

# Flexible sensitivity analysis for causal inference in observational studies subject to unmeasured confounding

Sizhu Lu

Joint work with Professor Peng Ding

Department of Statistics, UC Berkeley

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# Overview

Background: causal inference in observational studies

Sensitivity analysis with unmeasured confounding

Extensions

## Potential outcome framework

- ▶ Potential outcome framework.
- ▶ Potential outcomes:  $Y_i(1)$  and  $Y_i(0)$ .
- ▶ Binary treatment:  $Z_i$ .
- ▶ Observed outcome:  $Y_i = Y_i(Z_i) = Z_i Y_i(1) + (1 - Z_i) Y_i(0)$ .
- ▶ Stable unit treatment values assumption.
- ▶ Super population regime: independently and identically distributed  $\{X_i, Z_i, Y_i(1), Y_i(0) : i = 1, \dots, n\}$ .

## Parameter of interest

- ▶ Causal parameter of interest:  $\tau = E\{Y(1) - Y(0)\}$ , the average treatment effect, decomposes into

$$\begin{aligned}\tau &= [E(Y | Z = 1)\text{pr}(Z = 1) + \color{red}{E\{Y(1) | Z = 0\}}\text{pr}(Z = 0)] \\ &\quad - [\color{red}{E\{Y(0) | Z = 1\}}\text{pr}(Z = 1) + E(Y | Z = 0)\text{pr}(Z = 0)].\end{aligned}$$

- ▶ Fundamental challenge of causal inference: to estimate the counterfactual means  $E\{Y(1) | Z = 0\}$  and  $E\{Y(0) | Z = 1\}$ .
- ▶ Randomization leads to obvious identification, but in observational studies?

## Identification under unconfoundedness

- ▶ Unconfoundedness assumption:  $Z \perp\!\!\!\perp \{Y(1), Y(0)\} \mid X$  (Rosenbaum and Rubin, 1983).
- ▶ Under this assumption,  
 $E\{Y(1) \mid Z = 1, X\} = E\{Y(1) \mid Z = 0, X\}$ , thus  $\tau$  is nonparametrically identified.
- ▶ Two identification formulas:

$$\begin{aligned}\tau &= E\{\mu_1(X) - \mu_0(X)\} \\ &= E\left\{\frac{ZY}{e(X)} - \frac{(1-Z)Y}{1-e(X)}\right\},\end{aligned}$$

where

- ▶  $\mu_1(X) = E(Y \mid Z = 1, X)$  and  $\mu_0(X) = E(Y \mid Z = 0, X)$ : conditional expectation of outcomes;
- ▶  $e(X) = \text{pr}(Z = 1 \mid X)$ : propensity score.
- ▶ Implicitly assume overlap:  $0 < e(X) < 1$ .

## Estimation under unconfoundedness

- ▶ Estimators corresponding to the two identification formulas:

$$\hat{\tau}^{\text{reg}} = n^{-1} \sum_{i=1}^n \{\hat{\mu}_1(X_i) - \hat{\mu}_0(X_i)\},$$

$$\hat{\tau}^{\text{ht}} = n^{-1} \sum_{i=1}^n \left\{ \frac{Z_i Y_i}{\hat{e}(X_i)} - \frac{(1 - Z_i) Y_i}{1 - \hat{e}(X_i)} \right\},$$

where  $\hat{e}(X_i)$  and  $\hat{\mu}_z(X_i)$  are fitted propensity score and outcome models.

## Estimation under unconfoundedness

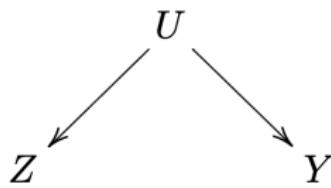
- ▶ Doubly robust estimator by combining both models (Bang and Robins, 2005):

$$\hat{\tau}^{\text{dr}} = \hat{\tau}^{\text{reg}} + n^{-1} \sum_{i=1}^n \left[ \frac{Z_i \{Y_i - \hat{\mu}_1(X_i)\}}{\hat{e}(X_i)} - \frac{(1 - Z_i) \{Y_i - \hat{\mu}_0(X_i)\}}{1 - \hat{e}(X_i)} \right].$$

- ▶ Modifies  $\hat{\tau}^{\text{reg}}$  by inverse propensity score weighted residuals.
- ▶ Consistent to  $\tau$  if either outcome models or propensity score model is correctly specified.

