Tipping Point Sensitivity Analyses

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Recall: Propensity scores

Rosenbaum and Rubin showed in observational studies, conditioning on **propensity scores** can lead to unbiased estimates of the exposure effect

1. **There are no unmeasured confounders**
2. **Every subject has a nonzero probability of receiving either exposure**

Quantifying Unmeasured Confounding

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EPIDEMIOLOGIC METHODS (P P HOWARDS, SECTION EDITOR)

Sensitivity Analyses for Unmeasured Confounders

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The Journal of Open Source Software

tipr: An R package for sensitivity analyses for unmeasured confounders

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Quantifying Unmeasured Confounding

1. The exposure-outcome
2. The exposure-unmeasured
3. The unmeasured confounder-outcome effect

Quantifying Unmeasured Confounding

Table 4 Sensitivity analysis equations and R code

Outcome	Effect of Interest	Sensitivity analysis equation	R function from tipr package
Unmeasured confounder, U, is Normally distributed with a difference in means between exposure groups of d, unit variance, and association with Y of $\beta_{Y\sim U\vert X+\mathbf{Z}}$			
Continuous	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - \beta_{Y\sim U\vert X+\mathbf{Z}} \times d$	`adjust_coef()`
Binary[a]	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - \beta_{Y\sim U\vert X+\mathbf{Z}} \times d$	`adjust_coef()`
Time to event	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} \approx \beta_{Y\sim X\vert\mathbf{Z}} - \beta_{Y\sim U\vert X+\mathbf{Z}} \times d$	`adjust_coef()`
Binary	Risk ratio	$RR_{Y\sim X\vert U+\mathbf{Z}} = \frac{RR_{Y\sim X\vert\mathbf{Z}}}{RR^{d}_{Y\sim U\vert X+\mathbf{Z}}}$	`adjust_rr()`
Binary	Odds ratio	$OR_{Y\sim X\vert U+\mathbf{Z}} \approx \frac{OR_{Y\sim X\vert\mathbf{Z}}}{OR^{d}_{Y\sim U\vert X+\mathbf{Z}}}$	`adjust_or()`
Time to event	Hazard ratio	$HR_{Y\sim X\vert U+\mathbf{Z}} \approx \frac{HR_{Y\sim X\vert\mathbf{Z}}}{HR^{d}_{Y\sim U\vert X+\mathbf{Z}}}$	`adjust_hr()`
Unmeasured confounder, U, is binary with prevalence in the unexposed group of p_0 in the exposed group of p_1, and association with Y of $\beta_{Y\sim U\vert X+\mathbf{Z}}$			
Continuous	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - \beta_{Y\sim U\vert X+\mathbf{Z}} \times (p_1 - p_0)$	`adjust_coef_with_binary()`
Binary[a]	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - log\frac{e^{\beta_{Y\sim U\vert X+\mathbf{Z}}}p_1+(1-p_1)}{e^{\beta_{Y\sim U\vert X+\mathbf{Z}}}p_0+(1-p_0)}$	`adjust_coef_with_binary()`
Time to event	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} \approx \beta_{Y\sim X\vert\mathbf{Z}} - log\frac{e^{\beta_{Y\sim U\vert X+\mathbf{Z}}}p_1+(1-p_1)}{e^{\beta_{Y\sim U\vert X+\mathbf{Z}}}p_0+(1-p_0)}$	`adjust_coef_with_binary()`
Binary	Risk ratio	$RR_{Y\sim X\vert U+\mathbf{Z}} = RR_{Y\sim X\vert\mathbf{Z}}\frac{RR_{Y\sim U\vert X+\mathbf{Z}}p_0+(1-p_0)}{RR_{Y\sim U\vert X+\mathbf{Z}}p_1+(1-p_1)}$	`adjust_rr_with_binary()`
Binary	Odds ratio	$OR_{Y\sim X\vert U+\mathbf{Z}} \approx OR_{Y\sim X\vert\mathbf{Z}}\frac{OR_{Y\sim U\vert X+\mathbf{Z}}p_0+(1-p_0)}{OR_{Y\sim U\vert X+\mathbf{Z}}p_1+(1-p_1)}$	`adjust_or_with_binary()`
Time to event	Hazard ratio	$HR_{Y\sim X\vert U+\mathbf{Z}} \approx HR_{Y\sim X\vert\mathbf{Z}}\frac{HR_{Y\sim U\vert X+\mathbf{Z}}p_0+(1-p_0)}{HR_{Y\sim U\vert X+\mathbf{Z}}p_1+(1-p_1)}$	`adjust_hr_with_binary()`
Unmeasured confounder, U, has relationships with X and Y characterized by $\beta_{U\sim X\vert\mathbf{Z}}$ and $\beta_{Y\sim U\vert X+\mathbf{Z}}$ or by partial R^2 as $R^2_{X\sim U\vert\mathbf{Z}}$ and $R^2_{Y\sim U\vert X+\mathbf{Z}}$			
Continuous	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - \beta_{Y\sim U\vert X+\mathbf{Z}} \times \beta_{U\sim X\vert\mathbf{Z}}$	`adjust_coef()`
Continuous	Coefficient	$\beta_{Y\sim X\vert U+\mathbf{Z}} = \beta_{Y\sim X\vert\mathbf{Z}} - \text{se}(\beta_{Y\sim X\vert\mathbf{Z}})\sqrt{\frac{R^2_{Y\sim U\vert X+\mathbf{Z}} \times R^2_{X\sim U\vert\mathbf{Z}}}{(1-R^2_{X\sim U\vert\mathbf{Z}})}\text{df}}$	`adjust_coef_with_r2()`

