500 Class 07

https://thomaselove.github.io/500-2024/

2024-02-29

Today's Agenda

- The Right Heart Catheterization Example
- Propensity Scores and Sensitivity Analysis
- Discussion of Rosenbaum Chapter 6

R Packages and Setup

```
knitr::opts_chunk$set(comment = NA)

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

Section 1

Right Heart Catheterization and the SUPPORT Study

The SUPPORT Study

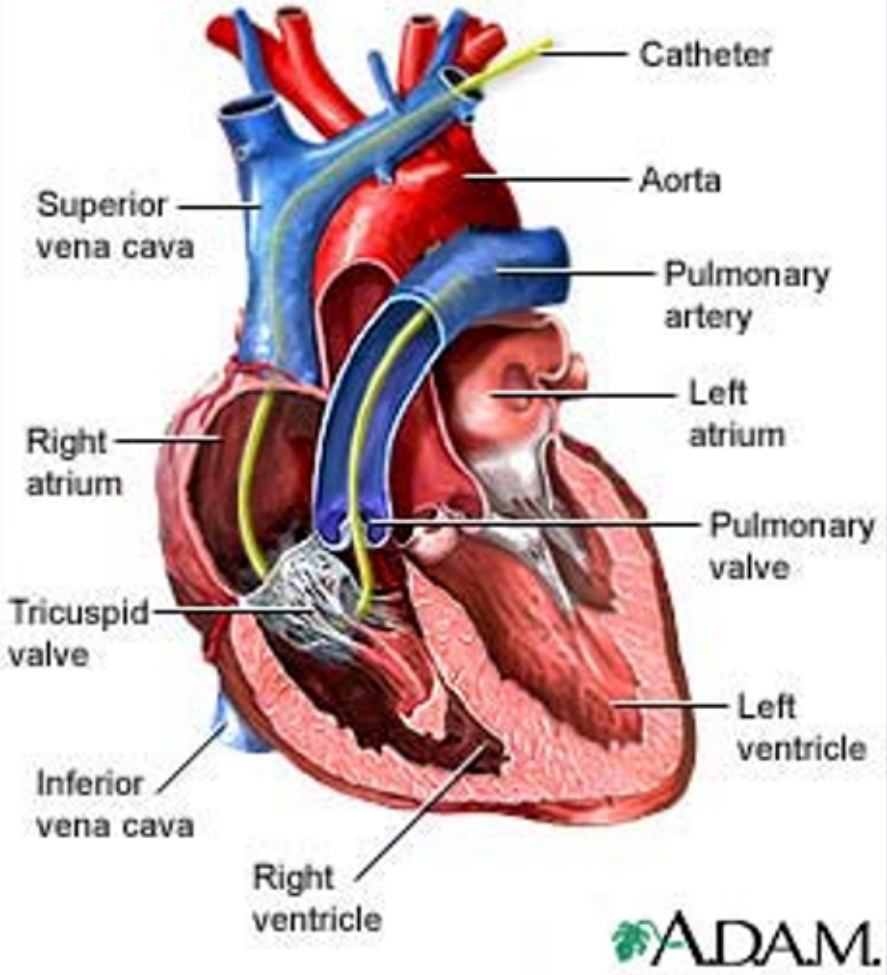
This example is based on the Right Heart Catheterization data set available at Vanderbilt University.

The key reference is Connors AF et al. (1996) The effectiveness of RHC in the initial care of critically ill patients. JAMA 276: 889-897.

Connors et al. used a logistic regression model to develop a propensity score then: [a] matched RHC to non-RHC patients and [b] adjusted for propensity score in models for outcomes, followed by a sensitivity analysis.

The key conclusions were that RHC patients had decreased survival time, and any unmeasured confounder would have to be somewhat strong to explain away the results.

Right Heart / Swan-Ganz / Pulmonary Artery Catheterization



Pass a thin flexible tube:

1. **to obtain diagnostic information about the heart**
2. **for monitoring of heart function in the critically ill.**

http://www.nlm.nih.gov/medlineplus/ency/imagepages/18087.htm

Does the RHC do more harm than good?

Prior (small) observational studies comparing RHC to non-RHC patients:

- RR of death higher in RHC elderly patients than non-RHC elderly
- RR of death higher in RHC patients with acute MI than non-RHC patients with MI
- Patients with higher than expected RHC use had higher mortality

Big Problem: Selection Bias. Physicians (mostly) decide who gets RHC and who doesn't.

Why not a RCT?

- RHC directly measures cardiac function
- Some MDs believe RHC is necessary to guide therapy for some critically ill patients
- Procedure is very popular - existing studies haven't created equipoise

Characteristics used to predict PS(RHC usage)

- Age, Sex, Race
- Education, Income, Insurance
- Primary and Secondary Disease category
- Admission diagnosis category (12 levels)
- ADL and DASI 2 weeks before admission
- DNR status on day 1
- Cancer (none, local, metastasized)
- 2 month survival model
- Weight, temperature, BP, heart rate, respiratory rate
- Comorbid illness (13 categories)
- Body chemistry (pH, WBC, PaCO_2_, etc.)

Panel (7 specialists in clinical care) specified important variables related to the decision to use or not use a RHC.

RHC vs. Non-RHC patients

RHC patients were more likely to

- Be male, have private insurance, enter the study with ARF, MOSF or CHF

RHC patients were less likely to

- Be over 80 years old, have cancer, have a DNR order in the first 24 hours of hospitalization

RHC patients had significantly

- Fewer comorbid conditions,
- More abnormal results of vital signs, WBC count, albumin, creatinine, etc.
- Lower model probability of 2-month survival

What's in the RHC Example?

- exposure/treatment is the installation of a Swan-Ganz (right heart) catheter on day 1
- 3 outcomes
  - binary: in-study mortality
  - quantitative: hospital length of stay, in days
  - time-to-event: time to death (with censoring)
- 50 covariates, including socio-demographics, presentation and diagnoses at admission, comorbid illness and transfer status, summary measures of presentation and lab results on day 1

What Analyses are Presented?

- Unadjusted analyses
- Estimating the PS and checking balance before adjustment
- Six different Matching Approaches and resulting outcomes
  - 1:1 greedy matching without replacement
  - 1:2 greedy matching without replacement
  - 1:1 matching without replacement using genetic search
  - 1:1 greedy matching with replacement
  - 1:1 caliper matching without replacement
  - 1:2 greedy matching with replacement
- ATT weighting using TWANG
- Double Robust (weighting + regression) analysis
- Sensitivity Analyses after Matching

Section 2

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 fit[1] 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%

[1] Love 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.

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- 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 outcome[2].

[2] See Rosenbaum 2002, 2017

The Role of Sensitivity Analysis

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- 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 outcome[2].
- Sensitivity analysis looks great, yet the findings were contradicted in a Mayo Clinic RCT.

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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 outcome[2].
- 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.

[2] See Rosenbaum 2002, 2017

Section 3

Surgery vs. Medicine for Coronary Artery Disease

CAD: Surgery or Medicine

Coronary bypass surgery or medical/drug therapy for CAD[3]?

- 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(sustained improvement at 6 mo).

[3] See 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(improved | Surgery) > Pr(improved | 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 conclusion[4].

[4] See 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."

Section 4

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: 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**	**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)	?-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)	?-tail P value (upper bound)	P-	P+		
29	**1.43**	**0.0000**	**0.0249**	0.412	0.588		

Section 5

Estimating Γ using R

A Simulated Data Set