## Sensitivity analysis

- ▶ Unconfoundedness assumption: untestable, cannot use data to validate.
- ▶ Existence of unmeasured confounding possibly overturns an observed association between the treatment and outcome.
- ▶ Hidden confounder  $U$ :



Source: Ding (2024).

- ▶ Sensitivity analysis: assess the impact of  $U$ ; how strong the unmeasured confounding needs to be to overturn the observed association.

## Sensitivity analysis

- ▶ Parametric models to assess the impact of  $U$  on the estimation of  $\tau$  (Rosenbaum and Rubin, 1983; Lin et al., 1998; Imbens, 2003).
- ▶ Sensitivity analysis to test the sharp null hypothesis of no unit-level causal effects in matched-pair observational studies (Rosenbaum, 1987).
- ▶ E-value: sensitivity analysis for causal estimates based on risk ratios (Cornfield et al., 1959; Ding and VanderWeele, 2016; VanderWeele and Ding, 2017).
- ▶ Sensitivity analysis methods for the inverse propensity score weighting estimator (Zhao et al., 2019; Dorn and Guo, 2022).
- ▶ Useful for specific estimation or testing strategies.
- ▶ Deal with the standard estimators  $\hat{\tau}^{\text{reg}}$ ,  $\hat{\tau}^{\text{ht}}$  and  $\hat{\tau}^{\text{dr}}$  simultaneously?

## Identification challenge revisit: two extreme solutions

$$\begin{aligned}\tau &= [E(Y | Z = 1)\text{pr}(Z = 1) + \color{red}E\{Y(1) | Z = 0\}\text{pr}(Z = 0)] \\ &\quad - [\color{red}E\{Y(0) | Z = 1\}\text{pr}(Z = 1) + E(Y | Z = 0)\text{pr}(Z = 0)].\end{aligned}$$

- ▶ Unconfoundedness assumption:  $Z \perp\!\!\!\perp \{Y(1), Y(0)\} | X$ .

$$\begin{aligned}E\{Y(1) | Z = 1, X\} &= E\{Y(1) | Z = 0, X\}, \\ E\{Y(0) | Z = 1, X\} &= E\{Y(0) | Z = 0, X\}.\end{aligned}$$

- ▶ Very restrictive—assumes the two treatment groups have **identical** conditional means.

## Identification challenge revisit: two extreme solutions

$$\begin{aligned}\tau &= [E(Y | Z = 1)\text{pr}(Z = 1) + \textcolor{red}{E\{Y(1) | Z = 0\}}\text{pr}(Z = 0)] \\ &\quad - [\textcolor{red}{E\{Y(0) | Z = 1\}}\text{pr}(Z = 1) + E(Y | Z = 0)\text{pr}(Z = 0)].\end{aligned}$$

- ▶ Partial identification method:
  - ▶ Assume the potential outcomes are bounded between  $[\ell, u]$ .
  - ▶  $E\{Y(1)\}$  has lower bound

$$E(Y | Z = 1)\text{pr}(Z = 1) + \ell\text{pr}(Z = 0)$$

and upper bound

$$E(Y | Z = 1)\text{pr}(Z = 1) + u\text{pr}(Z = 0).$$

- ▶ Similar lower and upper bounds for  $E\{Y(0)\}$ , leading to bounds for  $\tau$ .
- ▶ Problem: bounds are always too wide to provide valuable causal information.
- ▶ Is there a midground?

