the study is free of hidden bias
 - Subjects with the same observed covariates have the same odds (hence same probability) of exposure.
 - If $\Gamma = 2$, then two units who appear similar, who have the same set of observed covariates \mathbf{X} , could differ in their odds of receiving the treatment by as much as a factor of 2, so that one could be twice as likely as the other to receive the exposure.

Relating Γ to Sensitivity Statements

A study is **sensitive** if values of Γ close to 1 could lead to inferences that are very different from those obtained assuming the study is free of hidden bias.

- A study is *insensitive* if extreme values of Γ are required to alter the inference.

“To attribute the (observed significant) outcome to an unobserved covariate rather than to the treatment, that unobserved covariate has to increase the odds of treatment by a factor of Γ , and also predict our outcome quite well.”

Using a Spreadsheet

Getting the Message Across

Straightforward, Spreadsheet-Based Formal Sensitivity Analysis for Matched Samples

- Separate tabs for Outcomes: Binary, Continuous, Survival (w/censoring)
- All calculations based on base case formulas using sign-score tests as described in Rosenbaum 2002 [some nuances ignored (dealing with ties, etc.)]
- Available documents on our Data and Code page describe three examples

Demonstration: A Binary Outcome

- Exposure: Heavy Smoker vs. Non-Smoker
- Outcome: death due to lung cancer (no censoring)

Suppose we paired 1042 heavy smokers to 1042 nonsmokers on the basis of a series of baseline characteristics. Resulting data table on **the 1042 PAIRS** is (LCD = dies from lung cancer)...

–	Heavy Smoker LCD	Heavy Smoker No LCD	Total
Nonsmoker LCD	175	54	229
Nonsmoker No LCD	110	703	813
Total	285	757	1042

McNemar Test (if this was randomized)

```
test1 <- matrix(c(175, 54, 110, 703), nrow = 2)
mcnemar.test(test1, correct = F)
```

McNemar's Chi-squared test

data: test1

McNemar's chi-squared = 19.122, df = 1, p-value = 1.226e-05

This is an appropriate result if $\Gamma = 1$, but how much hidden bias would need to be present to change this conclusion?

How much hidden bias is needed?

- Pairs = 1042 matched pairs overall
- $D = 164$ discordant pairs (exactly one member had LCD)
- $T = 110$ discordant pairs in which Heavy Smoker had LCD

We find the binomial probability of obtaining a value of $T = 110$ or higher assuming a binomial distribution with $D = 164$ trials and common probability $= p^+$ and p^- for the upper and lower bounds. PDF specifies the details.

Spreadsheet Demonstration

	A	B	C	D	E	F	G
1	Sensitivity Analysis for McNemar's Test: Simplified 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	54	229			
6	Control, outcome = No	110	703	813			
7		285	757	1042			
8							
9	Computed Summaries						
10	# of Pairs	1042	# of matched pairs (overall)				
11	# of Discordant Pairs	164	# 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	0.0516	0.400	0.600		
18	2.0	0.0000	0.8538	0.333	0.667		
19	2.5	0.0000	1.7477	0.286	0.714		
20	3.0	0.0000	1.9723	0.250	0.750		
21	3.5	0.0000	1.9979	0.222	0.778		
22	4.0	0.0000	1.9999	0.200	0.800		
23	4.5	0.0000	2.0000	0.182	0.818		
24	5.0	0.0000	2.0000	0.167	0.833		
25	5.5	0.0000	2.0000	0.154	0.846		
26	6.0	0.0000	2.0000	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	1.43	0.0000	0.0249	0.412	0.588		
30	Stop when value for the upper bound of the P value (cell C29) is just below desired two-tailed significance level						
31							
32							

Running Sensitivity Analyses

Idealized Standards for a Sensitivity Evaluation

- Logic, Theory and Empirical Evidence
- “It is unlikely that a non-huge hidden bias would substantially change our conclusions”
 - Measured and incorporated every major known factor that we could identify.
 - Effects on health outcomes were generally large, consistent with earlier work and clinically plausible.

An omitted variable is most likely to change our conclusions about the exposure if it is

- closely related to the outcome,
- seriously imbalanced by exposure,
- uncorrelated with the propensity score.

The Design Sensitivity Parameter Γ

Γ measures degree of departure from a study that is free of hidden bias. A sensitivity analysis will consider possible values of Γ and show how the inference might change.

