

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

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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

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

- ▶ 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 τ 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:

$$\begin{aligned}\hat{\tau}^{\text{reg}} &= n^{-1} \sum_{i=1}^n \{ \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) \}, \\ \hat{\tau}^{\text{ht}} &= n^{-1} \sum_{i=1}^n \left\{ \frac{Z_i Y_i}{\hat{e}(X_i)} - \frac{(1 - Z_i) Y_i}{1 - \hat{e}(X_i)} \right\},\end{aligned}$$

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

Estimation under unconfoundedness

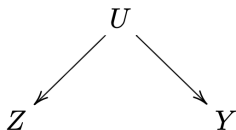
- ▶ Doubly robust estimator by combining both models (Bang and Robins, 2005):

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

- ▶ Modifies $\hat{\tau}^{\text{reg}}$ by inverse propensity score weighted residuals.
- ▶ Consistent to τ 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 τ (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

$$\tau = [E(Y | Z = 1)\text{pr}(Z = 1) + E\{Y(1) | Z = 0\}\text{pr}(Z = 0)] \\ - [E\{Y(0) | Z = 1\}\text{pr}(Z = 1) + E(Y | Z = 0)\text{pr}(Z = 0)].$$

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

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

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

Identification challenge revisit: two extreme solutions

$$\tau = [E(Y | Z = 1)\text{pr}(Z = 1) + E\{Y(1) | Z = 0\}\text{pr}(Z = 0)] \\ - [E\{Y(0) | Z = 1\}\text{pr}(Z = 1) + E(Y | Z = 0)\text{pr}(Z = 0)].$$

► 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 τ .
- 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 $\varepsilon_0(X)$,

$$\begin{aligned}E\{Y(1)\} &= E\left\{w_1(X)\frac{Z}{e(X)}Y\right\}, \\E\{Y(0)\} &= E\left\{w_0(X)\frac{1-Z}{1-e(X)}Y\right\},\end{aligned}$$

where

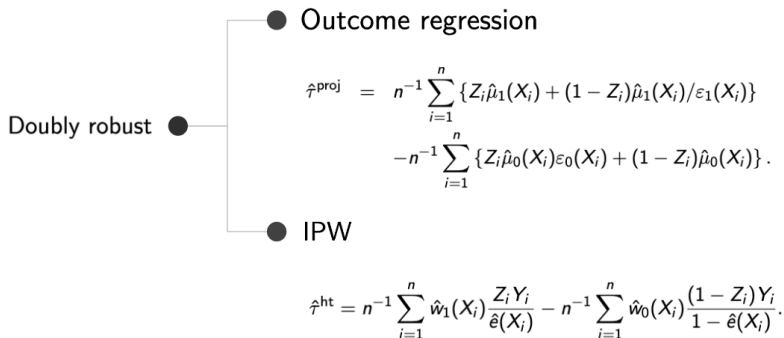
$$w_1(X) = e(X) + \{1 - e(X)\} / \varepsilon_1(X), \quad w_0(X) = e(X)\varepsilon_0(X) + 1 - e(X).$$

- ▶ 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 τ is $\phi_1 - \phi_0$.

- An estimator constructed based on the EIF:

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

- 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 $(\varepsilon_1(X), \varepsilon_0(X))$.

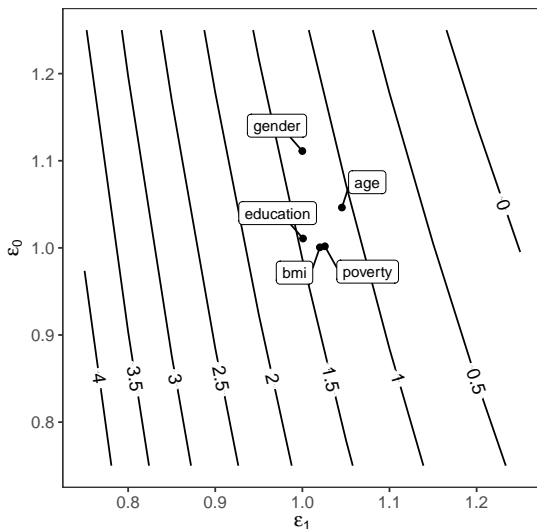
Sensitivity parameters: vary them with covariates or not

- ▶ 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 τ : 1.48 with a 95% confidence interval (0.78, 2.18).
- ▶ Unobserved confounders: genotype?

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



- Point estimates as a function of (ϵ_1, ϵ_0) .
- Plot maximums of $\hat{\epsilon}_z(X_{-j})$ 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 $* \in \{\text{pred}, \text{prod}, \text{ht}, \text{dr}\}$.

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:

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

- 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 $\hat{\tau}^{\text{dr}}$

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