Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

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Scan for slides

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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
- Stopped early after reaching predetermined cutoffs for efficacy futility [2]

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The Journal of Infectious Diseases

MAJOR ARTICLE

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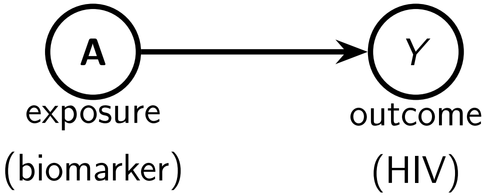
Estimand (**dose-response surface**): $\eta(\boldsymbol{a}) \equiv \mathrm{E}\{Y(\boldsymbol{a})\}$ for $\boldsymbol{a} \in \boldsymbol{\mathcal{A}}$

Confounding



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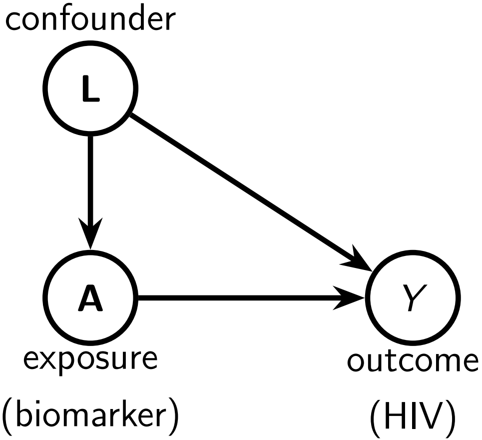

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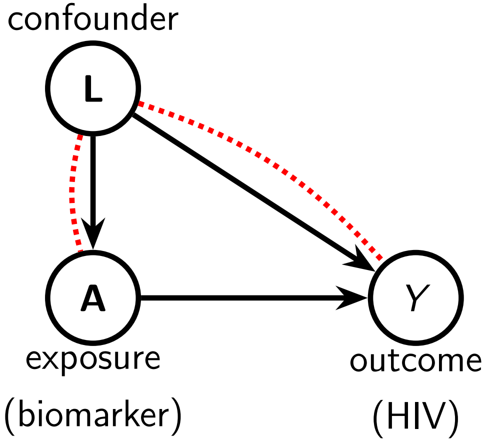
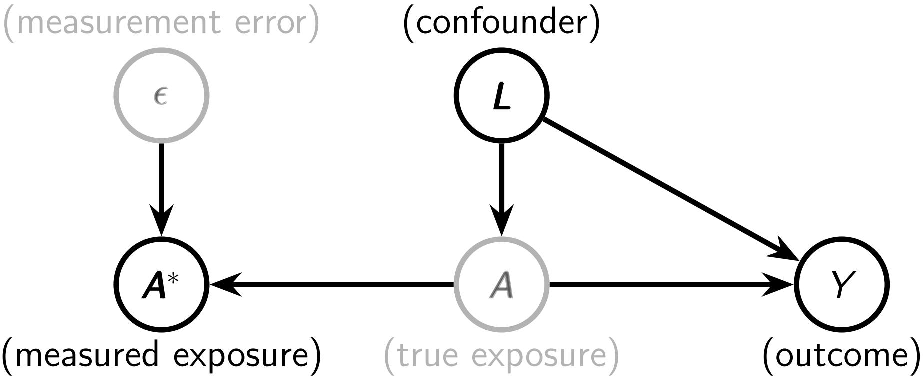


Measurement Error



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Addressing Confounding Alone

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  3. Doubly Robust Method (DR)
- These can all be framed as **M-estimators**

Crash Course on M-Estimation

Score Function: a function of the observed data and the parameter of interest

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$$\mathrm{E}\{\mathbf{\Psi}_0(Y, \mathbf{L}, \mathbf{A}; \underbrace{\boldsymbol{\theta}_0}_{\text{true}})\} = \mathbf{0}.$$

Crash Course on M-Estimation (cont'd)

- Given a score function $\boldsymbol{\Psi}_0$ 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].

