Causal Inference Methods for Infectious Disease Prevention Trials

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Outline

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- **Project 2**: Physical Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

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- **Project 3**: Causal Inference from Cluster Randomized Trials with Differential Nonresponse
- **Project 1**: Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

Project 2: Physical Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

Brian Richardson, Allison Aiello, Michael Hudgens

eX-FLU Trial

- **eX-FLU**: trial to evaluate a physical distancing intervention on a college campus during flu season (Aiello et al., 2016; Zivich et al., 2020)

Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial

Allison E. Aiello[a,*], Amanda M. Simanek[b,1], Marisa C. Eisenberg[c], Alison R. Walsh[c], Brian Davis[c], Erik Volz[d,1], Caroline Cheng[c], Jeanette J. Rainey[e], Amra Uzicanin[e], Hongjiang Gao[e], Nathaniel Osgood[f], Dylan Knowles[f], Kevin Stanley[f], Kara Tarter[c], Arnold S. Monto[c]

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- **Central question**: does the encouragement-to-isolate intervention reduce transmission of ILI?

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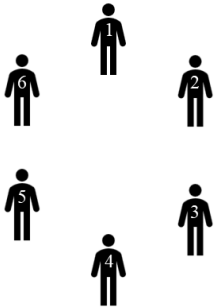
Transmission of Influenza-Like-Illness



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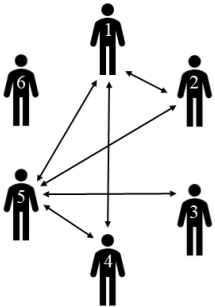

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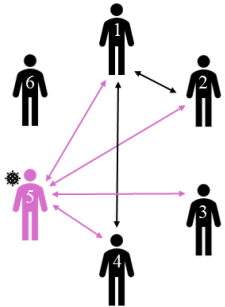

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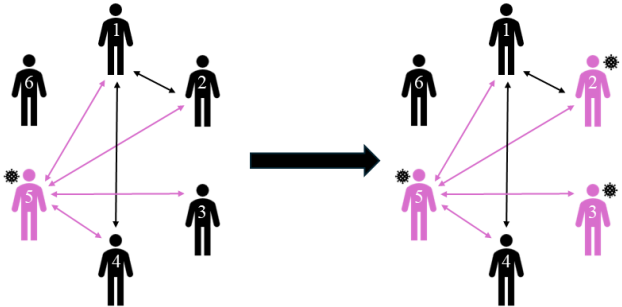
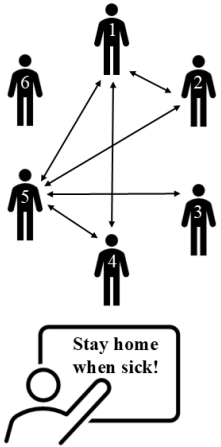


Example I: Intervention Affects Network and Transmission



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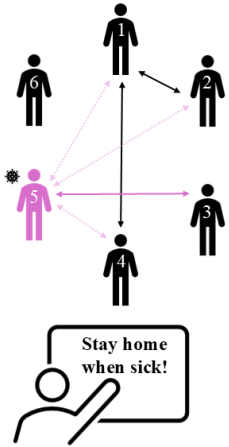

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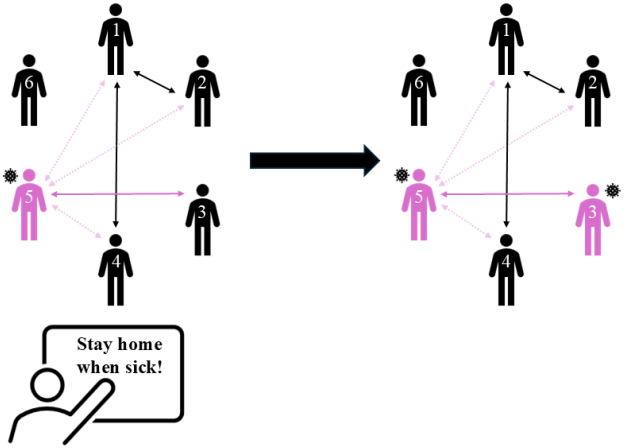
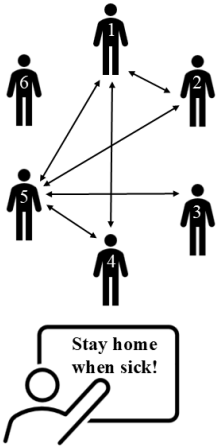


