Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

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Scan for slides

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UNC Chapel Hill

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Motivation: HVTN 505 trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 28, 2013 VOL. 369 NO. 22

Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine

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- **HVTN 505 trial**: trial of a preventive HIV vaccine

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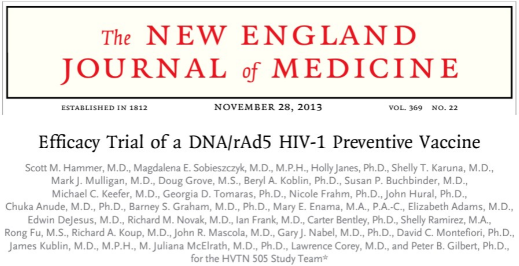

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- **HVTN 505 trial**: trial of a preventive HIV vaccine
- stopped early after reaching predetermined cutoffs for efficacy futility [2]

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The Journal of Infectious Diseases
MAJOR ARTICLE

Higher T-Cell Responses Induced by DNA/rAd5 HIV-1 Preventive Vaccine Are Associated With Lower HIV-1 Infection Risk in an Efficacy Trial

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IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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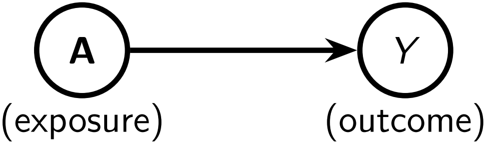
Estimand (**dose-response surface**): $\eta(\boldsymbol{a}) \equiv \mathrm{E}[Y(\boldsymbol{a})]$ for $\boldsymbol{a} \in \boldsymbol{\mathcal{A}}$

Confounding



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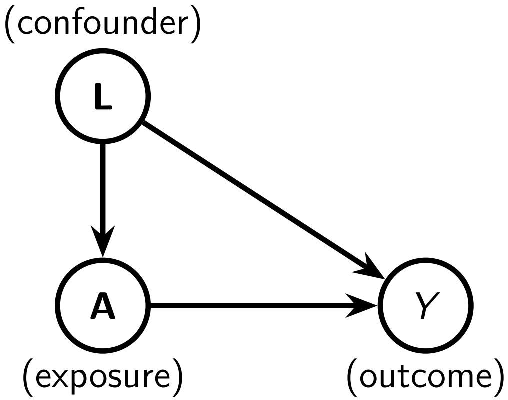

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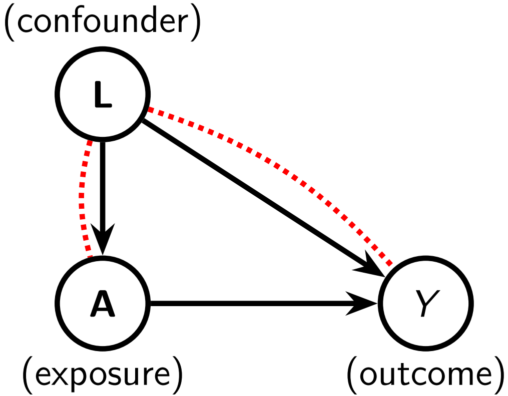

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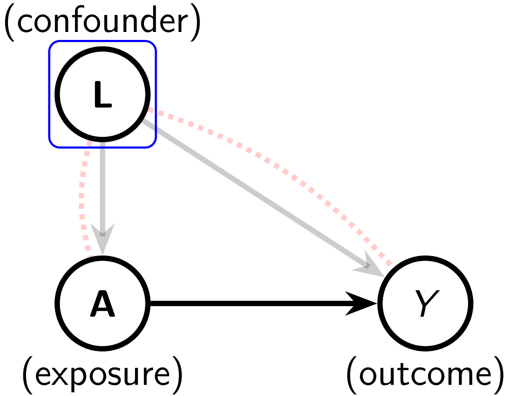

Addressing Confounding (3 Ways)

- G-Formula (GF)
- Inverse Probability Weighting (IPW)
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  - Marginalize over the distribution of confounders: $\widehat{\eta}(\boldsymbol{a}) = n^{-1} \sum_{i=1}^{n} \mu(\boldsymbol{L}_i, \boldsymbol{a}; \widehat{\beta})$.
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$$\mathrm{E}\{\boldsymbol{\Psi}(Y, \boldsymbol{L}, \boldsymbol{A}; \underbrace{\boldsymbol{\theta}_0}_{\text{true}})\} = \mathbf{0}.$$