[a] The equality will hold for binary outcomes fit via a loglinear model. Otherwise, this is an approximation

D'Agostino McGowan, L. Sensitivity Analyses for Unmeasured Confounders. Curr Epidemiol Rep 9, 361–375 (2022)

What will tip our confidence bound to cross zero?

Quantifying Unmeasured Confounding

Table 7 Tipping point equations and R code

From: Sensitivity Analyses for Unmeasured Confounders

Effect of Interest	Known relationship	Tipping point equation	R function from the `tipr` package
Unmeasured confounder, *U*, is Normally distributed with a difference in means between exposure groups of *d* , unit variance, and association with *Y* of $\beta_{Y\sim U\mid X+\mathbf{Z}}$			
Coefficient	*U* and *X*	$\beta_{Y\sim U\mid X+\mathbf{Z},tip=0} = \frac{\beta_{Y\sim X\mid\mathbf{Z}}}{d}$	tip_coef()
Coefficient	*U* and *Y*	$d_{tip=0} = \frac{\beta_{Y\sim X\mid\mathbf{Z}}}{\beta_{Y\sim U\mid X+\mathbf{Z}}}$	tip_coef()
Risk ratio	*U* and *X*	$RR_{Y\sim U\mid X+\mathbf{Z},tip=1} = RR_{Y\sim X\mid\mathbf{Z}}^{1/d}$	tip_rr() tip_or() tip_hr()
Risk ratio	*U* and *Y*	$d_{tip=1} = \frac{\log(RR_{Y\sim X\mid\mathbf{Z}})}{\log(RR_{Y\sim U\mid X+\mathbf{Z}})}$	tip_rr() tip_or() tip_hr()
Unmeasured confounder, *U*, is binary with prevalence in the unexposed group of p_0 **in the exposed group of** p_1 **, and association with *Y* of** $\beta_{Y\sim U\mid X+\mathbf{Z}}$			
Risk ratio	*U* and *X*	$RR_{Y\sim U\mid X+\mathbf{Z},tip=1} = \frac{(1-p_1)+RR_{Y\sim X\mid\mathbf{Z}}\times(p_0-1)}{RR_{Y\sim X\mid\mathbf{Z}}\times p_0-p_1}$	tip_rr_with_binary() tip_or_with_binary() tip_hr_with_binary()
Risk ratio	*U* and *Y*	$p_{1,tip=1} = \frac{RR_{Y\sim X\mid\mathbf{Z}}-1}{RR_{Y\sim U\mid X+\mathbf{Z}}-1} + (RR_{Y\sim X\mid\mathbf{Z}} \times p_0)$ $p_{0,tip=1} = \frac{p_1}{RR_{Y\sim X\mid\mathbf{Z}}} - \frac{RR_{Y\sim X\mid\mathbf{Z}}-1}{RR_{Y\sim X\mid\mathbf{Z}}\times(RR_{Y\sim U\mid X+\mathbf{Z}}-1)}$	tip_rr_with_binary() tip_or_with_binary() tip_hr_with_binary()
Unmeasured confounder, *U*, has relationships with *X* and *Y* characterized by $\beta_{U\sim X\mid\mathbf{Z}}$ **and** $\beta_{Y\sim U\mid X+\mathbf{Z}}$ **or by partial** R^2 **as** $R^2_{X\sim U\mid\mathbf{Z}}$ **and** $R^2_{Y\sim U\mid X+\mathbf{Z}}$			
Coefficient	*U* and *X*	$\beta_{Y\sim U\mid X+\mathbf{Z},tip=0} = \frac{\beta_{Y\sim X\mid\mathbf{Z}}}{\beta_{U\sim X\mid\mathbf{Z}}}$	tip_coef()
Coefficient	*U* and *Y*	$\beta_{U\sim X\mid\mathbf{Z},tip=0} = \frac{\beta_{Y\sim X\mid\mathbf{Z}}}{\beta_{Y\sim U\mid X+\mathbf{Z}}}$	tip_coef()
Coefficient	*U* and *X*	$R^2_{Y\sim U\mid X+\mathbf{Z},tip=0} = \frac{\beta^2_{Y\sim X\mid\mathbf{Z}}-\beta^2_{Y\sim X\mid\mathbf{Z}}\times R^2_{X\sim U\mid\mathbf{Z}}}{se^2(\beta_{Y\sim X\mid\mathbf{Z}})df\times R^2_{X\sim U\mid\mathbf{Z}}}$	tip_coef _with_r2()
Coefficient	*U* and *Y*	$R^2_{X\sim U\mid\mathbf{Z},tip=0} = \frac{\beta^2_{Y\sim X\mid\mathbf{Z}}}{\beta^2_{Y\sim X\mid\mathbf{Z}}+se^2(\beta_{Y\sim X\mid\mathbf{Z}})df\times R^2_{Y\sim U\mid X+\mathbf{Z}}}$	tip_coef _with_r2()