Example II: Intervention Affects Network, Not Transmission



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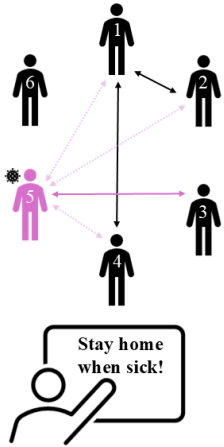

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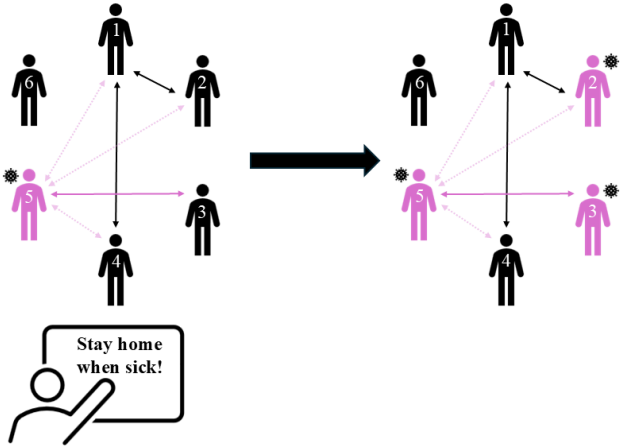

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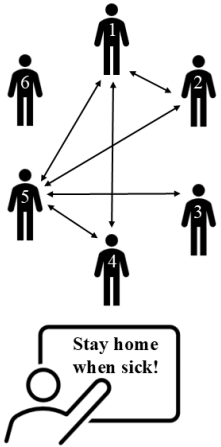

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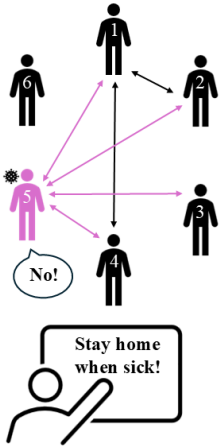

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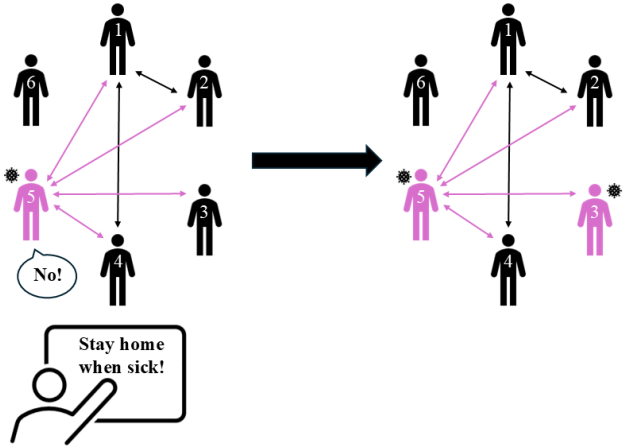
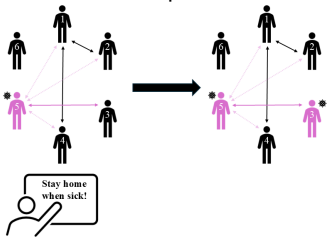


Central Question: Does the Intervention Affect Transmission of ILI?

Example I:



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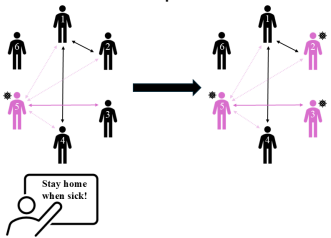

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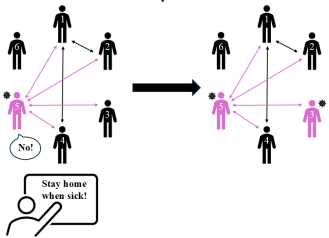
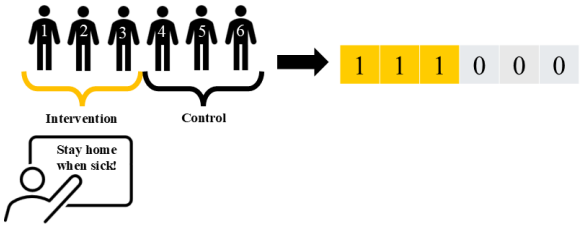


In Examples I and III, the answer is yes

eX-FLU Observed Data

- Baseline randomization assignments $\mathbf{Z} = (Z_1, \ldots, Z_n) \in \mathcal{Z}$, for $Z_i = \mathbb{1}(\text{student } i \text{ gets intervention})$



