

Tipping Point Sensitivity Analyses

Lucy D'Agostino McGowan
Wake Forest University


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

Sensitivity Analyses for Unmeasured Confounders


Lucy D'Agostino McGowan¹ 

Accepted: 15 September 2022 / Published online: 8 November 2022



tipr: An R package for sensitivity analyses for unmeasured confounders

Lucy D'Agostino McGowan ¹ 

¹ Wake Forest University, USA  Corresponding author

DOI: [10.21105/joss.04495](https://doi.org/10.21105/joss.04495)

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 <code>tipr</code> package
Unmeasured confounder, U, is Normally distributed with a difference in means between exposure groups of d, unit variance, and association with Y of $\beta_{Y \sim U X+Z}$			
Continuous	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \beta_{Y \sim U X+Z} \times d$	<code>adjust_coef()</code>
Binary ^a	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \beta_{Y \sim U X+Z} \times d$	<code>adjust_coef()</code>
Time to event	Coefficient	$\beta_{Y \sim X U+Z} \approx \beta_{Y \sim X Z} - \beta_{Y \sim U X+Z} \times d$	<code>adjust_coef()</code>
Binary	Risk ratio	$RR_{Y \sim X U+Z} = \frac{RR_{Y \sim X Z}}{RR_{Y \sim U X+Z}^d}$	<code>adjust_rr()</code>
Binary	Odds ratio	$OR_{Y \sim X U+Z} \approx \frac{OR_{Y \sim X Z}}{OR_{Y \sim U X+Z}^d}$	<code>adjust_or()</code>
Time to event	Hazard ratio	$HR_{Y \sim X U+Z} \approx \frac{HR_{Y \sim X Z}}{HR_{Y \sim U X+Z}^d}$	<code>adjust_hr()</code>
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 $\beta_{Y \sim U X+Z}$			
Continuous	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \beta_{Y \sim U X+Z} \times (p_1 - p_0)$	<code>adjust_coef_with_binary()</code>
Binary ^a	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \log \frac{e^{\beta_{Y \sim U X+Z} p_1 + (1-p_1)}}{e^{\beta_{Y \sim U X+Z} p_0 + (1-p_0)}}$	<code>adjust_coef_with_binary()</code>
Time to event	Coefficient	$\beta_{Y \sim X U+Z} \approx \beta_{Y \sim X Z} - \log \frac{e^{\beta_{Y \sim U X+Z} p_1 + (1-p_1)}}{e^{\beta_{Y \sim U X+Z} p_0 + (1-p_0)}}$	<code>adjust_coef_with_binary()</code>
Binary	Risk ratio	$RR_{Y \sim X U+Z} = RR_{Y \sim X Z} \frac{RR_{Y \sim U X+Z} p_0 + (1-p_0)}{RR_{Y \sim U X+Z} p_1 + (1-p_1)}$	<code>adjust_rr_with_binary()</code>
Binary	Odds ratio	$OR_{Y \sim X U+Z} \approx OR_{Y \sim X Z} \frac{OR_{Y \sim U X+Z} p_0 + (1-p_0)}{OR_{Y \sim U X+Z} p_1 + (1-p_1)}$	<code>adjust_or_with_binary()</code>
Time to event	Hazard ratio	$HR_{Y \sim X U+Z} \approx HR_{Y \sim X Z} \frac{HR_{Y \sim U X+Z} p_0 + (1-p_0)}{HR_{Y \sim U X+Z} p_1 + (1-p_1)}$	<code>adjust_hr_with_binary()</code>
Unmeasured confounder, U, has relationships with X and Y characterized by $\beta_{U \sim X Z}$ and $\beta_{Y \sim U X+Z}$ or by partial R^2 as $R_{X \sim U Z}^2$ and $R_{Y \sim U X+Z}^2$			
Continuous	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \beta_{Y \sim U X+Z} \times \beta_{U \sim X Z}$	<code>adjust_coef()</code>
Continuous	Coefficient	$\beta_{Y \sim X U+Z} = \beta_{Y \sim X Z} - \text{se}(\beta_{Y \sim X Z}) \sqrt{\frac{R_{Y \sim U X+Z}^2 \times R_{X \sim U Z}^2}{(1-R_{X \sim U Z}^2)}} \text{df}$	<code>adjust_coef_with_r2()</code>