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This can be expressed as an M-estimator with score function

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

IPW

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

Addressing Confounding and Measurement Error

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

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We need a new score function $\boldsymbol{\Psi}_{CS}$ such that

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1. Add additional *imaginary* measurement error $i\widetilde{\boldsymbol{\epsilon}}$ to the mismeasured exposure

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Given the "oracle" score function $\mathbf{\Psi}_0$, the "corrected score" function $\mathbf{\Psi}_{CS}$ can be created following Novick and Stefanski (2002) [5]:

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

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3. Take the expectation over the additional measurement error $\widetilde{\boldsymbol{\epsilon}}$.

Corrected Score Functions (contd)

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

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

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The G-Formula, IPW, and DR score 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

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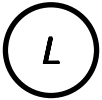
Simulation Setting

$$L \sim \mathcal{N}(0, 0.36)$$



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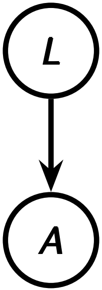

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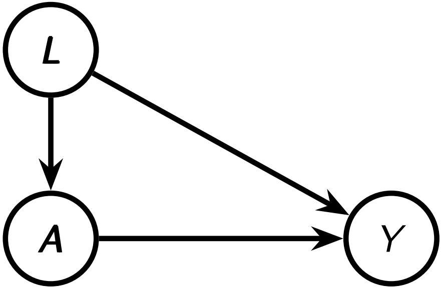

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$Y | L, \boldsymbol{A} \sim \mathcal{N}(A_1 + A_2 + L, 1)$

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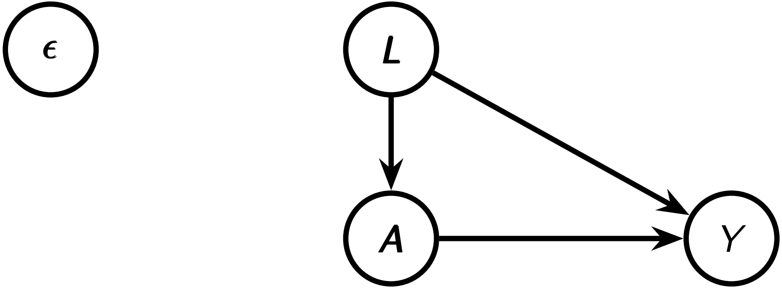

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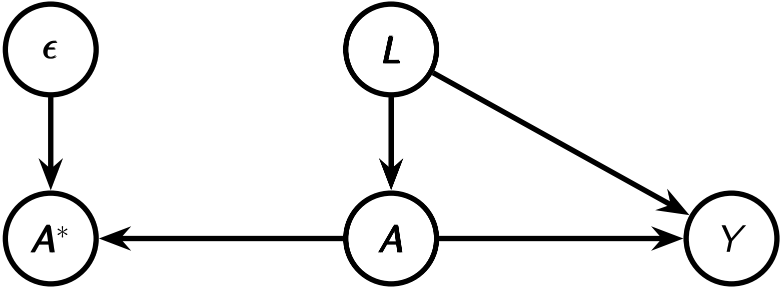

$\boldsymbol{A}^* = \boldsymbol{A} + \boldsymbol{\epsilon}$ $\quad$ $\boldsymbol{A}|L \sim \mathcal{N}_2(\mathbf{0}, \boldsymbol{I})$

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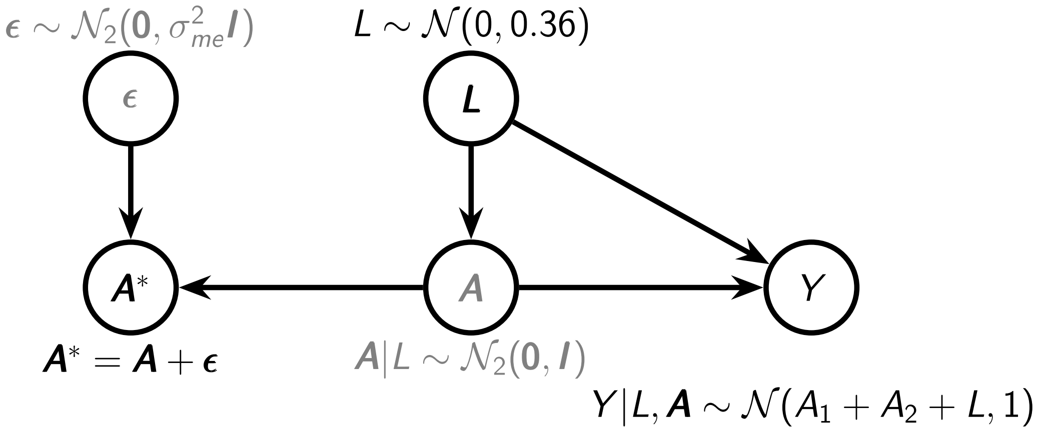