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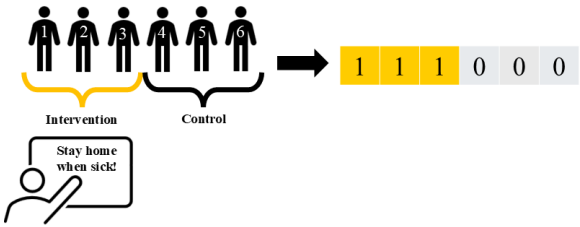

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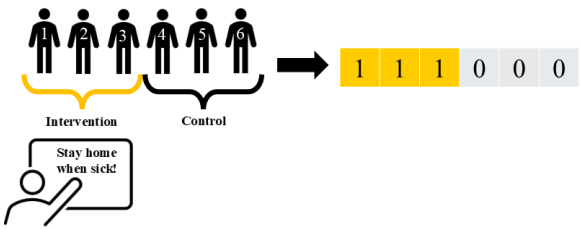

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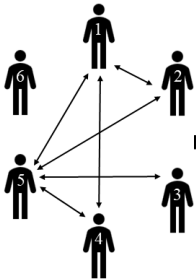

	1	2	3	4	5	6
1	0	1	0	1	1	0
2	1	0	0	0	1	0
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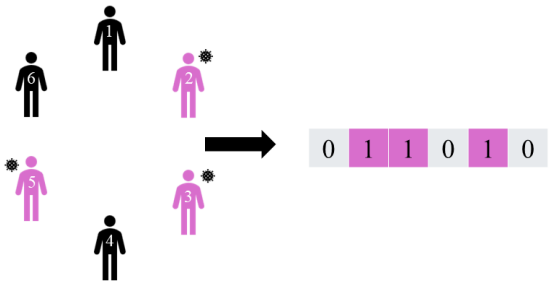

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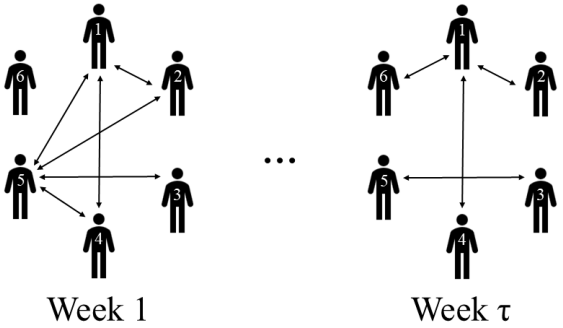

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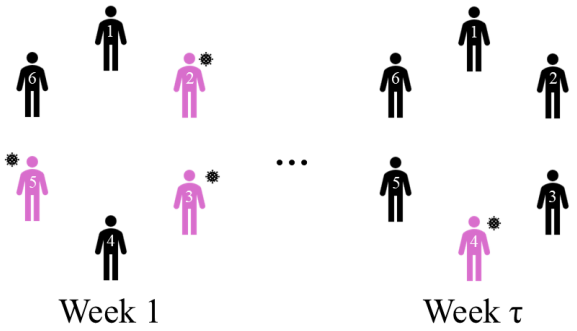

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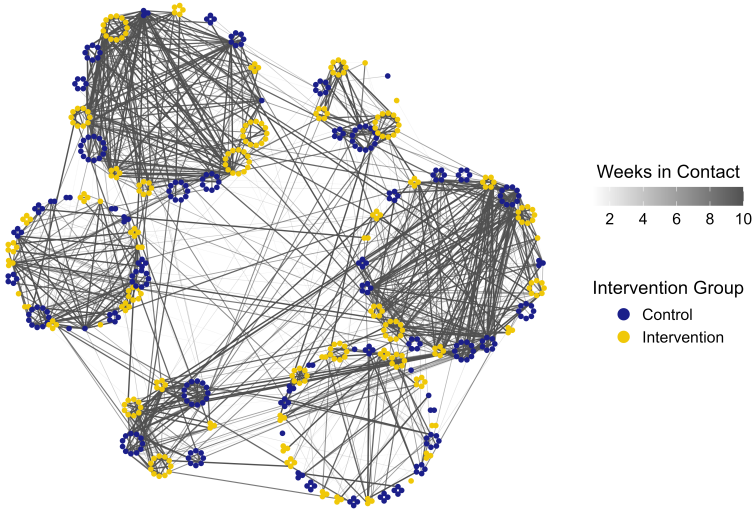

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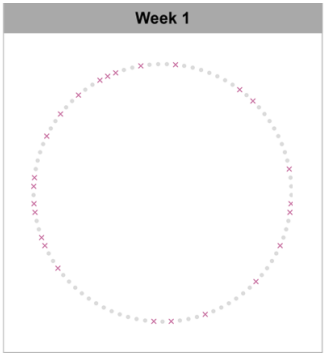