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## Sensitivity analysis with unmeasured confounding

- ▶ Define sensitivity parameters:

$$\frac{E\{Y(1) \mid Z = 1, X\}}{E\{Y(1) \mid Z = 0, X\}} = \varepsilon_1(X), \quad \frac{E\{Y(0) \mid Z = 1, X\}}{E\{Y(0) \mid Z = 0, X\}} = \varepsilon_0(X).$$

- ▶  $\varepsilon_1(X)$  and  $\varepsilon_0(X)$ : two sensitivity parameters.
- ▶ Quantifies the violation of the unconfoundedness assumption.
- ▶  $\varepsilon_1(X) = \varepsilon_0(X) = 1$ : the unconfoundedness assumption.
- ▶ First fix them to obtain the corresponding estimators and then vary them within a range to obtain a sequence of estimators.

# Identification and estimation under sensitivity analysis

## Outcome regression

- ▶ With known  $\varepsilon_1(X)$  and  $\varepsilon_0(X)$ ,

$$\begin{aligned} E\{Y(1) \mid Z = 0\} &= E\{\mu_1(X)/\varepsilon_1(X) \mid Z = 0\}, \\ E\{Y(0) \mid Z = 1\} &= E\{\mu_0(X)\varepsilon_0(X) \mid Z = 1\}. \end{aligned}$$

- ▶ Estimator:

$$\begin{aligned} \hat{\tau}^{\text{proj}} &= n^{-1} \sum_{i=1}^n \{Z_i \hat{\mu}_1(X_i) + (1 - Z_i) \hat{\mu}_1(X_i)/\varepsilon_1(X_i)\} \\ &\quad - n^{-1} \sum_{i=1}^n \{Z_i \hat{\mu}_0(X_i) \varepsilon_0(X_i) + (1 - Z_i) \hat{\mu}_0(X_i)\}. \end{aligned}$$

# Identification and estimation under sensitivity analysis

## Inverse propensity score weighting

- With known  $\varepsilon_1(X)$  and  $\varepsilon_0(X)$ ,

$$E\{Y(1)\} = E\left\{w_1(X) \frac{Z}{e(X)} Y\right\},$$

$$E\{Y(0)\} = E\left\{w_0(X) \frac{1-Z}{1-e(X)} Y\right\},$$

where

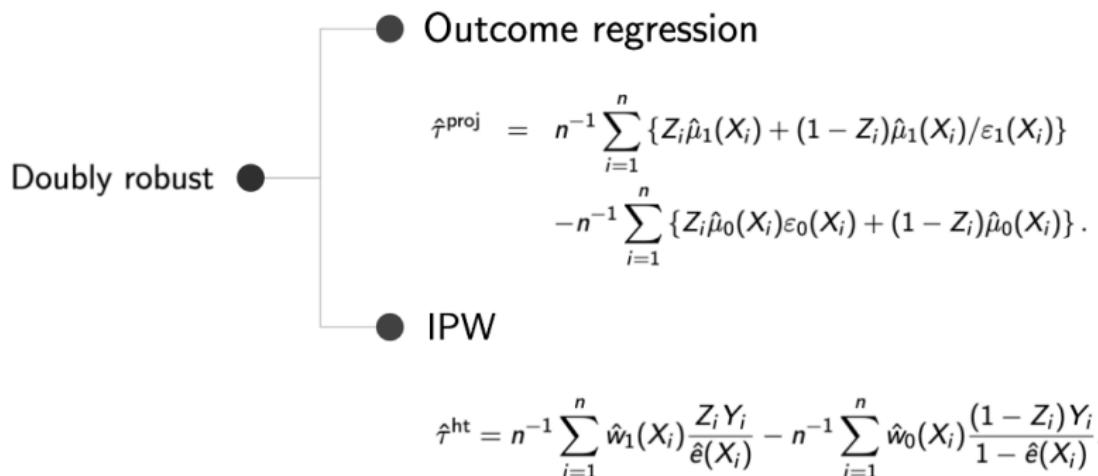
$$w_1(X) = e(X) + \{1 - e(X)\}/\varepsilon_1(X), \quad w_0(X) = e(X)\varepsilon_0(X) + 1 - e(X).$$

- Estimator:

$$\hat{\tau}^{\text{ht}} = n^{-1} \sum_{i=1}^n \hat{w}_1(X_i) \frac{Z_i Y_i}{\hat{e}(X_i)} - n^{-1} \sum_{i=1}^n \hat{w}_0(X_i) \frac{(1 - Z_i) Y_i}{1 - \hat{e}(X_i)}.$$

# Identification and estimation under sensitivity analysis

- ▶ When  $\varepsilon_1(X) = \varepsilon_0(X) = 1$ , reduces to the unconfoundedness assumption. Recover previous results.
- ▶ Motivates a combined strategy: doubly robust estimation (Bang and Robins, 2005; Bickel et al., 1993).



