500 Class 8 Slides

github.com/THOMASELOVE/2020-500

2020-03-26

Running Sensitivity Analyses

Setup

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

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
   <chr>       <dbl>      <dbl>      <dbl>     <dbl>
 1 S003            0      0.431          0      450.
 2 S004            0      0.879          0      244.
 3 S012            0      0.223          0      377.
 4 S013            0      0.887          0      442.
 5 S018            0      0.562          0      306.
 6 S020            0      0.529          0      231.
 7 S022            0      0.578          0      172.
 8 S025            0      0.276          0      339.
 9 S028            0      0.533          0      255.
10 S029            0      0.668          0      314.
# ... with 490 more rows, and 2 more variables:
#   censored <dbl>, out time <dbl>
```

sim_obs data

```
mosaic::inspect(sim_obs)
```

```
categorical variables:
     name     class levels   n missing
1 subject character    500 500       0
                                   distribution
1 S001 (0.2%), S002 (0.2%) ...

quantitative variables:
        name   class    min       Q1  median       Q3
1  treatment numeric  0.000   0.0000   0.000   1.00000
2 propensity numeric  0.003   0.2875   0.453   0.65525
3 out_binary numeric  0.000   0.0000   1.000   1.00000
4  out_quant numeric  2.900 137.1500 209.000 286.25000
5   censored numeric  0.000   0.0000   0.000   0.00000
6   out_time numeric 17.000 283.7500 543.500 808.50000
      max       mean          sd   n missing
```

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%)
```

summary(sim_obs)

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
```

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 %>%
  tbl_df() %>% 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
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
  censored out_time
1        0      572
2        1      735
3        0      144
4        0      149
5        0      559
6        0      994
```

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?

So our 2x2 table would be:

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
```

	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)	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 Γ = 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 = 3, 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
  2.75           0      0.7649
  3.00           0      0.8868
```

Refining our Γ estimate

```
psens(m.obj2, Gamma = 2, GammaInc = 0.05)$bounds %>%
  tbl_df() %>% 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 for Hodges-Lehmann Point 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
```

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 %>% tbl_df() %>%
  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					

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

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.