(93 out of 579 students with at least one infection)

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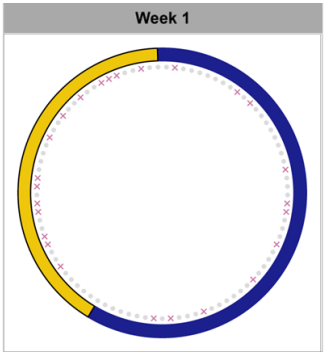


Nodes

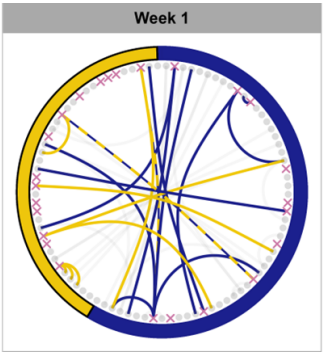
uninfected student

infected student

intervention group

control group

eX-FLU Observed Data



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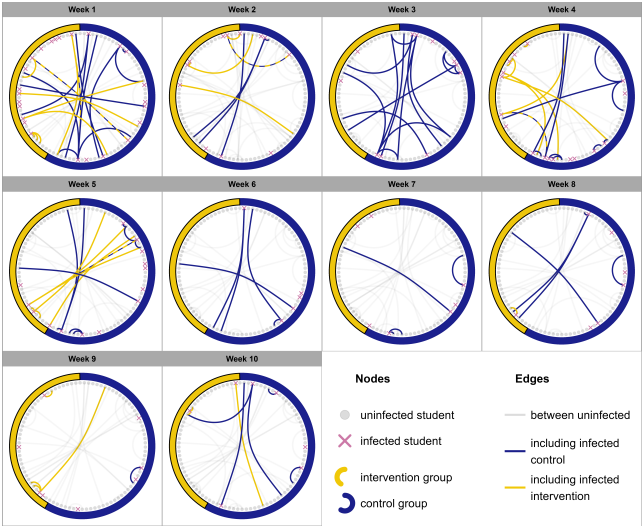

eX-FLU Potential Outcomes

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Potential outcomes are defined for the networks and ILI infections:

$$\overline{\mathbf{A}}(\mathbf{z}), \quad \overline{\mathbf{Y}}(\mathbf{z}) \quad \text{for } \mathbf{z} \in \mathcal{Z}$$

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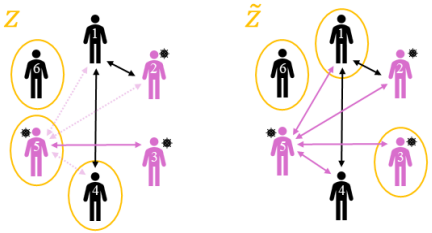
- Both of these depend on the entire vector $\mathbf{z}$
  - potential outcomes for one student depend on intervention assignment of other students (**interference**) (Hudgens and Halloran, 2008)
- Assume **causal consistency**:

$$\overline{\mathbf{A}} = \overline{\mathbf{A}}(\mathbf{Z}) \text{ and } \overline{\mathbf{Y}} = \overline{\mathbf{Y}}(\mathbf{Z})$$

eX-FLU Null Hypotheses

$$H_0^Y : \overline{\mathbf{Y}}(\mathbf{z}) = \overline{\mathbf{Y}}(\widetilde{\mathbf{z}}) \text{ for all } \mathbf{z}, \widetilde{\mathbf{z}} \in \mathcal{Z}$$

("the intervention has no effect on the infections")



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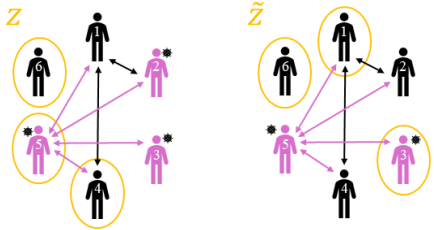

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$$H_0^\sharp = H_0^Y \cap H_0^A : \overline{\mathbf{Y}}(\mathbf{z}) = \overline{\mathbf{Y}}(\tilde{\mathbf{z}}) \text{ and } \overline{\mathbf{A}}(\mathbf{z}) = \overline{\mathbf{A}}(\tilde{\mathbf{z}}) \text{ for all } \mathbf{z}, \tilde{\mathbf{z}} \in \mathcal{Z}$$