Table 1. Grammar of `tipr` functions.

category	Function term	Use
action	`adjust`	These functions adjust observed effects, requiring both the unmeasured | confounder-exposure relationship and unmeasured confounder-outcome relationship to be specified.
	`tip`	These functions tip observed effects. Only one relationship, either the unmeasured confounder-exposure relationship or unmeasured confounder-outcome relationship needs to be specified.
effect	`coef`	These functions specify an observed coefficient from a linear, log-linear, logistic, or Cox proportional hazards model
	`rr`	These functions specify an observed relative risk
	`or`	These functions specify an observed odds ratio
	`hr`	These functions specify an observed hazard ratio
what	`continuous`	These functions specify an unmeasured standardized Normally distributed confounder. These functions will include the parameters `exposure_confounder_effect` and `confounder_outcome_effect`
	`binary`	These functions specify an unmeasured binary confounder. These functions will include the parameters `exposed_confounder_prev`, `unexposed_confounder_prev`, and `confounder_outcome_effect`
	`r2`	These functions specify an unmeasured confounder parameterized by specifying the percent of variation in the exposure / outcom explained by the unmeasured confounder. These functions will include the parameters `confounder_exposure_r2` and `outcome_exposure_r2`

- `{action}_{effect}_with_{what`
- `tip_rr_with_continous()`
- `adjust_coef_with_r2()`

D'Agostino McGowan, L., (2022). tipr: An R package for sensitivity analyses for unmeasured confounders. Journal of Open Source Software, 7(77), 4495

tipr

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ORIGINAL PAPER

Metformin use and incidence cancer risk: evidence for a selective protective effect against liver cancer

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Question

Metformin → Cancer

VERSUS
SULFONYLUREAS

Analysis

- New-user design
- **Matched** 42,217 new metformin users to 42,217 new sulfonylurea users
- Fit **adjusted Cox proportional hazards model** on the matched cohort

Results

- **Outcome:** Lung Cancer
- **Adjusted Hazard Ratio:** 0.87 (0.79, 0.96)

What if **alcohol consumption** is an unmeasured confounder?

What if heavy alcohol consumption is prevalent among 4% of Metformin users and 6% of Sulfonylurea users?