- Γ describes the odds ratio comparing the odds of being selected for treatment for two units who are similar on all observed covariates.
 - If $\Gamma = 1$, this means that the study is free of hidden bias
 - Subjects with the same observed covariates have the same odds (hence same probability) of exposure.
 - If $\Gamma = 2$, then two units who appear similar, who have the same set of observed covariates \mathbf{X} , could differ in their odds of receiving the treatment by as much as a factor of 2, so that one could be twice as likely as the other to receive the exposure.

Relating Γ to Sensitivity Statements

A study is **sensitive** if values of Γ close to 1 could lead to inferences that are very different from those obtained assuming the study is free of hidden bias.

- A study is *insensitive* if extreme values of Γ are required to alter the inference.

“To attribute the (observed significant) outcome to an unobserved covariate rather than to the treatment, that unobserved covariate has to increase the odds of treatment by a factor of Γ , and also predict our outcome quite well.”

Estimating Γ in a Simulated Situation

A Simulated Data Set

```
sim_obs <- read_csv("data/sim_sens_2020.csv") %>% clean_names()
sim_obs
```

```
# A tibble: 500 x 7
```

	subject	treatment	propensity	out_binary	out_quant	censored
	<chr>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>
1	S003	0	0.431	0	450.	1
2	S004	0	0.879	0	244.	0
3	S012	0	0.223	0	377.	0
4	S013	0	0.887	0	442.	0
5	S018	0	0.562	0	306.	0
6	S020	0	0.529	0	231.	0
7	S022	0	0.578	0	172.	0
8	S025	0	0.276	0	339.	0
9	S028	0	0.533	0	255.	0
10	S029	0	0.668	0	314.	0

```
# ... with 490 more rows
```


sim_obs data

```
summary(sim_obs)
```

subject	treatment	propensity	out_binar
Length:500	Min. :0.0	Min. :0.0030	Min. :0.0
Class :character	1st Qu.:0.0	1st Qu.:0.2875	1st Qu.:0.0
Mode :character	Median :0.0	Median :0.4530	Median :1.0
	Mean :0.4	Mean :0.4592	Mean :0.5
	3rd Qu.:1.0	3rd Qu.:0.6552	3rd Qu.:1.0
	Max. :1.0	Max. :0.9380	Max. :1.0
out_quant	censored	out_time	
Min. : 2.9	Min. :0.000	Min. : 17.0	
1st Qu.:137.2	1st Qu.:0.000	1st Qu.: 283.8	
Median :209.0	Median :0.000	Median : 543.5	
Mean :217.4	Mean :0.172	Mean : 547.9	
3rd Qu.:286.2	3rd Qu.:0.000	3rd Qu.: 808.5	
Max. :466.7	Max. :1.000	Max. :1140.0	

Study A: A Binary Outcome

```
sim_obs %>% tabyl(treatment, out_binary) %>%  
  adorn_totals() %>%  
  adorn_percentages() %>%  
  adorn_pct_formatting() %>%  
  adorn_ns(position = "front")
```

treatment	0	1
0	147 (49.0%)	153 (51.0%)
1	58 (29.0%)	142 (71.0%)
Total	205 (41.0%)	295 (59.0%)

Binary Outcome (1:1 Match)

```
set.seed(500)
m.obj <- Match(Y = sim_obs$out_binary,
               Tr = as.logical(sim_obs$treatment),
               X = sim_obs$propensity,
               M = 1, replace = FALSE)
```

Why set a seed? Because if you don't, the match can change on you (tied propensity scores...)

```
summary(m.obj)
```

```
Estimate... 0.205  
SE..... 0.046528  
T-stat..... 4.4059  
p.val..... 1.0533e-05
```

```
Original number of observations..... 500  
Original number of treated obs..... 200  
Matched number of observations..... 200  
Matched number of observations (unweighted). 200
```

Estimating Γ with binarysens

```
binarysens(m.obj, Gamma = 2.5, GammaInc = 0.25)
```

Rosenbaum Sensitivity Test

Unconfounded estimate 0

Gamma	Lower bound	Upper bound
1.00	2e-05	0.00002
1.25	0e+00	0.00098
1.50	0e+00	0.01270
1.75	0e+00	0.06459
2.00	0e+00	0.18283
2.25	0e+00	0.35488
2.50	0e+00	0.53873

Note: Gamma is Odds of Differential Assignment To Treatment Due to Unobserved Factors