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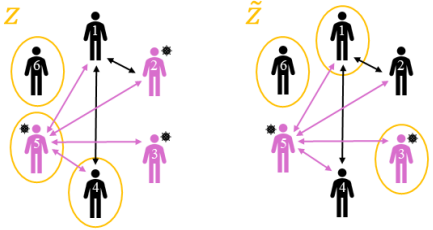

eX-FLU Null Hypotheses

$$H_0^Y : \overline{\mathbf{Y}}(\mathbf{z}) = \overline{\mathbf{Y}}(\widetilde{\mathbf{z}}) \text{ for all } \mathbf{z}, \widetilde{\mathbf{z}} \in \mathcal{Z}$$

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Previous analyses of the eX-FLU trial (Alexandria et al., 2023) tested $H_0^\sharp$, but no analyses have tested H_0^Y

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"How unlikely are the observed data under $H_0^\sharp$?"

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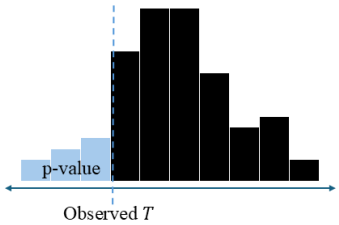
is the **cumulative distribution function** (CDF) of T



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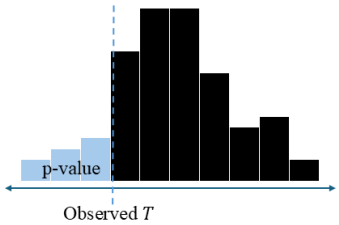
  is the **cumulative distribution function** (CDF) of T
- Reject $H_0^\sharp$ if $\rho^\sharp \leq 0.05$



Testing $H_0^\sharp$

- This test of $H_0^\sharp$ controls the **type I error rate** exactly:

$$\Pr\left(\rho^\sharp \leq \alpha | H_0^\sharp\right) \leq \alpha$$

for any $\alpha \in [0, 1]$, for any sample size, and for any choice of test statistic

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- The **power** of this test:

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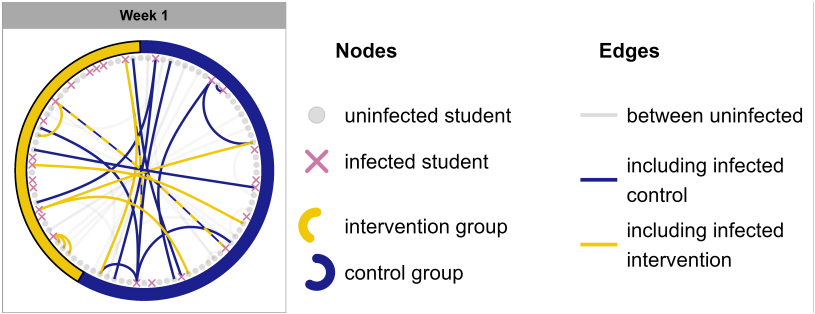
depends on the choice of test statistic

Choice of Test Statistic

- 93 (out of 579) students with at least one infection



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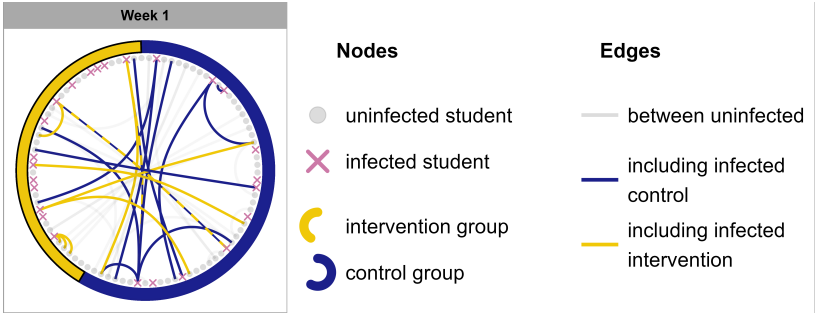