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- Given an estimating function $\boldsymbol{\Psi}$ and observed data $\{(Y_i, \boldsymbol{L}_i, \boldsymbol{A}_i) : i = 1, \ldots, n\}$, we can find an estimator $\widehat{\boldsymbol{\theta}}$ as the solution to

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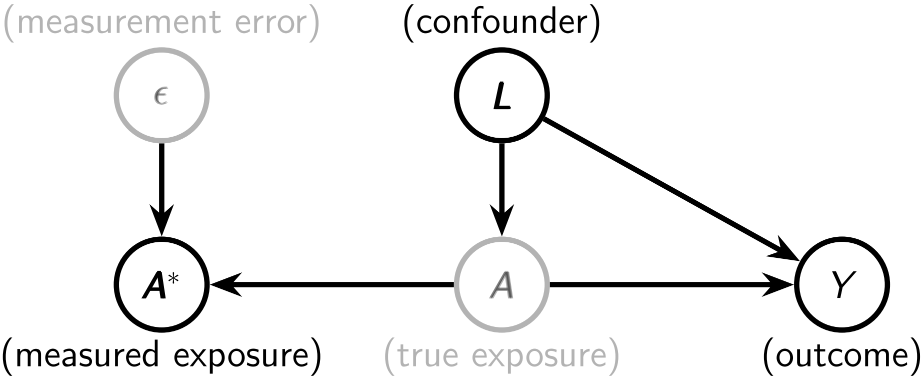
- $\widehat{\boldsymbol{\theta}}$ is consistent and asymptotically normal and has a simple variance estimator [6].
- The G-formula, IPW, and DR estimators are all solutions to estimating equations with functions $\boldsymbol{\Psi}_{GF}, \boldsymbol{\Psi}_{IPW}, \boldsymbol{\Psi}_{DR}$.

Measurement Error



Addressing Confounding and Measurement Error

Can we just substitute $\boldsymbol{A}^*$ for $\boldsymbol{A}$ and find the solution to

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No! This leads to bias in $\widehat{\boldsymbol{\theta}}$ because

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No! This leads to bias in $\widehat{\boldsymbol{\theta}}$ because

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We need a new estimating function $\widetilde{\boldsymbol{\Psi}}$ such that

$$\mathrm{E}\{\underbrace{\widetilde{\boldsymbol{\Psi}}}_{\text{new est. fun.}}(Y, \boldsymbol{L}, \underbrace{\boldsymbol{A}^*}_{\text{mismeasured}}; \boldsymbol{\theta}_0)\} = \mathbf{0}.$$

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$$\boldsymbol{\Psi}_{CS}\left(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}\right) = \mathrm{E}\left[\mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \widetilde{\boldsymbol{A}}; \boldsymbol{\theta})\right\} | Y, \boldsymbol{L}, \boldsymbol{A}^*\right]$$

Corrected Score Functions (contd)

Under certain conditions, the corrected score function $\boldsymbol{\Psi}_{CS}$ is then unbiased, meaning

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The G-Formula, IPW, and DR estimating functions all satisfy these conditions, and so can be "corrected."

$$\boldsymbol{\Psi}_{GF} \longrightarrow \boldsymbol{\Psi}_{CS-GF}$$

$$\boldsymbol{\Psi}_{IPW} \longrightarrow \boldsymbol{\Psi}_{CS-IPW}$$

$$\boldsymbol{\Psi}_{DR} \longrightarrow \boldsymbol{\Psi}_{CS-DR}$$

Monte Carlo Corrected Score Functions

- Sometimes we can find a closed-form algebraic expression for

$$\boldsymbol{\Psi}_{CS}\left(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}\right) = \underbrace{\mathrm{E}\left[\mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \boldsymbol{A}^* + i\widetilde{\boldsymbol{\epsilon}}; \boldsymbol{\theta})\right\} \,\middle|\, Y, \boldsymbol{L}, \boldsymbol{A}^*\right]}_{\mathrm{E}\{f(\widetilde{\boldsymbol{\epsilon}})\}}.$$