Meadows SO, Engel CC, Collins RL, Beckman RL, Cefalu M, Hawes-Dawson J, et al. 2015 health related behaviors survey: Substance use among US active-duty service members. RAND; 2018.

tipr Example

What if we assume the effect of alcohol consumption on lung cancer after adjusting for other confounders is 2?

```r
library(tipr)
adjust_hr_with_binary(
  effect_observed = c(0.79, 0.87, 0.96),
  exposed_confounder_prev = .04,
  unexposed_confounder_prev = .06,
  confounder_outcome_effect = 2)
```

tipr Example

What if we assume the effect of alcohol consumption on lung cancer after adjusting for other confounders is 2?

```r
library(tipr)
adjust_hr_with_binary(
  effect_observed = c(0.79, 0.87, 0.96),
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  unexposed_confounder_prev = .06,
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Results

- **Outcome:** Lung Cancer

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tipr Example

What if we assume the effect of alcohol consumption on lung cancer after adjusting for other confounders is 2?

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  effect_observed = c(0.79, 0.87, 0.96),
  exposed_confounder_prev = .04,
  unexposed_confounder_prev = .06,
  confounder_outcome_effect = 2)
```

tipr Example

```
# A tibble: 3 × 5
  hr_adjusted hr_observed exposed_confounder_prev
unexposed_confounder_prev
        <dbl>       <dbl>                   <dbl>
<dbl>
1       0.805        0.79                    0.04
0.06
2       0.887        0.87                    0.04
0.06
3       0.978        0.96                    0.04
0.06
# ℹ 1 more variable: confounder_outcome_effect <dbl>
```

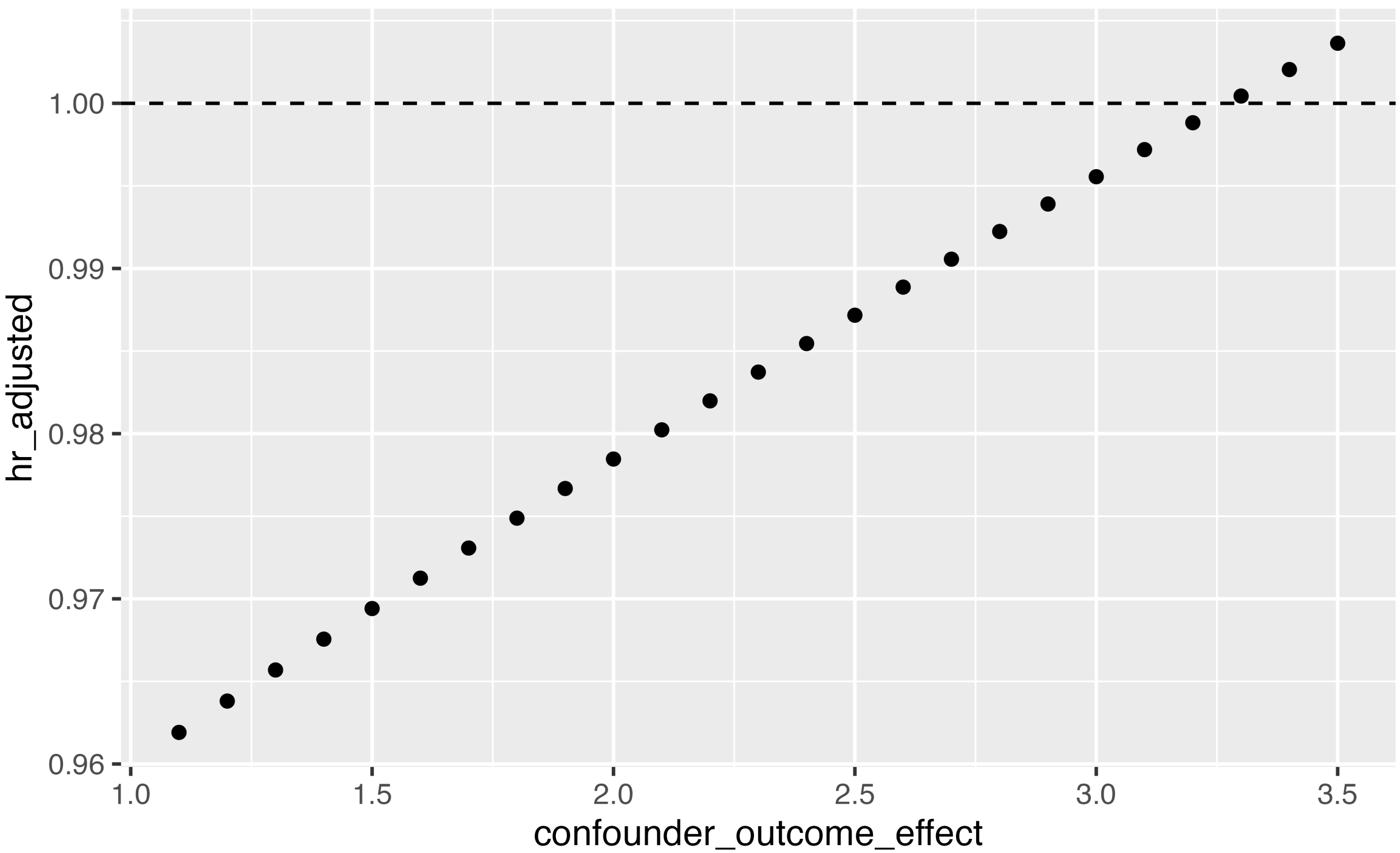
"If heavy alcohol consumption differed between groups, with 4% prevalence among metformin users and 6% among sulfonylureas users, and had an HR of 2 with lung cancer incidence the updated adjusted effect of metformin on lung cancer incidence would be an HR of *0.89 (95% CI: 0.81–0.98)*. Should an unmeasured confounder like this exist, our effect of metformin on lung cancer incidence would be attenuated and fall much closer to the null.