## Efficient influence function

- Under our definition of sensitivity parameters, the efficient influence functions for  $E\{Y(1)\}$  and  $E\{Y(0)\}$  are respectively

$$\phi_1 = w_1(X) \frac{Z}{e(X)} Y - \frac{\{Z - e(X)\}\mu_1(X)}{e(X)\varepsilon_1(X)} - E\{Y(1)\},$$

$$\phi_0 = w_0(X) \frac{1-Z}{1-e(X)} Y - \frac{\{e(X)-Z\}\mu_0(X)\varepsilon_0(X)}{1-e(X)} - E\{Y(0)\},$$

so the efficient influence function for  $\tau$  is  $\phi_1 - \phi_0$ .

- An estimator constructed based on the EIF:

$$\begin{aligned}\hat{\tau}^{\text{dr}} &= n^{-1} \sum_{i=1}^n \left[ \hat{w}_1(X_i) \frac{Z_i Y_i}{\hat{e}(X_i)} - \frac{\{Z_i - \hat{e}(X_i)\} \hat{\mu}_1(X_i)}{\hat{e}(X_i) \varepsilon_1(X_i)} \right] \\ &\quad - n^{-1} \sum_{i=1}^n \left[ \hat{w}_0(X_i) \frac{(1-Z_i) Y_i}{1-\hat{e}(X_i)} - \frac{\{\hat{e}(X_i) - Z_i\} \hat{\mu}_0(X_i) \varepsilon_0(X_i)}{1-\hat{e}(X_i)} \right].\end{aligned}$$

- Can be written as modifications of  $\hat{\tau}^{\text{proj}}$  and  $\hat{\tau}^{\text{ht}}$ .

## Double robustness and semiparametric efficiency

$$\begin{aligned}\hat{\tau}^{\text{dr}} = & n^{-1} \sum_{i=1}^n \left[ \hat{w}_1(X_i) \frac{Z_i Y_i}{\hat{e}(X_i)} - \frac{\{Z_i - \hat{e}(X_i)\} \hat{\mu}_1(X_i)}{\hat{e}(X_i) \varepsilon_1(X_i)} \right] \\ & - n^{-1} \sum_{i=1}^n \left[ \hat{w}_0(X_i) \frac{(1 - Z_i) Y_i}{1 - \hat{e}(X_i)} - \frac{\{\hat{e}(X_i) - Z_i\} \hat{\mu}_0(X_i) \varepsilon_0(X_i)}{1 - \hat{e}(X_i)} \right].\end{aligned}$$

- ▶ Double robustness: consistent if either the propensity score or the outcome model is correctly specified.
- ▶ Semiparametric efficiency bound is achieved with
  1. consistency of both models,
  2. mild requirements on their convergence rates.

## Implementation—calibration of sensitivity parameters

- ▶ Observed data do not provide information on sensitivity parameters.
- ▶ How can we make meaningful progress?
  - ▶ A standard strategy: leave one covariate out.
  - ▶ Pretending an observed covariate is an unmeasured confounder.
  - ▶ Assume ignorability  $Z \perp\!\!\!\perp \{Y(1), Y(0)\} \mid X$  and calculate

$$\varepsilon_z(X_{-j}) = \frac{E\{Y(z) \mid Z = 1, X_{-j}\}}{E\{Y(z) \mid Z = 0, X_{-j}\}}, \quad (z = 0, 1).$$

- ▶ Use the range of  $\hat{\varepsilon}_z(X_{-j})$  to specify the range of  $(\varepsilon_1(X), \varepsilon_0(X))$ .