```
sim_obs <- read_csv("c07/data/sim_sens_2020.csv",
                    show_col_types = FALSE) |>
  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
```

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...)

```r
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
```

Create Matched Outcomes 2x2 Table for McNemar's Test

```
## Extract Matched Outome Data
Rc <- m.obj$mdata$Y[m.obj$mdata$Tr==0]
Rt <- m.obj$mdata$Y[m.obj$mdata$Tr==1]

## Table of Matched Outcomes for McNemar's Test
out.tab <- matrix(c(table(Rc, Rt)), nrow = 2)
out.tab
```

```
     [,1] [,2]
[1,]   31   68
[2,]   27   74
```

Estimating Γ with `binarysens`

```
binarysens(out.tab[2,1], out.tab[1,2],
           Gamma = 2, GammaInc = 0.25)
```

```
 Rosenbaum Sensitivity Test

Unconfounded estimate ....  0

 Gamma Lower bound Upper bound
  1.00       1e-05     0.00001
  1.25       0e+00     0.00046
  1.50       0e+00     0.00704
  1.75       0e+00     0.04100
  2.00       0e+00     0.12960

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

Making our Γ Estimate more precise: `binarysens`

```
binarysens(out.tab[2,1], out.tab[1,2],
           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       0.00704
2  1.55             0       0.0107
3  1.6              0       0.0156
4  1.65             0       0.0222
5  1.7              0       0.0305
6  1.75             0       0.041
```

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: 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**	**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)	?-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)	?-tail P value (upper bound)	P-	P+		

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
```

Create Matched Outcomes Table

```
## Extract Matched Outome Data
Rc2 <- m.obj2$mdata$Y[m.obj2$mdata$Tr==0]
Rt2 <- m.obj2$mdata$Y[m.obj2$mdata$Tr==1]
```

Using psens to estimate Γ

```
psens(Rc2, Rt2, 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
```

Refining our Γ estimate

```
psens(Rc2, Rt2, 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(Rc2, Rt2, 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       40.65       69.65
  1.50       28.95       80.95
  1.75       19.15       90.35
  2.00       10.95       98.95
  2.25        4.35      106.55
  2.50       -1.95      113.35

 Note: Gamma is Odds of Differential Assignment To
```

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 treatment censored out_time subject propensity
  <fct>       <dbl>    <dbl>    <dbl> <chr>         <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 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
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					

Our PS "Formula" for the Heart Failure papers

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

Our Examples (links to our 500-data page)

- The Toy Example has a sensitivity analysis for a quantitative outcome.
- Right Heart Catheterization has sensitivity analyses for a quantitative outcome, a binary outcome and a time-to-event outcome.

Section 6

Augmenting a Sensitivity Analysis

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.

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

Rosenbaum *DoOS*, 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.

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.

Section 7

Discussion of Rosenbaum, Chapter 6

Rosenbaum, Chapter 6

1. What was the most important thing you learned from reading Chapter 6?
2. What was the muddiest, least clear thing that arose in your reading?

Next Time

- Some Extensions to Matching (finally)
- Tanenbaum 2019
- Elbadawi 2021
- Discussion of Rosenbaum Chapter 7