

Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

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Motivation: HVTN 505 trial

- **HVTN 505 trial:** trial of a preventive HIV vaccine
- stopped administering immunizations early after reaching predetermined cutoffs for efficacy futility [Hammer et al., 2013]



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

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Motivation: HVTN 505 trial

- later analyses identified several immunologic biomarker correlates of HIV acquisition among HIV vaccine recipients [Janes et al., 2017, Fong et al., 2018, Neidich et al., 2019]
- of interest to assess the effect of these biomarkers on risk of HIV acquisition
- measurement of the biomarkers is subject to error and the association between the biomarkers and HIV risk is likely confounded

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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Goal

To estimate the effect of a continuous exposure on an outcome when

- (i) the exposure-outcome association is potentially confounded
- (ii) the exposure is measured with error



Approach

To estimate the effect of a continuous exposure on an outcome when

- (i) the exposure-outcome association is potentially confounded
 - (a) g-formula
 - (b) inverse probability weighting (IPW)
 - (c) doubly-robust (DR)
- (ii) the exposure is measured with error
 - (a) corrected score (CS) method



Notation

- true exposure: $\mathbf{A} = (A_1, \dots, A_m)$
- measured exposure: $\mathbf{A}^* = (A_1^*, \dots, A_m^*) = \mathbf{A} + \boldsymbol{\epsilon}$
- measurement error: $\boldsymbol{\epsilon} \sim \mathcal{N}_m(0, \boldsymbol{\Sigma}_{me})$
- potential outcome: $Y(\mathbf{a})$
- observed outcome: $Y(\mathbf{A})$
- confounders: $\mathbf{L} = (L_1, L_2, \dots, L_p)$

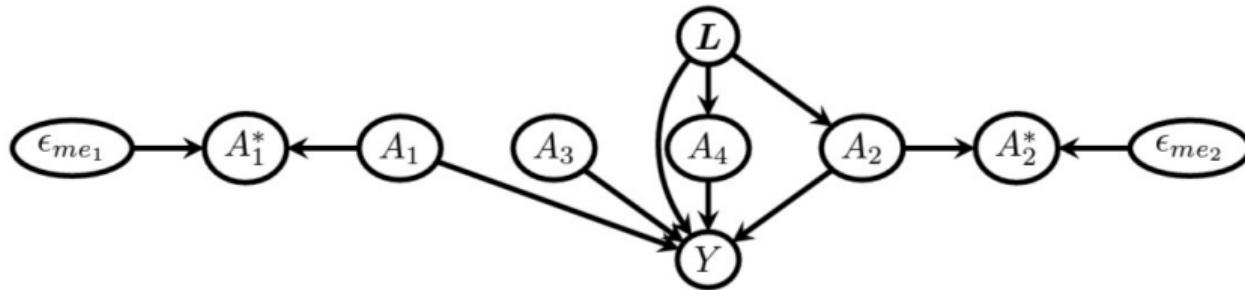
Observe: iid copies of $(Y_i, \mathbf{A}_i^*, \mathbf{L}_i)$.

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



Assumptions

- (i) **causal consistency:** $Y = Y(\mathbf{a})$ when $\mathbf{A} = \mathbf{a}$
- (ii) **conditional exchangeability:** $Y(\mathbf{a}) \perp\!\!\!\perp \mathbf{A} | \mathbf{L}$ for all $\mathbf{a} \in \mathcal{A}$
- (iii) **positivity:** $f_{\mathbf{A}|\mathbf{L}}(\mathbf{a}|\mathbf{l}) > 0$ for all \mathbf{l} such that $f_{\mathbf{L}}(\mathbf{l}) > 0$ and for all $\mathbf{a} \in \mathcal{A}$
- (iv) **independent measurement error:** $\epsilon \perp\!\!\!\perp (Y, \mathbf{A}, \mathbf{L})$



Addressing Confounding: G-Formula

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

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



Addressing Confounding: IPW

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

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

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

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



Addressing Confounding: IPW

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

$$\begin{bmatrix} \Psi_{PS}(\mathbf{L}, \mathbf{A}) \\ SW(\mathbf{L}, \mathbf{A})\{Y - \mu(\mathbf{L}, \mathbf{A}; \beta)\}\partial_\beta\mu(\mathbf{L}, \mathbf{A}; \beta) \\ \eta(\mathbf{a}) - \mu(\mathbf{L}, \mathbf{a}; \beta) \end{bmatrix},$$

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



How to Address Measurement Error?