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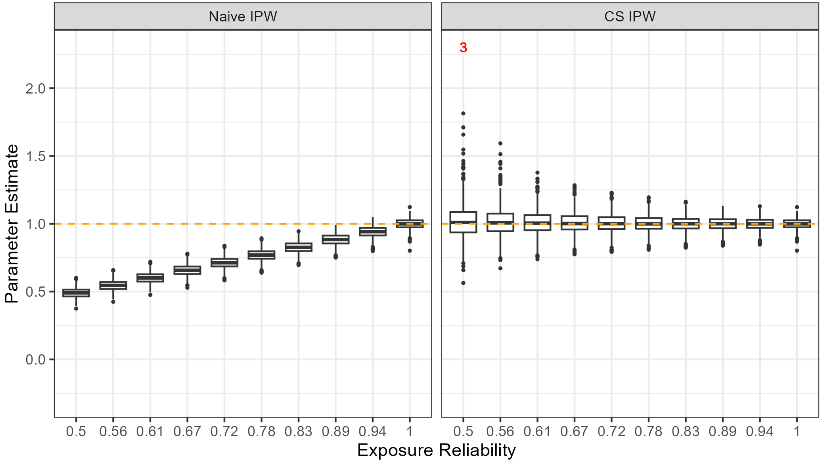
$$\mathrm{E}\{f(\widetilde{\boldsymbol{\epsilon}})\} \approx B^{-1} \textstyle\sum_{b=1}^{B} f(\widetilde{\boldsymbol{\epsilon}}_b)$$

$$\implies \boldsymbol{\Psi}_{MCCS}^{B}(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}) = B^{-1} \textstyle\sum_{b=1}^{B} \mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \boldsymbol{A}^* + i\widetilde{\boldsymbol{\epsilon}}_b; \boldsymbol{\theta})\right\}$$

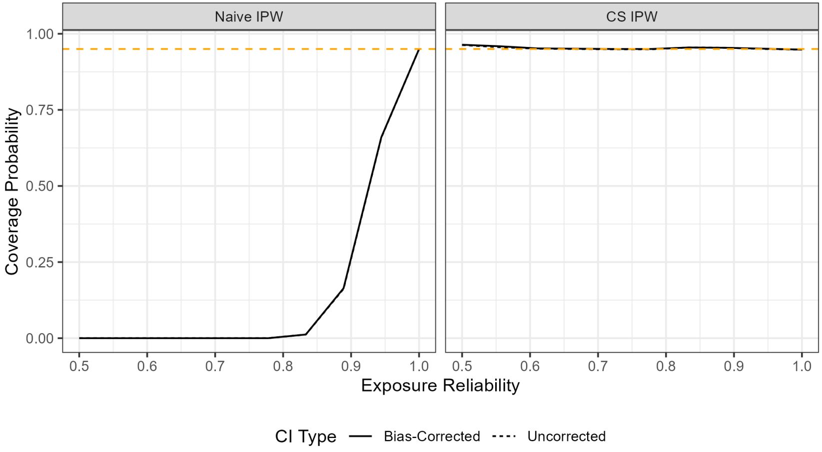
Simulation Setting

- confounder $L \sim \mathcal{N}(0, 0.36)$
- exposure $\boldsymbol{A} = (A_1, A_2)$ with $\boldsymbol{A}|L \sim \mathcal{N}_2(\boldsymbol{0}, \boldsymbol{I})$
- exposure measurement error $\boldsymbol{\epsilon} \sim \mathcal{N}_2(\boldsymbol{0}, \sigma^2_{me}\boldsymbol{I})$
- outcome Y with $Y|L, \boldsymbol{A} \sim \mathcal{N}(A_1 + A_2 + L, 1)$
- implied MSM of $\eta(\boldsymbol{a}; \boldsymbol{\gamma}) = \gamma_0 + \gamma_1 a_1 + \gamma_2 a_2$ for $\boldsymbol{\gamma} = (\gamma_0, \gamma_1, \gamma_2) = (0, 1, 1)$
- sample size n $= 800$