tipr Example

```r
library(tipr)
sens <- adjust_hr_with_binary(
  effect_observed = 0.96,
  exposed_confounder_prev = .04,
  unexposed_confounder_prev = .06,
  confounder_outcome_effect = seq(1.1, 3.5, by = 0.1))
```

tipr Example

```
library(ggplot2)
ggplot(sens, aes(x = confounder_outcome_effect, y = hr_adjusted)
  geom_point() +
  geom_hline(yintercept = 1, lty = 2)
```



tipr Example

```r
library(tipr)
tip_hr_with_binary(
  effect_observed = 0.96,
  exposed_confounder_prev = .04,
  unexposed_confounder_prev = .06)
```

tipr Example

```
# A tibble: 1 × 6
  effect_adjusted effect_observed exposed_confounder_prev
unexposed_confounder…¹
            <dbl>           <dbl>                   <dbl>
<dbl>
1               1            0.96                    0.04
0.06
# ℹ abbreviated name: ¹unexposed_confounder_prev
# ℹ 2 more variables: confounder_outcome_effect <dbl>,
#   n_unmeasured_confounders <dbl>
```

"If heavy alcohol consumption differed between groups, with *4%* prevalence among metformin users and *6%* among sulfonylureas users, it would need to have an association with lung cancer incidence of *3.27 to tip this analysis* at the 5% level, rendering it inconclusive. This effect is larger than the understood association between lung cancer and alcohol consumption."

What is known about the unmeasured confounder?

Both exposure and outcome relationship is known	Only one of the exposure/outcome relationships is known	Nothing is known
• `adjust_*` functions	• `adjust_*` functions in an array • `tip_*` functions	• `adjust_*` functions in an array • `tip_*` functions in an array • `tip_coef_with_r2()` (measured confounders) • Robustness value `r_value()` & E-values `e_value()`

Disney Data

`tip_coef()`

- `effect_observed`: observed exposure - outcome effect **4.45 minutes (95% CI: 0.17, 8.37)**

Disney Data

`tip_coef()`

- `exposure_confounder_effect`: scaled mean difference between the unmeasured confounder in the exposed and unexposed population

Disney Data

`tip_coef()`

- `confounder_outcome_effect`: relationship between the unmeasured confounder and outcome

Disney Data

`tip_coef()`: specify one, it will estimate the other

- `exposure_confounder_effect`
- `confounder_outcome_effect`

Disney Data

Our causal effect estimate: 4.45 minutes (95% CI: 0.17, 8.37)

```
# A tibble: 1 × 4
  effect_observed exposure_confounder_effect confounder_outcome_effect
            <dbl>                      <dbl>                     <dbl>
1            0.17                        0.1                       1.7
# ℹ 1 more variable: n_unmeasured_confounders <dbl>
```

```r
library(tipr)
tip_coef(
  effect_observed = 0.17,
  exposure_confounder_effect = 0.1
)
```

Your turn

Use the `tip_coef()` function to conduct a sensitivity analysis for the estimate from your previous exercises.

05:00