Making our Γ Estimate more precise: binarysens

```
binarysens(m.obj, Gamma = 1.75, GammaInc = 0.05)$bounds %>%  
  tibble() %>% slice(11:17)
```

```
# A tibble: 6 x 3
```

	Gamma	`Lower bound`	`Upper bound`
	<dbl>	<dbl>	<dbl>
1	1.5	0	0.0127
2	1.55	0	0.0187
3	1.6	0	0.0266
4	1.65	0	0.0367
5	1.7	0	0.0493
6	1.75	0	0.0646

Obtaining the Matched Sample

If we wanted to use the spreadsheet software to calculate Γ , we'd need the matched sample.

```
matches <- factor(rep(m.obj$index.treated, 2))

sim.matchedsample1 <-
  cbind(matches,
        sim_obs[c(m.obj$index.control,
                  m.obj$index.treated),]) %>%
  arrange(matches)
```

The Matched Sample

```
head(sim.matchedsample1)
```

	matches	subject	treatment	propensity	out_binary	out_quant	ce
1	301	S091	0	0.516	1	145.8	
2	301	S001	1	0.516	0	260.0	
3	302	S053	0	0.488	0	178.1	
4	302	S005	1	0.487	0	334.7	
5	303	S040	0	0.047	1	167.9	
6	303	S027	1	0.044	0	225.8	

Building a 2x2 table from the Matched Sample

```
tmp <- sim.matchedsample1 %>%  
  mutate(res = 10*treatment + out_binary) %>%  
  group_by(matches) %>%  
  summarize(out.treated = out_binary[2],  
            out.control = out_binary[1])
```

```
tmp %>% tabyl(out.control, out.treated) %>% adorn_title()
```

	out.treated	
out.control	0	1
0	31	68
1	27	74

What would we put into the spreadsheet?

2x2 Table	Treated has out1	Treated no out1
Control has out1	74	27
Control no out1	68	31

In our 200 matched pairs, we have 95 pairs in the off-diagonal. There are 68 pairs where only the treated subject has the outcome. Assuming no hidden bias, we calculate an approximate 95% confidence interval for the McNemar odds ratio (which is $68/27$ or 2.52) with

```
ci.p <- prop.test(x = 68, n = 68+27)$conf
ci.odds <- ci.p/(1 - ci.p)
ci.odds
```

```
[1] 1.581067 4.032518
attr(,"conf.level")
[1] 0.95
```

Sensitivity Spreadsheet (2008) Results?

	A	B	C	D	E	F	G
1	Sensitivity Analysis for McNemar's Test: Simplified 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	74	27	101			
6	Control, outcome = No	68	31	99			
7		142	58	200			
8							
9	Computed Summaries						
10	# of Pairs	200	# of matched pairs (overall)				
11	# of Discordant Pairs	95	# of matched pairs in which exactly one has the outcome				
12	Test Statistic	68	# 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	0.0141	0.400	0.600		
18	2.0	0.0000	0.2592	0.333	0.667		
19	2.5	0.0000	0.8967	0.286	0.714		
20	3.0	0.0000	1.4925	0.250	0.750		
21	3.5	0.0000	1.8116	0.222	0.778		
22	4.0	0.0000	1.9381	0.200	0.800		
23	4.5	0.0000	1.9808	0.182	0.818		
24	5.0	0.0000	1.9942	0.167	0.833		
25	5.5	0.0000	1.9982	0.154	0.846		
26	6.0	0.0000	1.9995	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	1.57	0.0000	0.0249	0.389	0.611		
30	Stop when value for the upper bound of the P value (cell C29) is just below desired two-tailed significance level						

OK, so let's say Γ is about 1.6. What next?

Assuming no hidden bias, the propensity-matched result describes a strong relationship (McNemar odds ratio = 2.52, with 95% CI (1.58, 4.03)) between treatment receipt and our binary outcome.

To attribute the higher rate of our binary outcome to an unobserved covariate rather than to the effect of our treatment, that unobserved covariate would need to produce more than a 60% increase (or a $\Gamma = 1.6$ -fold increase) in the odds of receiving the treatment, and be a very strong predictor of the binary outcome.