- The three estimators proposed so far are solutions to **estimating equations**

$$\sum_{i=1}^n \Psi_0(Y_i, L_i, A_i; \theta) = 0$$

that are **unbiased** in the sense that $E\{\Psi_0(Y, L, A; \theta)\}$.

- **Problem:** the true exposure values A are not observed. Instead we observe the mismeasured version $A^* = A + \epsilon$.
- **Solution:** Create a **corrected score** function Ψ_{CS} that takes A^* as an argument and satisfies

$$E\{\Psi_{CS}(Y, L, A^*; \theta) | Y, L, A\} = \Psi_0(Y, L, A; \theta)$$



Addressing Exposure Measurement Error: Corrected Score Functions

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

$$E\{\Psi_0(Y, L, A; \theta) | A\} = 0.$$

- Then we can create a corrected score function (following Novick and Stefanski [2002]) as

$$\Psi_{CS}(Y, L, A^*; \theta) = E \left[\text{Re} \left\{ \Psi_0(Y, L, \tilde{A}; \theta) \right\} | Y, L, A^* \right],$$

where $\tilde{A} = A^* + i\tilde{\epsilon}$, $i = \sqrt{-1}$, $\text{Re}(\cdot)$ denotes the real component of a complex number, and $\tilde{\epsilon} \sim \mathcal{N}(\mathbf{0}, \Sigma_{me})$.



Computing Conditional Score Functions

The corrected score method involves evaluating an expectation of the form

$$E[\text{Re}\{\Psi_0(Y, L, \tilde{A}; \theta)\} | Y, L, A^*]$$

- sometimes this expectation has a closed form
- can also be approximated with the **Monte-Carlo corrected score** (MCCS) function

$$\Psi_{MCCS}^B(Y, L, A^*; \theta) = B^{-1} \sum_{b=1}^B \text{Re} \left\{ \Psi_0(Y, L, \tilde{A}_b; \theta) \right\},$$

where $\tilde{A}_b = A^* + i\tilde{\epsilon}_b$, and $\tilde{\epsilon}_b$ are iid simulated measurement errors.



Addressing Confounding and Exposure Measurement Error

The corrected score method can be applied to the g-formula, IPW, and DR estimators

$$\begin{aligned}\Psi_{0-GF}(Y, L, A; \theta_{GF}) &\longrightarrow \Psi_{CS-GF}(Y, L, A^*; \theta_{GF}) \\ \Psi_{0-IPW}(Y, L, A; \theta_{IPW}) &\longrightarrow \Psi_{CS-IPW}(Y, L, A^*; \theta_{IPW}) \\ \Psi_{0-DR}(Y, L, A; \theta_{DR}) &\longrightarrow \Psi_{CS-DR}(Y, L, A^*; \theta_{DR})\end{aligned}$$