Simulation Results: Estimator



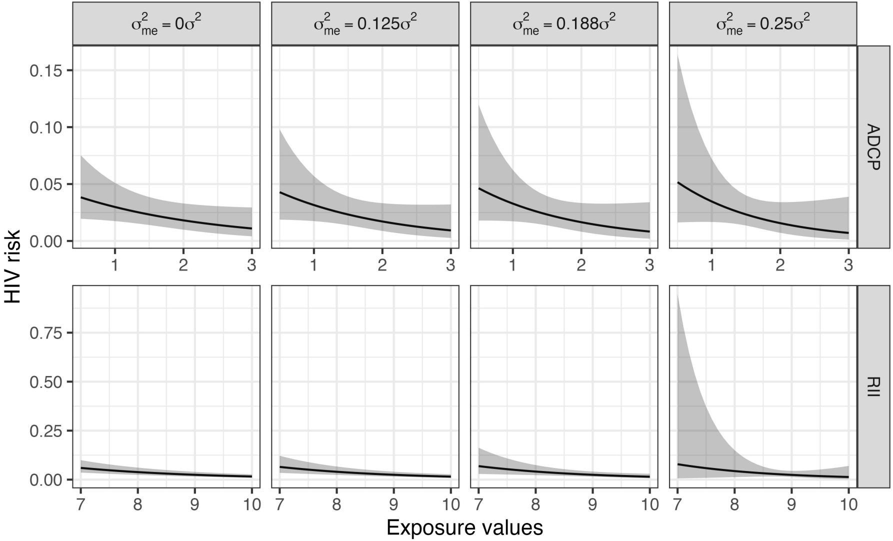
Simulation Results: Confidence Interval



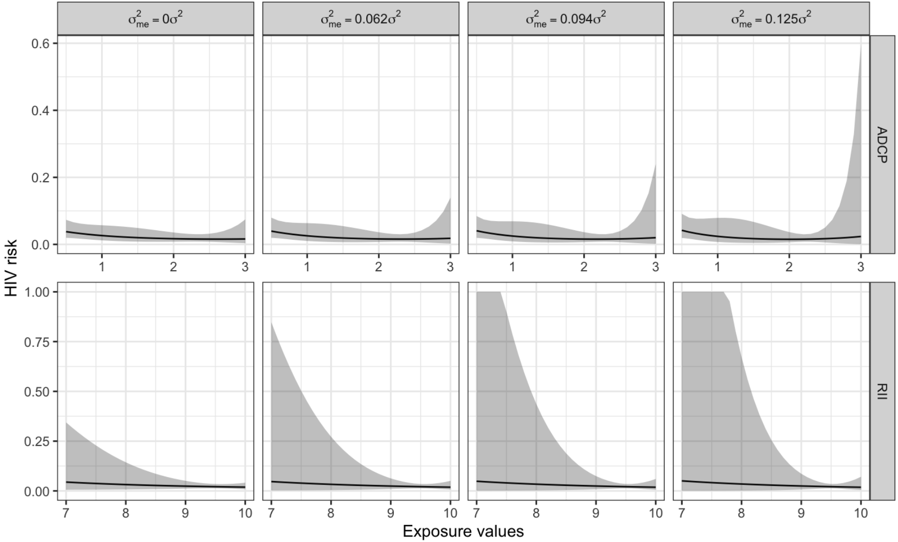
Application: HVTN 505 Trial

- **two exposures** (both log-transformed):
  (i) antibody-dependent cellular phagocytosis (ADCP)
  (ii) recruitment of FcγRIIa of the H131-Con S gp140 protein (RII)
- **case-cohort sampling**: immunologic markers only measured in stratified random sample of controls
- **covariates**: age, race, BMI, behavior risk, CD4-P, and CD8-P
- **two analyses**:
  (i) DR estimator with a log-linear outcome model
  (ii) g-formula with a log-quadratic outcome model

Application: DR Method with Linear Outcome Model



Application: G-Formula with Quadratic Outcome Model



Mismex: Causal Inference for **Mism**easured **Ex**posures

Paper in *Biometrics*

GitHub R package

References

[1] Youyi Fong, Xiaoying Shen, Vicki C Ashley, Aaron Deal, Kelly E Seaton, Chenchen Yu, Shannon P Grant, Guido Ferrari, Allan C deCamp, Robert T Bailer, et al. Modification of the association between T-cell immune responses and human immunodeficiency virus type 1 infection risk by vaccine-induced antibody responses in the HVTN 505 trial. *The Journal of Infectious Diseases*, 217(8):1280–1288, 2018.