Study B: A Quantitative Outcome

```
set.seed(500)
m.obj2 <- Match(Y = sim_obs$out_quant,
                Tr = as.logical(sim_obs$treatment),
                X = sim_obs$propensity,
                M = 1, replace = FALSE)
```

Estimate from Matching of Treatment Effect

```
summary(m.obj2)
```

```
Estimate... -56.681
```

```
SE..... 9.99
```

```
T-stat..... -5.6738
```

```
p.val..... 1.397e-08
```

```
Original number of observations..... 500
```

```
Original number of treated obs..... 200
```

```
Matched number of observations..... 200
```

```
Matched number of observations (unweighted). 200
```

Using psens to estimate Γ

```
psens(m.obj2, Gamma = 2.5, GammaInc = 0.25)
```

Rosenbaum Sensitivity Test for Wilcoxon Signed Rank P-Value

Unconfounded estimate 0

Gamma	Lower bound	Upper bound
1.00	0	0.0000
1.25	0	0.0001
1.50	0	0.0036
1.75	0	0.0353
2.00	0	0.1453
2.25	0	0.3453
2.50	0	0.5753

Note: Gamma is Odds of Differential Assignment To
Treatment Due to Unobserved Factors

Refining our Γ estimate

```
psens(m.obj2, Gamma = 2, GammaInc = 0.05)$bounds %>%  
  tibble() %>% slice(13:18)
```

```
# A tibble: 6 x 3
```

	Gamma	`Lower bound`	`Upper bound`
	<dbl>	<dbl>	<dbl>
1	1.6	0	0.0103
2	1.65	0	0.0161
3	1.7	0	0.0243
4	1.75	0	0.0353
5	1.8	0	0.0496
6	1.85	0	0.0675

Rosenbaum Bounds: Hodges-Lehmann Estimate

```
hlsens(m.obj2, pr = 0.1, Gamma = 2.5, GammaInc = 0.25)
```

Rosenbaum Sensitivity Test for Hodges-Lehmann Point Estimate

Unconfounded estimate -54.65

Gamma	Lower bound	Upper bound
1.00	-54.65	-54.65
1.25	-69.65	-40.65
1.50	-80.95	-28.95
1.75	-90.35	-19.15
2.00	-98.95	-10.95
2.25	-106.55	-4.35
2.50	-113.35	1.95

Note: Gamma is Odds of Differential Assignment To
Treatment Due to Unobserved Factors

Study C: Survival (Time to Event) Outcome

For the spreadsheet, we need to identify the number of pairs with a clear winner, and the number of those “clear winner” pairs where the winner is the “treatment = 1” subject.

```
match3 <- sim.matchedsample1 %>% tibble() %>%  
  select(matches, treatment, censored, out_time,  
         subject, propensity) %>%  
  arrange(matches, -treatment)  
  
head(match3, 2)
```

A tibble: 2 x 6

	matches	treatment	censored	out_time	subject	propensity
	<fct>	<dbl>	<dbl>	<dbl>	<chr>	<dbl>
1	301	1	1	735	S001	0.516
2	301	0	0	572	S091	0.516

Determining “Clear Winners” (1)

What if there is no censoring?

```
match3 %>% filter(matches %in% c(302, 308))
```

```
# A tibble: 4 x 6
```

	matches <fct>	treatment <dbl>	censored <dbl>	out_time <dbl>	subject <chr>	propensity <dbl>
1	302	1	0	149	S005	0.487
2	302	0	0	144	S053	0.488
3	308	1	0	322	S082	0.524
4	308	0	0	369	S061	0.522

- Which subject in match 302 has the longer out_time?
- Which subject in match 308 has the longer out_time?
- Will we have a clear winner if neither subject's time is censored?

Determining “Clear Winners” (2)

What if both subjects in the pair are censored?

```
match3 %>% filter(matches == 310)
```

```
# A tibble: 2 x 6
```

	matches	treatment	censored	out_time	subject	propensity
	<fct>	<dbl>	<dbl>	<dbl>	<chr>	<dbl>
1	310	1	1	75	S089	0.818
2	310	0	1	1095	S094	0.819

- Which subject in match 310 has the longer out_time?
- Will we have a clear winner if both subjects' time is censored?

Determining “Clear Winners” (3)

What if only the treated subject in the pair is censored?

```
match3 %>% filter(matches %in% c(301, 307))
```

```
# A tibble: 4 x 6
```

	matches <fct>	treatment <dbl>	censored <dbl>	out_time <dbl>	subject <chr>	propensity <dbl>
1	301	1	1	735	S001	0.516
2	301	0	0	572	S091	0.516
3	307	1	1	460	S076	0.811
4	307	0	0	980	S273	0.813

- Which subject in match 301 has the longer out_time?
- Which subject in match 307 has the longer out_time?
- Will we have a clear winner if exactly one subject's time is censored?