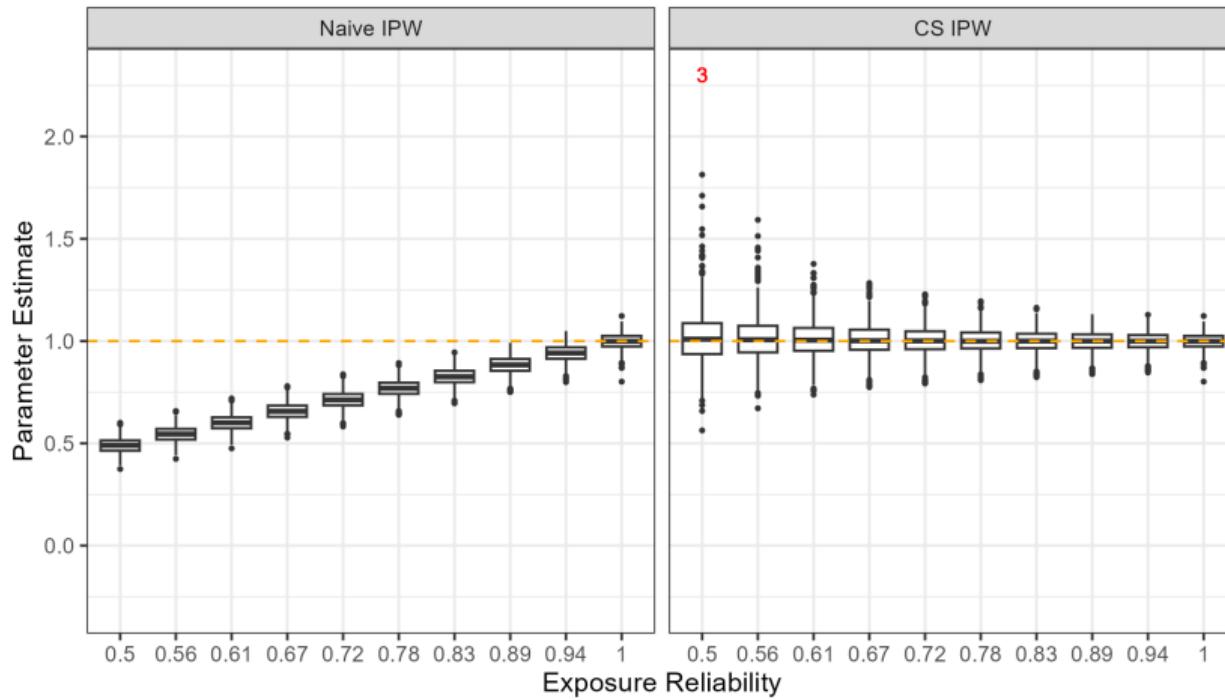


Simulation Setting

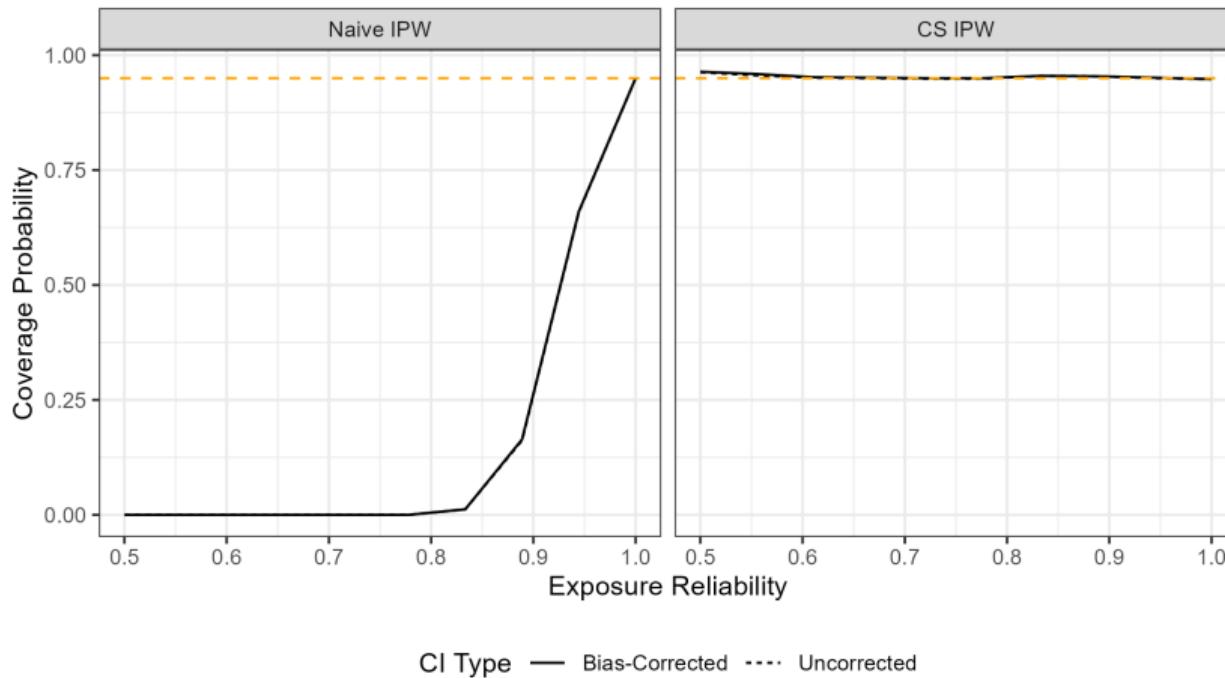
- confounder $L \sim \mathcal{N}(0, 0.36)$
- exposure $\mathbf{A} = (A_1, A_2)$ with $\mathbf{A}|L \sim \mathcal{N}_2(\mathbf{0}, \mathbf{I})$
- exposure measurement error $\epsilon \sim \mathcal{N}_2(\mathbf{0}, \sigma_{me}^2 \mathbf{I})$
- outcome Y with $Y|L, \mathbf{A} \sim \mathcal{N}(A_1 + A_2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