[2] Scott M Hammer, Magdalena E Sobieszczyk, Holly Janes, Shelly T Karuna, Mark J Mulligan, Doug Grove, Beryl A Koblin, Susan P Buchbinder, Michael C Keefer, Georgia D Tomaras, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *New England Journal of Medicine*, 369(22):2083–2092, 2013.

[3] Holly E Janes, Kristen W Cohen, Nicole Frahm, Stephen C De Rosa, Brittany Sanchez, John Hural, Craig A Magaret, Shelly Karuna, Carter Bentley, Raphael Gottardo, et al. Higher T-cell responses induced by DNA/rAd5 HIV-1 preventive vaccine are associated with lower HIV-1 infection risk in an efficacy trial. *The Journal of Infectious Diseases*, 215(9):1376–1385, 2017.

[4] Scott D Neidich, Youyi Fong, Shuying S Li, Daniel E Geraghty, Brian D Williamson, William Chad Young, Derrick Goodman, Kelly E Seaton, Xiaoying Shen, Sheetal Sawant, et al. Antibody Fc effector functions and IgG3 associate with decreased HIV-1 risk. *Journal of Clinical Investigation*, 129(11):4838–4849, 2019.

[5] Steven J Novick and Leonard A Stefanski. Corrected score estimation via complex variable simulation extrapolation. *Journal of the American Statistical Association*, 97(458):472–481, June 2002. ISSN 0162-1459, 1537-274X. doi: 10.1198/016214502760047005. URL http://www.tandfonline.com/doi/abs/10.1198/016214502760047005.

[6] Leonard A Stefanski and Dennis D Boos. The calculus of M-estimation. *The American Statistician*, 56(1):29–38, 2002.

Appendix

Appendix: Notation

- true exposure: $\boldsymbol{A} = (A_1, \ldots, A_m)$
- measured exposure: $\boldsymbol{A}^* = (A_1^*, \ldots, A_m^*) = \boldsymbol{A} + \boldsymbol{\epsilon}$
- measurement error: $\boldsymbol{\epsilon}$
- potential outcome: $Y(\boldsymbol{a})$
- observed outcome: Y
- confounders: $\boldsymbol{L} = (L_1, L_2, \ldots, L_p)$

Observe: iid copies of $(Y_i, \boldsymbol{L}_i, \boldsymbol{A}_i^*)$.

Estimand: dose-response curve $\eta(\boldsymbol{a}) \equiv \mathrm{E}[Y(\boldsymbol{a})]$ for $\boldsymbol{a} \in \boldsymbol{\mathcal{A}}$.

Appendix: Assumptions

(i) **causal consistency**: $Y = Y(\boldsymbol{a})$ when $\boldsymbol{A} = \boldsymbol{a}$

(ii) **conditional exchangeability**: $Y(\boldsymbol{a}) \perp\!\!\!\perp \boldsymbol{A}|\boldsymbol{L}$ for all $\boldsymbol{a} \in \boldsymbol{\mathcal{A}}$

(iii) **positivity**: $f_{\boldsymbol{A}|\boldsymbol{L}}(\boldsymbol{a}|\boldsymbol{l}) > 0$ for all $\boldsymbol{l}$ such that $f_{\boldsymbol{L}}(\boldsymbol{l}) > 0$ and for all $\boldsymbol{a} \in \boldsymbol{\mathcal{A}}$

(iv) **independent measurement error**: $\boldsymbol{\epsilon} \perp\!\!\!\perp (Y, \boldsymbol{L}, \boldsymbol{A})$

(v) **classical additive measurement error**: $\boldsymbol{\epsilon} \sim \mathcal{N}_m(0, \boldsymbol{\Sigma}_{me})$

Appendix: G-Formula

- fit the **outcome model** $\mu(\boldsymbol{L}, \boldsymbol{A}; \beta) \equiv \mathrm{E}(Y|\boldsymbol{L}, \boldsymbol{A})$
- estimate the dose-response curve by marginalizing over the distribution of confounders: $\widehat{\eta}(\boldsymbol{a}) = n^{-1} \sum_{i=1}^{n} \mu(\boldsymbol{L}_i, \boldsymbol{a}; \widehat{\beta})$
- This can be expressed as an M-estimator with estimating function

$$\boldsymbol{\Psi}_{0-GF}(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta}_{GF}) = \begin{bmatrix} \{Y - \mu(\boldsymbol{L}, \boldsymbol{A}; \beta)\}\, \partial_{\boldsymbol{\beta}} \mu(\boldsymbol{L}, \boldsymbol{A}; \beta) \\ \eta(\boldsymbol{a}) - \mu(\boldsymbol{L}, \boldsymbol{a}; \beta) \end{bmatrix}$$