Determining “Clear Winners” (4)

What if only the control subject in the pair is censored?

```
match3 %>% filter(matches %in% c(305, 337))
```

```
# A tibble: 4 x 6
```

	matches	treatment	censored	out_time	subject	propensity
	<fct>	<dbl>	<dbl>	<dbl>	<chr>	<dbl>
1	305	1	0	595	S045	0.305
2	305	0	1	266	S350	0.306
3	337	1	0	194	S345	0.034
4	337	0	1	553	S197	0.033

- Which subject in match 305 has the longer out_time?
- Which subject in match 337 has the longer out_time?
- How do we know if we will have a clear winner if exactly one subject's time is censored?

Getting the Counts for the Spreadsheet

```
write_csv(match3, "data/match3.csv")
```

Across our 200 matches, I hand-counted the number of clear winners, and in each case, who wins. This is certainly an area where a more patient programmer could do the job faster.

- If both treated and control are censored, no clear winner (2 pairs)
- If both treated and control are NOT censored, clear winner (134 pairs) unless there is a tie (0 pairs)
 - In 73 of those 134 pairs, the treated subject had the longer `out_time`.
- If either treated or control is censored but not both, then there is a clear winner only if the censored subject had the longer `out_time`.
 - 10 pairs where treated subject clearly wins despite being censored.
 - 12 pairs where control subject clearly wins despite being censored.

So, in total, we have $134 + 10 + 12 = 156$ pairs with a clear winner. In 83 of those, the treated subject had the longer `out_time`.

Result from the Spreadsheet

	A	B	C	D	E
1	Sensitivity Analysis for A Simple Comparison for Censored Survival				
2	Section 4.4.8. of Rosenbaum PR (2002) Observational Studies, 2nd Edition.				
3	INSERT VALUES (IN RED) IN CELLS HIGHLIGHTED IN YELLOW.				
4					
5	Data				
6	Total # of Pairs With A Clear Winner	156			
7	T = # of Pairs Where Exposed Outlives Control	83			
8					
9	Sensitivity Analysis				
10	Gamma Values	2-tail P value (lower bound)	2-tail P value (upper bound)	P-	P+
11	1.0	0.4233	0.4233	0.500	0.500
12	1.5	0.0008	1.0000	0.400	0.600
13	2.0	0.0000	1.0000	0.333	0.667
14	2.5	0.0000	1.0000	0.286	0.714
15	3.0	0.0000	1.0000	0.250	0.750
16	3.5	0.0000	1.0000	0.222	0.778
17	4.0	0.0000	1.0000	0.200	0.800
18	4.5	0.0000	1.0000	0.182	0.818
19	5.0	0.0000	1.0000	0.167	0.833
20	5.5	0.0000	1.0000	0.154	0.846
21	6.0	0.0000	1.0000	0.143	0.857
22					
23	Insert Gamma Value Below	2-tail P value (lower bound)	2-tail P value (upper bound)	P-	P+
24	1.76	0.0000	1.0000	0.362	0.638
25	Stop when value for the upper bound of the P value (cell C24) is just below desired two-tailed significance level				
26					

What if it had been 113 out of 156 instead?

	A	B	C	D	E
1	Sensitivity Analysis for A Simple Comparison for Censored Survival				
2	Section 4.4.8. of Rosenbaum PR (2002) Observational Studies, 2nd Edition.				
3	INSERT VALUES (IN RED) IN CELLS HIGHLIGHTED IN YELLOW.				
4					
5	Data				
6	Total # of Pairs With A Clear Winner	156			
7	T = # of Pairs Where Exposed Outlives Control	113			
8					
9	Sensitivity Analysis				
10	Gamma Values	2-tail P value (lower bound)	2-tail P value (upper bound)	P-	P+
11	1.0	0.0000	0.0000	0.500	0.500
12	1.5	0.0000	0.0015	0.400	0.600
13	2.0	0.0000	0.1264	0.333	0.667
14	2.5	0.0000	0.7806	0.286	0.714
15	3.0	0.0000	1.0000	0.250	0.750
16	3.5	0.0000	1.0000	0.222	0.778
17	4.0	0.0000	1.0000	0.200	0.800
18	4.5	0.0000	1.0000	0.182	0.818
19	5.0	0.0000	1.0000	0.167	0.833
20	5.5	0.0000	1.0000	0.154	0.846
21	6.0	0.0000	1.0000	0.143	0.857
22					
23	Insert Gamma Value Below	2-tail P value (lower bound)	2-tail P value (upper bound)	P-	P+
24	1.76	0.0000	0.0243	0.362	0.638
25	Stop when value for the upper bound of the P value (cell C24) is just below desired two-tailed significance level				
26					