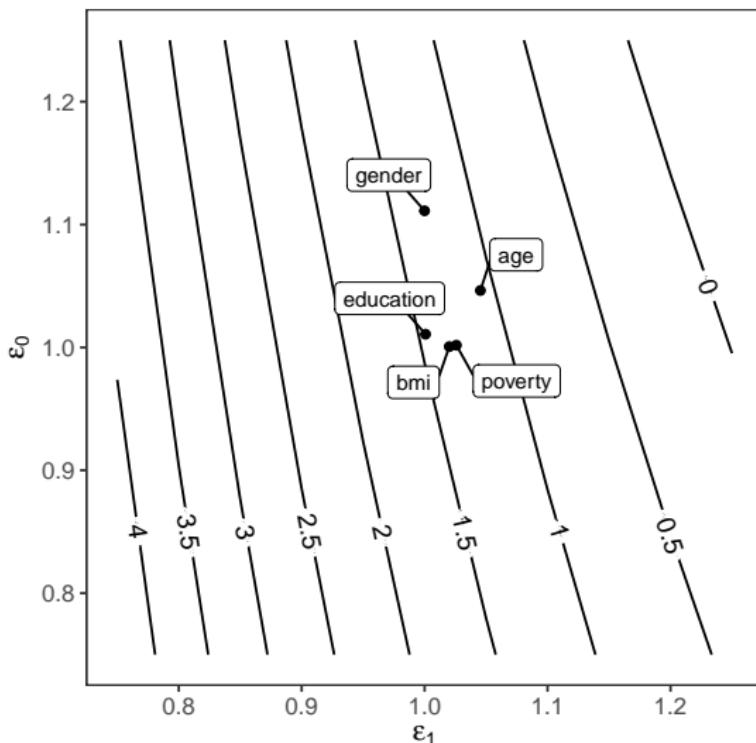
## Sensitivity parameters: vary them with covariates or not

- ▶ Our theory allows for the dependence of sensitivity parameters on  $X$ .
  - ▶ Complicated in implementation.
  - ▶ Not easy to visualize the sensitivity analysis results.
- ▶ Practically, specify  $(\varepsilon_1(X), \varepsilon_0(X)) = (\varepsilon_1, \varepsilon_0)$  independent of  $X$ .
  - ▶ Point estimates are monotonic in  $\varepsilon_1, \varepsilon_0$ : easy to interpret.
  - ▶ For non-negative outcomes: can also be interpreted as the worst-case result even with  $(\varepsilon_1(X), \varepsilon_0(X))$  depending on  $X$ .
  - ▶ Formal result in the paper.

## Demo with an example

- ▶ Re-analyze the observational study in Bazzano et al. (2003): whether cigarette smoking has a causal effect on homocysteine levels.
- ▶ Elevation of homocysteine level is a risk factor for cardiovascular disease.
- ▶ Data: the U.S. National Health and Nutrition Examination Survey 2005– 2006.
- ▶ Observed covariates: gender, age, education level, body mass index (BMI), and poverty.
- ▶  $\hat{\tau}^{\text{dr}}$  for  $\tau$ : 1.48 with a 95% confidence interval (0.78, 2.18).
- ▶ Unobserved confounders: genotype?

## Demo with an example – visualization based on $\hat{\gamma}^{\text{dr}}$



- ▶ Point estimates as a function of  $(\varepsilon_1, \varepsilon_0)$ .
- ▶ Plot maximums of  $\hat{\gamma}_z(X_{-j})$  for observed covariates.

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## Extension to nonlinear causal parameters

- ▶ A more general class of nonlinear causal parameters  $g(\mu_1, \mu_0)$ .
- ▶ Previous results:  $g(\mu_1, \mu_0) = \mu_1 - \mu_0$ .
- ▶ Binary outcomes: the causal risk ratio and the causal odds ratio,

$$\text{RR} = \frac{\mu_1}{\mu_0} \quad \text{and} \quad \text{OR} = \frac{\mu_1/(1-\mu_1)}{\mu_0/(1-\mu_0)}.$$

- ▶ Plug-in estimators  $g(\hat{\mu}_1^*, \hat{\mu}_0^*)$  for  $* \in \{\text{pred, prod, ht, dr}\}$ .