^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 <code>tipr</code> package
Unmeasured confounder, U , is Normally distributed with a difference in means between exposure groups of d , unit variance, and association with Y of $\beta_{Y \sim U X+Z}$			
Coefficient	U and X	$\beta_{Y \sim U X+Z, tip=0} = \frac{\beta_{Y \sim X Z}}{d}$	<code>tip_coef()</code>
Coefficient	U and Y	$d_{tip=0} = \frac{\beta_{Y \sim X Z}}{\beta_{Y \sim U X+Z}}$	<code>tip_coef()</code>
Risk ratio	U and X	$RR_{Y \sim U X+Z, tip=1} = RR_{Y \sim X Z}^{1/d}$	<code>tip_rr()</code> <code>tip_or()</code> <code>tip_hr()</code>
Risk ratio	U and Y	$d_{tip=1} = \frac{\log(RR_{Y \sim X Z})}{\log(RR_{Y \sim U X+Z})}$	<code>tip_rr()</code> <code>tip_or()</code> <code>tip_hr()</code>
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 $\beta_{Y \sim U X+Z}$			
Risk ratio	U and X	$RR_{Y \sim U X+Z, tip=1} = \frac{(1-p_1) + RR_{Y \sim X Z}(p_0-1)}{RR_{Y \sim X Z}(p_0-1)}$	<code>tip_rr_with_binary()</code> <code>tip_or_with_binary()</code> <code>tip_hr_with_binary()</code>
Risk ratio	U and Y	$p_{1, tip=1} = \frac{RR_{Y \sim X Z}-1}{RR_{Y \sim U X+Z}-1}$ $p_{0, tip=1} = \frac{p_1}{RR_{Y \sim X Z}}$ $+ (RR_{Y \sim X Z} \times p_0) - \frac{RR_{Y \sim X Z}-1}{RR_{Y \sim X Z}(RR_{Y \sim U X+Z}-1)}$	<code>tip_rr_with_binary()</code> <code>tip_or_with_binary()</code> <code>tip_hr_with_binary()</code>
Unmeasured confounder, U , has relationships with X and Y characterized by $\beta_{U \sim X Z}$ and $\beta_{Y \sim U X+Z}$ or by partial R^2 as $R^2_{X \sim U Z}$ and $R^2_{Y \sim U X+Z}$			
Coefficient	U and X	$\beta_{Y \sim U X+Z, tip=0} = \frac{\beta_{Y \sim X Z}}{\beta_{U \sim X Z}}$	<code>tip_coef()</code>
Coefficient	U and Y	$\beta_{U \sim X Z, tip=0} = \frac{\beta_{Y \sim X Z}}{\beta_{Y \sim U X+Z}}$	<code>tip_coef()</code>
Coefficient	U and X	$R^2_{Y \sim U X+Z, tip=0} = \frac{\beta_{Y \sim X Z}^2 - \beta_{Y \sim X Z}^2 Z^2 R^2_{X \sim U Z}}{se^2(\beta_{Y \sim X Z})d^2 f \times R^2_{X \sim U Z}}$	<code>tip_coef_with_r2()</code>
Coefficient	U and Y	$R^2_{X \sim U Z, tip=0} = \frac{\beta_{Y \sim X Z}^2}{\beta_{Y \sim X Z}^2 + se^2(\beta_{Y \sim X Z})d^2 f \times R^2_{Y \sim U X+Z}}$	<code>tip_coef_with_r2()</code>

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

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
what	hr	These functions specify an observed hazard ratio
	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



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

Harvey J. Murff^{1,2,5} · Christianne L. Roumie^{1,2} · Robert A. Greevy^{1,3} · Amber J. Hackstadt³ · Lucy E. D'Agostino McGowan³ · Adriana M. Hung^{1,2} · Carlos G. Grijalva^{1,4} · Marie R. Griffin^{1,2,4}

Received: 22 April 2017 / Accepted: 13 July 2018 / Published online: 18 July 2018
© Springer Nature Switzerland AG 2018

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?

```
1 library(tipr)
2 adjust_hr_with_binary(
3   effect_observed = c(0.79, 0.87, 0.96),
4   exposed_confounder_prev = .04,
5   unexposed_confounder_prev = .06,
6   confounder_outcome_effect = 2
7 )
```

Results

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

tipr Example

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

```
1 library(tipr)
2 adjust_hr_with_binary(
3   effect_observed = c(0.79, 0.87, 0.96),
4   exposed_confounder_prev = .04,
5   unexposed_confounder_prev = .06,
6   confounder_outcome_effect = 2
7 )
```

**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?

```
1 library(tipr)
2 adjust_hr_with_binary(
3   effect_observed = c(0.79, 0.87, 0.96),
4   exposed_confounder_prev = .04,
5   unexposed_confounder_prev = .06,
6   confounder_outcome_effect = 2
7 )
```