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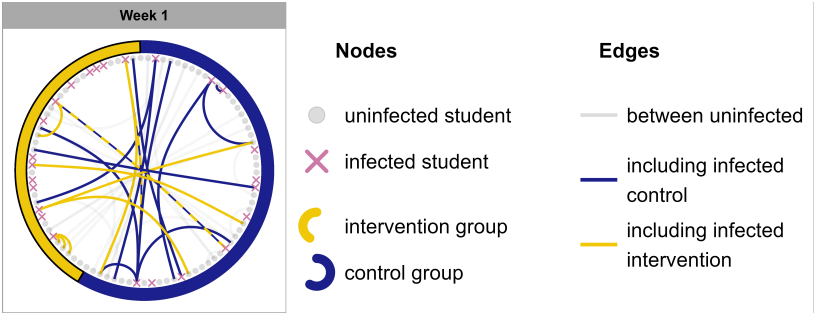
- 93 (out of 579) students with at least one infection
- Bold edges represent possible transmission events
  - Proportion of possible transmission events attributable to students in the intervention group:

$$T = \frac{\text{number of yellow edges}}{\text{total number of edges}} = \frac{\sum_{k=2}^{\tau}\sum_{i=1}^{n}\sum_{j\neq i} Z_i Y_i^{k-1} A_{ij}^{k-1}}{\sum_{k=2}^{\tau}\sum_{i=1}^{n}\sum_{j\neq i} Y_i^{k-1} A_{ij}^{k-1}} = 0.359$$



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  - If/when the double sum $\sum_{\mathbf{z}\in\mathcal{Z}} \sum_{\bar{\mathbf{a}}\in\mathcal{A}}$ cannot be computed exactly, approximate it using a Monte-Carlo method

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Testing Procedure:

1. Estimate the unknown parameter θ in the PMF $q(\bar{\mathbf{a}}, \mathbf{z}; \theta)$ of $\overline{\mathbf{A}}(\mathbf{z})$

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Proposition: This procedure will **asymptotically** control the type I error rate

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- Test statistic (proportion of possible transmission events attributable to students in the intervention group): $T = 0.359$.

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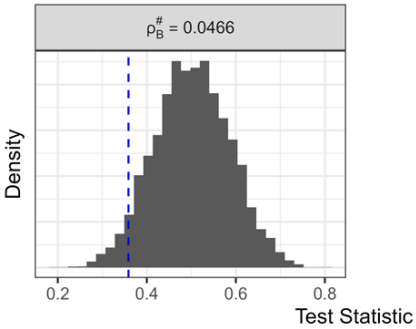

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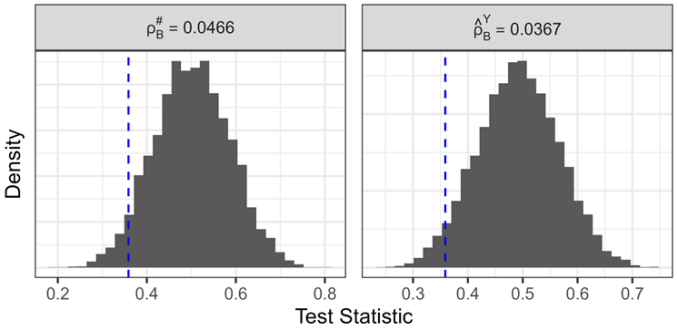

- Encouragement to isolate affects the social network and/or influenze-like illness ($\rho_B^{\sharp} = 0.0466$)
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- Developed a new randomization-based inference procedure
  - Established theoretical properties (asymptotic control of Type I error)
  - Demonstrated empirical performance through simulations
- Applied the method to the **eX-FLU trial** to find a protective effect of an encouragement-to-isolate intervention on a college campus
- **Future directions**:
  - Account for **measurement error** in the self-reported social networks

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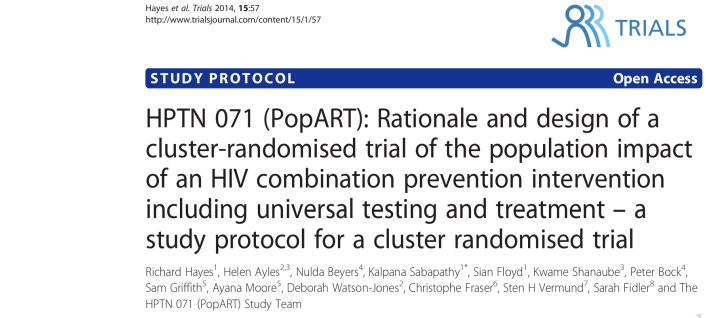
  - **Design future trials** with independent clusters
    - can allow **identification** of more causal estimands
- **Status**: under revision at *Proceedings of the National Academy of Sciences*

Project 3 : Causal Inference from Cluster Randomized Trials with Differential Nonresponse

Brian Richardson, Bonnie Shook-Sa, Michael Hudgens

PopART Trial

- **PopART (HPTN 071) Trial**: large **cluster randomized trial** designed to evaluate a combination **HIV prevention intervention** in Zambia and South Africa (Hayes et al., 2014)



Hayes *et al. Trials* 2014, **15**:57
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TRIALS