## Extension to bias-corrected matching estimator

- ▶ Matching: impute the missing counterfactual  $Y_i(0)$  for  $Z_i = 1$  by finding  $M$  nearest neighbors of  $i$  in the control group.
- ▶ Use the average observed outcomes of the  $M$  nearest neighbors as the imputed value of the counterfactual  $Y_i(0)$ . Similar procedure for  $Y_i(1)$ .
- ▶ Matching-based estimator: average of the imputed individual treatment effect. Generally inconsistent (Abadie and Imbens, 2006).
- ▶ Abadie and Imbens (2011) proposed a bias-corrected version of the matching estimator by estimating the conditional outcome models  $\mu_z(X)$  and combining it with the original matching estimator.

## Extension to bias-corrected matching estimator

- ▶ Rewrite the bias-corrected matching estimator as (Lin et al., 2023):

$$\begin{aligned}\hat{\tau}_M^{\text{bc}} &= \hat{\tau}^{\text{reg}} + n^{-1} \sum_{i=1}^n \left\{ 1 + \frac{K_M^1(X_i)}{M} \right\} Z_i \{ Y_i - \hat{\mu}_1(X_i) \} \\ &\quad - n^{-1} \sum_{i=1}^n \left\{ 1 + \frac{K_M^0(X_i)}{M} \right\} (1 - Z_i) \{ Y_i - \hat{\mu}_0(X_i) \},\end{aligned}$$

where  $M$  is the fixed number of matches for each observation and  $K_M^z(X_i)$  is the number of matched times of unit  $i$  in treatment group  $z$ ,  $z \in \{0, 1\}$ .

## Extension to bias-corrected matching estimator

- ▶ Under our sensitivity analysis framework, the bias-corrected matching estimator:

$$\begin{aligned}\hat{\tau}_M^{\text{bc}} &= \hat{\tau}^{\text{pred}} + n^{-1} \sum_{i=1}^n \frac{K_M^1(X_i)}{M} \frac{1}{\varepsilon_1(X_i)} Z_i \{Y_i - \hat{\mu}_1(X_i)\} \\ &\quad - n^{-1} \sum_{i=1}^n \frac{K_M^0(X_i)}{M} \varepsilon_0(X_i) (1 - Z_i) \{Y_i - \hat{\mu}_0(X_i)\}.\end{aligned}$$

- ▶ Lin et al. (2023) views matching as a nonparametric method of estimating the propensity score. We essentially use  $1 + K_M^1(X_i)/M$  and  $1 + K_M^0(X_i)/M$  to estimate  $1/e(X_i)$  and  $1/\{1 - e(X_i)\}$ , respectively.

## Extension to multi-level treatment

- ▶ Observational studies with a multi-level treatment,  $Z \in \{1, \dots, K\}$ .
- ▶ Each unit has  $K$  potential outcomes  $\{Y(1), \dots, Y(K)\}$  corresponding to the  $K$  treatment levels.
- ▶ Causal parameters of interest: comparisons of potential outcomes

$$\tau_c = \sum_{k=1}^K c_k E\{Y(k)\},$$

where  $\sum_{k=1}^K c_k = 0$ .

- ▶ For any two treatment levels  $k$  and  $l$ , the sensitivity parameters:

$$\varepsilon_{k,l}(X) = \frac{E\{Y(k) \mid Z = k, X\}}{E\{Y(k) \mid Z = l, X\}}.$$

## Extension to multi-level treatment

► Identification:

$$\begin{aligned} E\{Y(k)\} &= \sum_{l=1}^K E \left\{ 1(Z = l) \frac{\mu_k(X)}{\varepsilon_{k,l}(X)} \right\} \\ &= \sum_{l=1}^K E \left\{ \frac{e_l(X)}{\varepsilon_{k,l}(X)} \frac{1(Z = k) Y}{e_k(X)} \right\}, \end{aligned}$$

where

- ▶  $e_k(X) = \text{pr}(Z = k | X)$ : the generalized propensity score (Imbens, 2000; Imai and Van Dyk, 2004);
- ▶  $\mu_k(X) = E\{Y | Z = k, X\}$ : conditional outcome mean.