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>
```

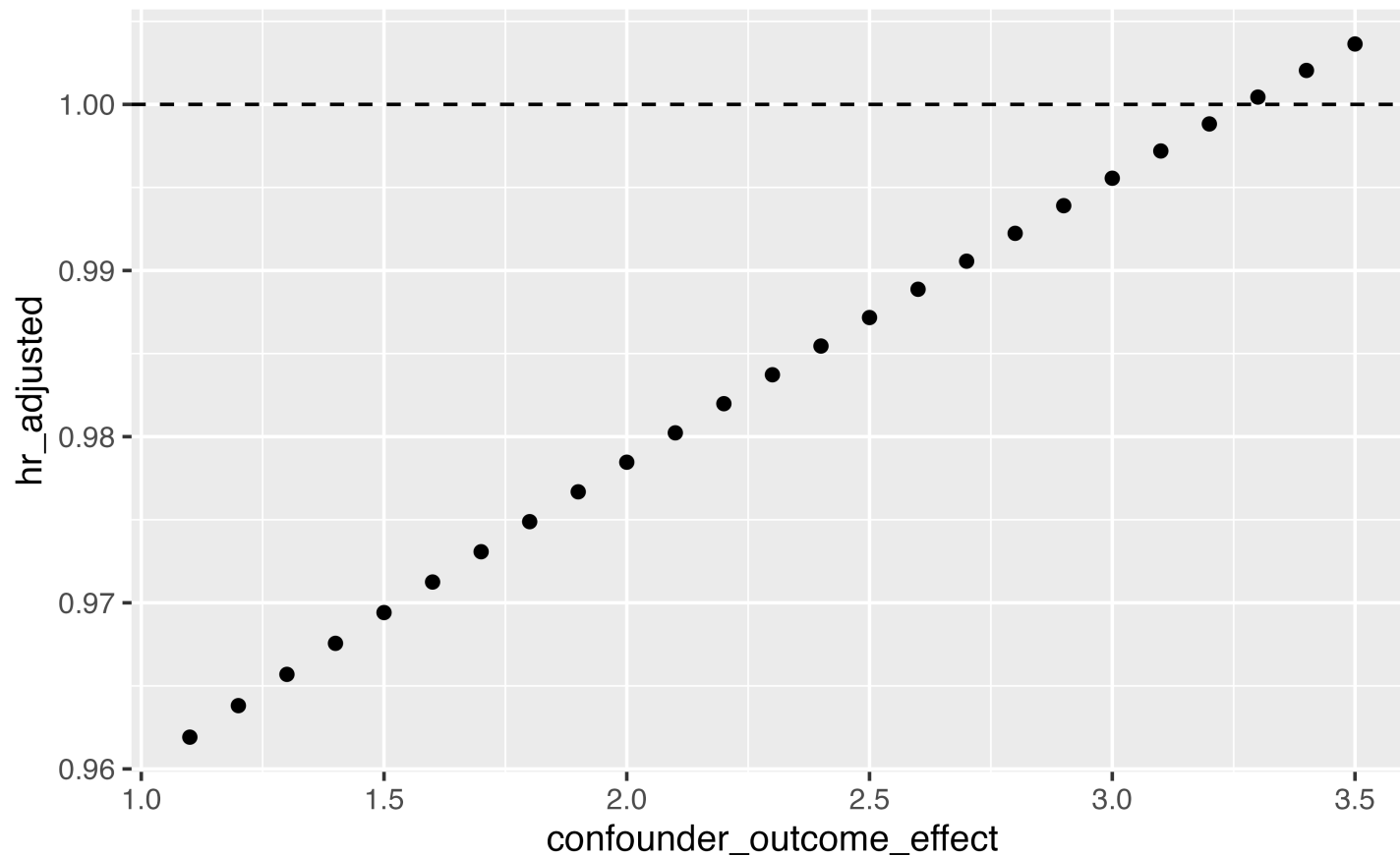
“If heavy alcohol consumption differed between groups, with 4% prevalence among metformin users and 6% among sulfonylureas users, and had an HR of 2 with lung cancer incidence the updated adjusted effect of metformin on lung cancer incidence would be an HR of 0.89 (95% CI: 0.81–0.98). Should an unmeasured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

tipr Example

```
1 sens <- adjust_hr_with_binary(  
2   effect_observed = 0.96,  
3   exposed_confounder_prev = .04,  
4   unexposed_confounder_prev = .06,  
5   confounder_outcome_effect = seq(1.1, 3.5, by = 0.1)  
6 )
```


tipr Example

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



tipr Example

```
1 library(dplyr)
2 tip_hr_with_binary(
3   effect_observed = 0.96,
4   exposed_confounder_prev = .04,
5   unexposed_confounder_prev = .06
6 ) |>
7   select(confounder_outcome_effect)
```

tipr Example

```
# A tibble: 1 × 1
  confounder_outcome_effect
  <dbl>
1          3.27
```

“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

- `adjust_*` functions

Only one of the exposure/outcome relationships is known

- `adjust_*` functions in an array

- `tip_*` functions

Nothing is known

- `adjust_*` or `tip_*` functions in an array
- `tip_coef_with_r2()` (measured confounders)
- Robustness value `r_value()` & E-values `e_value()`

Disney Data: Extra magic morning & wait times

`tip_coef()`

- `effect_observed`: observed exposure - outcome effect 6.17 minutes (95% CI: 2.02, 10.40)

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

Your turn

Use the **tip_coef()** function to conduct a sensitivity analysis for the estimate from your previous exercises. Use the lower bound of the confidence interval for the effect and **0.1** for the exposure-confounder effect.