Appendix: IPW

- obtain/estimate **standardized propensity score weights**

$$SW(\boldsymbol{L}, \boldsymbol{A}) = \frac{f_{\boldsymbol{A}}(\boldsymbol{A})}{f_{\boldsymbol{A}|\boldsymbol{L}}(\boldsymbol{A}|\boldsymbol{L})}$$

- use weighted observations to estimate the dose-response curve $\eta(\boldsymbol{a}; \gamma)$
- This can be expressed as an M-estimator with estimating function

$$\boldsymbol{\Psi}_{0-IPW}(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta}_{IPW}) = \begin{bmatrix} \boldsymbol{\Psi}_{PS}(\boldsymbol{L}, \boldsymbol{A}) \\ SW(\boldsymbol{L}, \boldsymbol{A}) \{Y - \eta(\boldsymbol{A}; \gamma)\} \partial_{\gamma}\eta(\boldsymbol{A}; \gamma) \end{bmatrix}$$

Appendix: DR

- obtain/estimate **standardized propensity score weights** $SW(\boldsymbol{L}, \boldsymbol{A})$
- use weighted observations to estimate the **outcome model** $\mu(\boldsymbol{L}, \boldsymbol{A}; \beta) \equiv \mathrm{E}(Y|\boldsymbol{L}, \boldsymbol{A})$
- estimate the dose-response curve by marginalizing over the distribution of confounders
- This can be expressed as an M-estimator with estimating function

$$\boldsymbol{\Psi}_{0-DR}(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta}_{DR}) = \begin{bmatrix} \boldsymbol{\Psi}_{PS}(\boldsymbol{L}, \boldsymbol{A}) \\ SW(\boldsymbol{L}, \boldsymbol{A})\{Y - \mu(\boldsymbol{L}, \boldsymbol{A}; \beta)\}\partial_{\boldsymbol{\beta}}\mu(\boldsymbol{L}, \boldsymbol{A}; \beta) \\ \eta(\boldsymbol{a}) - \mu(\boldsymbol{L}, \boldsymbol{a}; \beta) \end{bmatrix}$$

- doubly robust* to models for $\mu(\boldsymbol{L}, \boldsymbol{A}; \beta)$ and $f_{\boldsymbol{A}|\boldsymbol{L}}(\boldsymbol{A}|\boldsymbol{L})$.

Appendix: Corrected Score Functions

- Suppose the oracle estimating function is **conditionally unbiased**, meaning

$$\mathrm{E}\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta}) | \boldsymbol{A}\} = \boldsymbol{0}.$$

- Define the corrected score function as

$$\boldsymbol{\Psi}_{CS}(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}) = \mathrm{E}\left[\mathrm{Re}\left\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \widetilde{\boldsymbol{A}}; \boldsymbol{\theta})\right\} | Y, \boldsymbol{L}, \boldsymbol{A}^*\right],$$

where $\widetilde{\boldsymbol{A}} = \boldsymbol{A}^* + i\widetilde{\boldsymbol{\epsilon}}$, $i = \sqrt{-1}$, $\mathrm{Re}(\cdot)$ denotes the real component of a complex number, and $\widetilde{\boldsymbol{\epsilon}} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Sigma}_{me})$.

- Then

$$\begin{aligned} &\mathrm{E}\{\boldsymbol{\Psi}_{CS}(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}) | Y, \boldsymbol{L}, \boldsymbol{A}\} = \boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta}) \\ \implies &\mathrm{E}[\mathrm{E}\{\boldsymbol{\Psi}_{CS}(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta}) | Y, \boldsymbol{L}, \boldsymbol{A}\}] = \mathrm{E}\{\boldsymbol{\Psi}_0(Y, \boldsymbol{L}, \boldsymbol{A}; \boldsymbol{\theta})\} \\ \implies &\mathrm{E}\{\boldsymbol{\Psi}_{CS}(Y, \boldsymbol{L}, \boldsymbol{A}^*; \boldsymbol{\theta})\} = \boldsymbol{0} \end{aligned}$$