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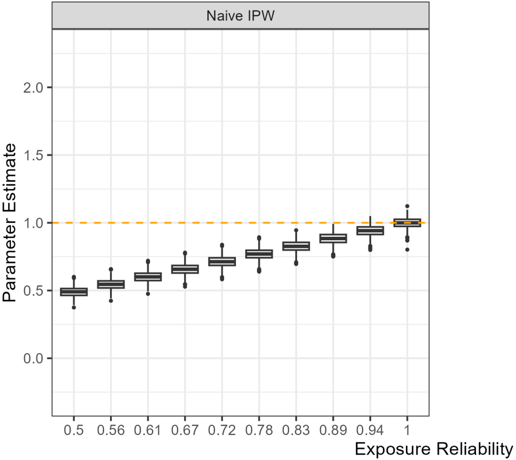
  2. Corrected Score IPW

Simulation Results: Estimator



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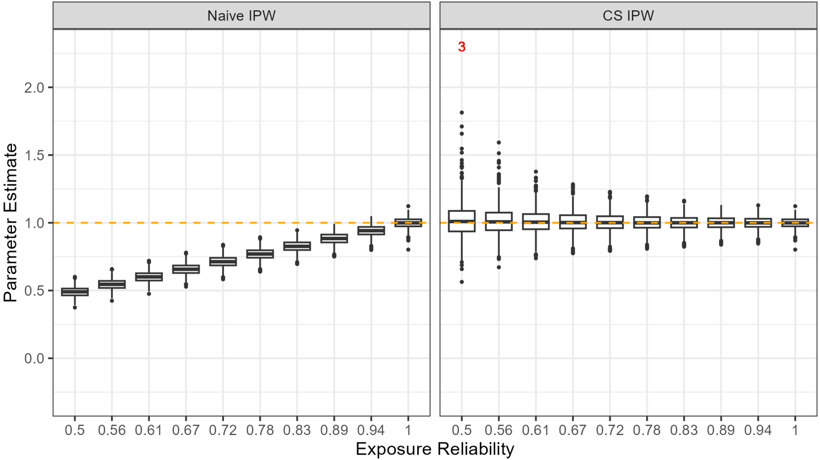
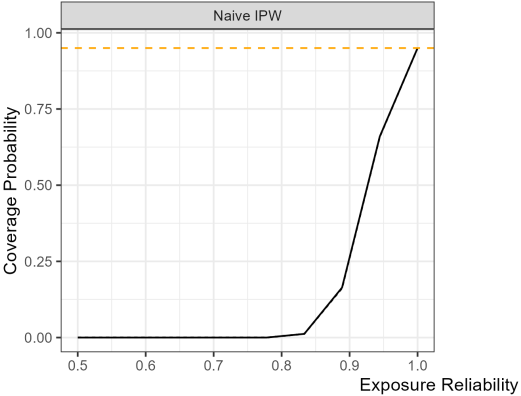


Simulation Results: Confidence Interval



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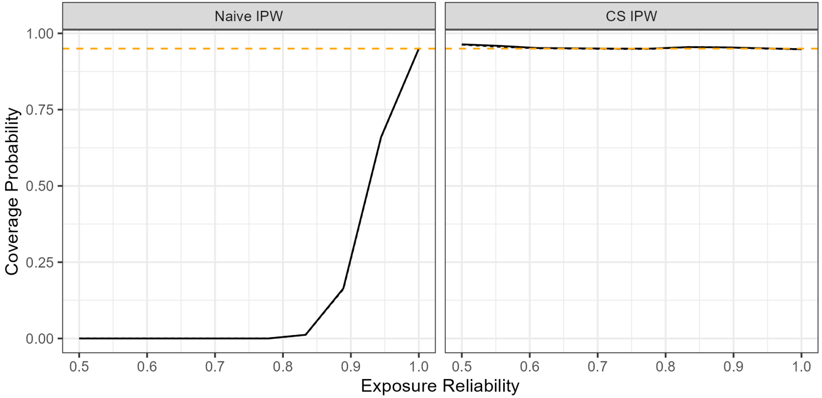