► Estimation:

$$\begin{aligned} \hat{\mu}_k^{dr} &= \hat{\mu}_k^{\text{reg}} + n^{-1} \sum_{i=1}^n \sum_{l=1}^K \frac{\hat{e}_l(X_i) 1(Z_i = k) \{Y_i - \hat{\mu}_k(X_i)\}}{\varepsilon_{k,l}(X_i) \hat{e}_k(X_i)}, \\ \hat{\tau}_c^{dr} &= \sum_{k=1}^K c_k \hat{\mu}_k^{dr}. \end{aligned}$$

## Other extensions in the paper

- ▶ Hajek-type weighting estimators.
- ▶ Average treatment effect on the treated:

$$\tau_T = E\{Y(1) - Y(0) \mid Z = 1\} = E(Y \mid Z = 1) - E\{Y(0) \mid Z = 1\}.$$

- ▶ Survival outcomes under right-censoring:

$$\tau(t) = S_1(t) - S_0(t),$$

where  $S_z(t) = \text{pr}\{Y(z) > t\}$  denotes the potential survival functions for  $z \in \{0, 1\}$ .

- ▶ Controlled direct effect.
- ▶ Discussion on another sensitivity parameter, difference scale.

## Summary

- ▶ **Flexible** sensitivity analysis framework.
- ▶ Simultaneously deal with weighting, outcome regression, and doubly robust estimators.
- ▶ Only requires simple modifications of the standard estimators.
- ▶ Extends to many other causal inference settings.
- ▶ Easy to implement – R package `saci`.

Thank you very much!

ArXiv: <https://arxiv.org/abs/2305.17643>

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## More equivalent forms for $\hat{\tau}$ with outcome regression

$$\begin{aligned}\hat{\tau}^{\text{pred}} &= n^{-1} \sum_{i=1}^n \{Z_i Y_i + (1 - Z_i) \hat{\mu}_1(X_i) / \varepsilon_1(X_i)\} \\ &\quad - n^{-1} \sum_{i=1}^n \{Z_i \hat{\mu}_0(X_i) \varepsilon_0(X_i) + (1 - Z_i) Y_i\},\end{aligned}$$

and

$$\begin{aligned}\hat{\tau}^{\text{proj}} &= n^{-1} \sum_{i=1}^n \{Z_i \hat{\mu}_1(X_i) + (1 - Z_i) \hat{\mu}_1(X_i) / \varepsilon_1(X_i)\} \\ &\quad - n^{-1} \sum_{i=1}^n \{Z_i \hat{\mu}_0(X_i) \varepsilon_0(X_i) + (1 - Z_i) \hat{\mu}_0(X_i)\}.\end{aligned}$$

## More equivalent forms for $\hat{\tau}^{\text{dr}}$

$$\begin{aligned}\hat{\tau}^{\text{dr}} &= \hat{\tau}^{\text{ht}} - n^{-1} \sum_{i=1}^n \check{Z}_i \left\{ \frac{\hat{\mu}_1(X_i)}{\hat{e}(X_i)\varepsilon_1(X_i)} + \frac{\hat{\mu}_0(X_i)\varepsilon_0(X_i)}{1-\hat{e}(X_i)} \right\} \\ &= \hat{\tau}^{\text{pred}} + n^{-1} \sum_{i=1}^n \left\{ \frac{1-\hat{e}(X_i)}{\varepsilon_1(X_i)} \frac{Z_i \check{Y}_i}{\hat{e}(X_i)} - \hat{e}(X_i)\varepsilon_0(X_i) \frac{(1-Z_i)\check{Y}_i}{1-\hat{e}(X_i)} \right\} \\ &= \hat{\tau}^{\text{proj}} + n^{-1} \sum_{i=1}^n \left\{ \hat{w}_1(X_i) \frac{Z_i \check{Y}_i}{\hat{e}(X_i)} - \hat{w}_0(X_i) \frac{(1-Z_i)\check{Y}_i}{1-\hat{e}(X_i)} \right\},\end{aligned}$$