Summary: Sensitivity Analysis

Hidden bias is the great problem with observational studies, and with PS models.

- Sensitivity analysis after matching can be applied in many scenarios.
- We hope to find that an unobserved covariate would have to be very powerful to alter our conclusions.
- That doesn't mean that such a covariate (or set of them) doesn't exist.

Our PS “Formula” for the Heart Failure papers

- ➊ Identify available data related to selection for the exposure, and to risk for the outcome.
- ➋ Demonstrate need for PS modeling (imbalance in key characteristics), and evaluate PS balance after matching, usually through standardized difference plots (usually significance, too, unfortunately.)
- ➌ Model exposure effect (Cox models stratified by matched pair identifiers, typically.)
- ➍ Formal sensitivity analysis **if** effect is significant.

**This is the end of the pre-recorded lecture for
Class 7.**

In-class materials

- Augmenting Sensitivity Analyses (Rosenbaum Chapter 9)

Augmenting a Sensitivity Analysis

Lots of things can be described as part of a sensitivity analysis. We are focusing on one issue: quantifying departures from randomized (i.e. ignorable) treatment assignment.

Ignorable treatment assignment means that if two people have the same values of the observed covariates (and thus, for example, the same propensity score) then they have the same probability of treatment.

- Rosenbaum's bounds on Γ are just one possibility.
- Γ and Θ_p and Λ and Δ are just different methods of describing departure from ignorable treatment assignment in matched pairs, although only Γ applies outside of matched pairs.

Γ and Θ_p

We can express this in terms of Γ or Θ_p pretty easily in the matched pairs setting.

$$\frac{1}{1 + \Gamma} \leq \Theta_p \leq \frac{\Gamma}{1 + \Gamma}$$

$\Gamma = 2$ is the same magnitude of departure from ignorable treatment assignment as the interval from 0.33 to 0.67 for Θ_p .

If $\Gamma = 2$, then Harry might be twice as likely as Sally to receive the treatment (so Harry's probability Θ_H is 2/3 and Sally's is 1/3) or Sally might be twice as likely as Harry (so Harry's probability could be as low as 1/3) to receive the treatment.

Amplifying the Γ value with Λ and Δ

This approach, like Θ_p bounds, applies only in the case of matched pairs.

- Λ tells you about the relationship of an unobserved covariate with treatment assignment.
- Δ tells you about the relationship of an unobserved covariate with the outcome.

$$\Gamma = (\Lambda\Delta + 1)/(\Lambda + \Delta)$$

Table 9.1

Table 9.1. Understanding the sensitivity parameter Γ

Γ	Range of possible values of θ_p		Λ	Δ
1	0.50	0.50	1	1
1.05	0.49	0.51	1.37	1.37
1.1	0.48	0.52	1.40	1.80
1.25	0.44	0.56	2	2
1.5	0.40	0.60	2	4
2	0.33	0.67	3	5
2.5	0.29	0.71	4	6
3	0.25	0.75	5	7
3.5	0.22	0.78	6	8
4	0.20	0.80	7	9
4.5	0.18	0.82	8	10
5	0.17	0.83	9	11
6	0.14	0.86	11	13
7	0.12	0.88	13	15
8	0.11	0.89	15	17
9	0.10	0.90	17	19
10	0.09	0.91	19	21

Using the Amplification

If $\Gamma = 1.5$ then, for example we could use

- a bound on Θ_p from 0.40 to 0.60
- or a combination of $\Lambda = 2$ and $\Delta = 4$
- or a combination of $\Lambda = 4$ and $\Delta = 2$
- or a requirement that $\Lambda = 1.5$ and that the unobserved covariate be a perfect predictor of the outcome.
- or a requirement that $\Delta = 1.5$ and that the unobserved covariate be a perfect predictor of treatment assignment.