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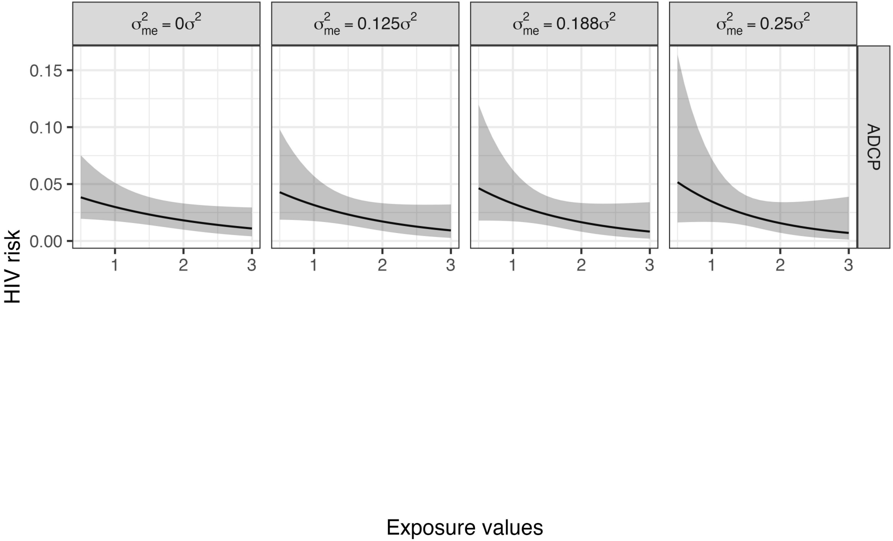
- **analysis**: DR estimator with a log-linear outcome model

Application: HVTN 505 Trial



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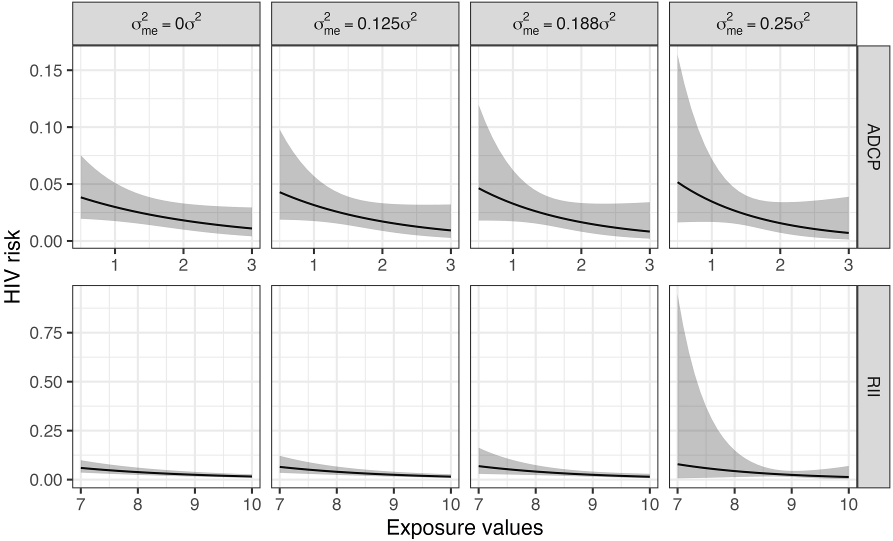

Mismex: Causal Inference for **Mis**measured **Ex**posures

Paper in *Biometrics*

GitHub R package

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Appendix

Appendix: Corrected Score Functions

- Suppose the oracle score 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

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

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

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