STUDY PROTOCOL Open Access

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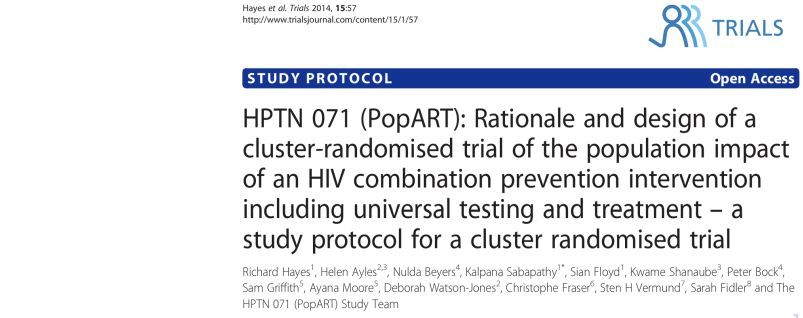

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- **Outcome**: HIV Incidence

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PopART Trial

- **Initial Findings**: no protective effect of the Arm A intervention (Hayes et al., 2019)
  - "unanticipated and not consistent with the data on viral suppression"
- **Later Analyses**: identified possibly differential nonresponse that could bias trial results (Shook-Sa et al., 2025)
  - Males were less likely to respond (i.e., have data collected)
  - The intervention appeared more effective among males

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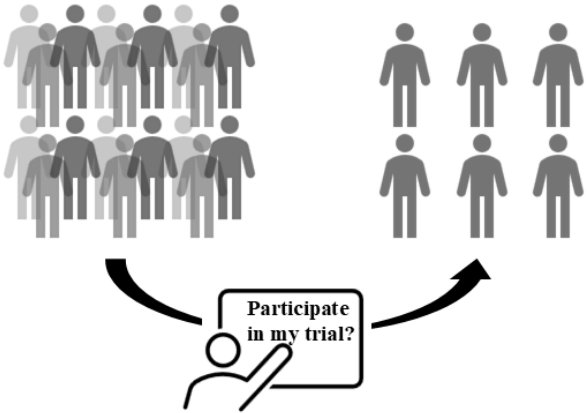

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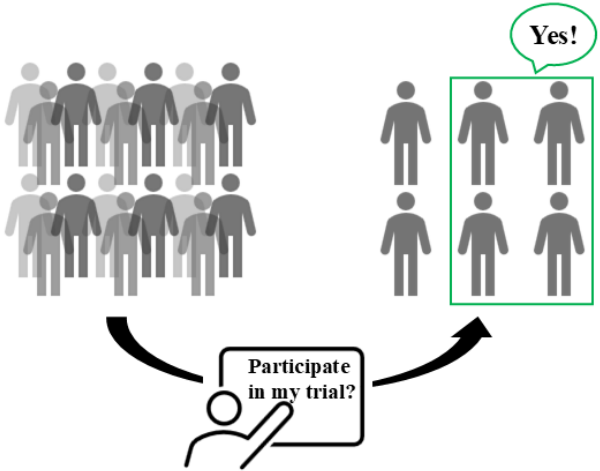

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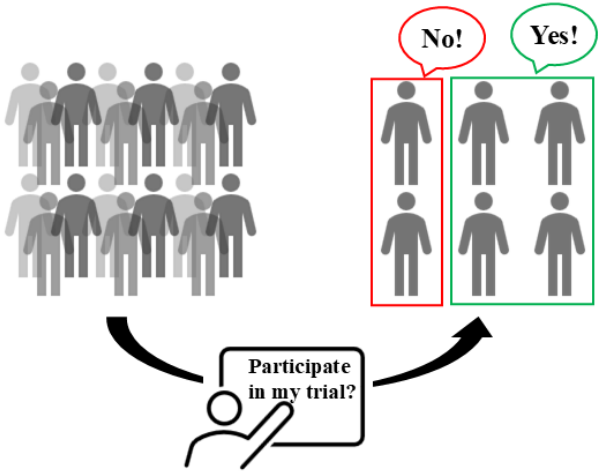