Simulation Results



Simulation Results



Application: HVTN 505 Trial

- **two exposures:**

- (i) antibody-dependent cellular phagocytosis (ADCP)
- (ii) recruitment of Fc γ RIIa of the H131-Con S gp140 protein (RII)

- **case-cohort sampling:** immunologic markers only measured in stratified random sample of vaccine recipients

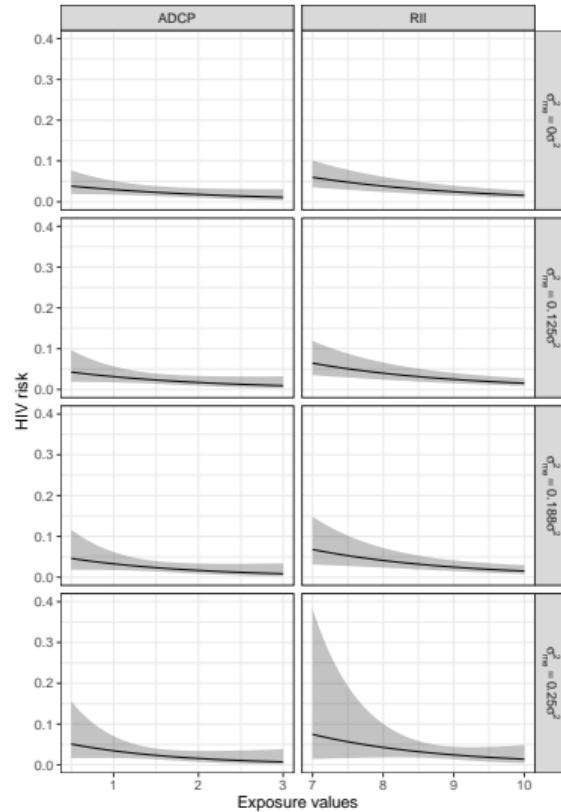
- **covariates:** age, race, BMI, behavior risk, CD4-P, and CD8-P

- **two analyses:**

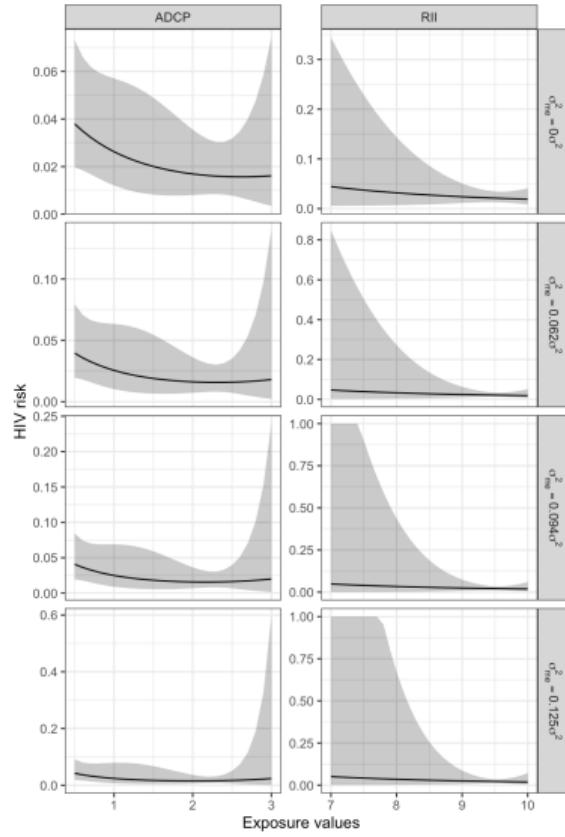
- (i) DR estimator with a linear outcome model
- (ii) g-formula with a quadratic outcome model



Application: DR Method with Linear Outcome Model



Application: G-Formula with Quadratic Outcome Model



Mismex: Mismeasured Exposures



Paper on arXiv



GitHub R package



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