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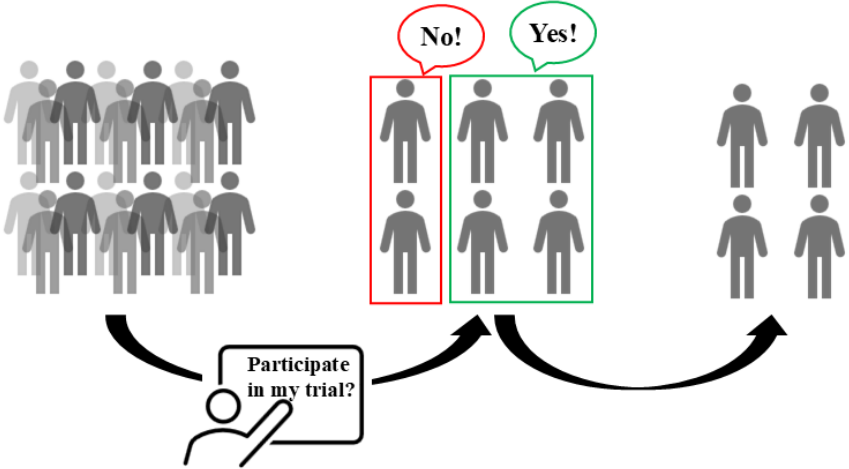

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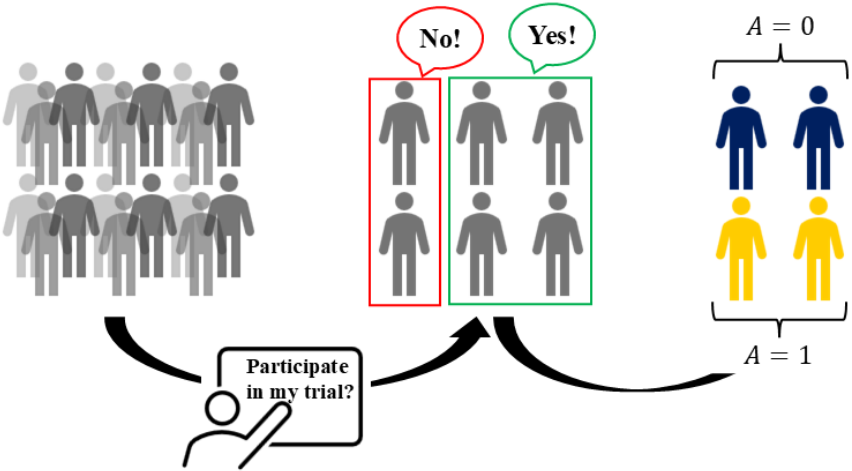

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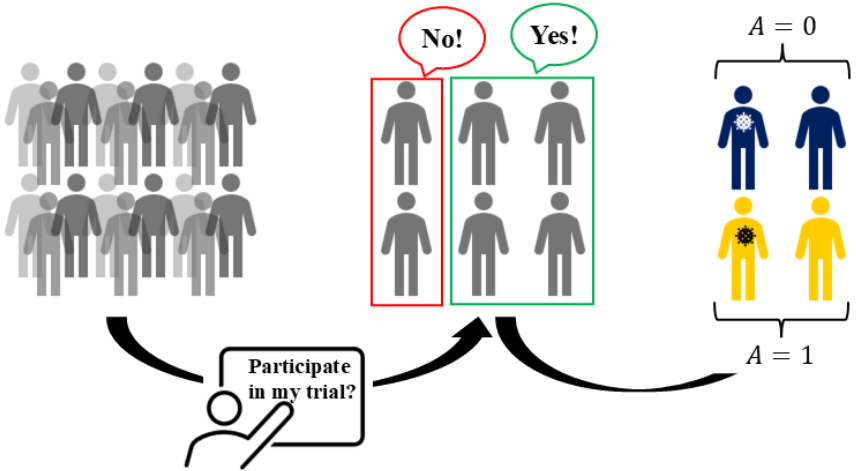

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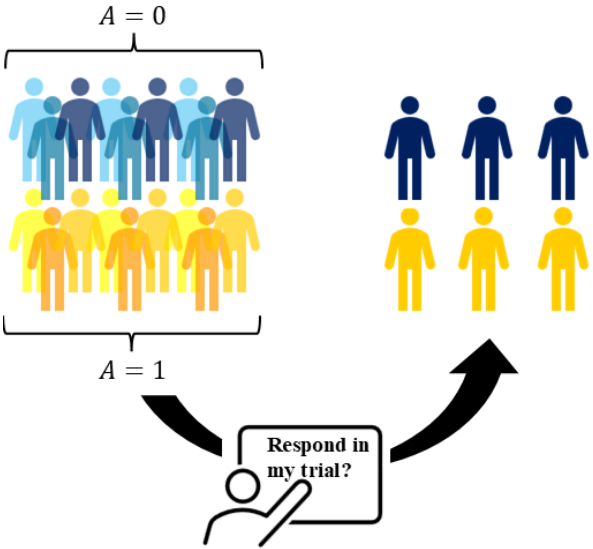

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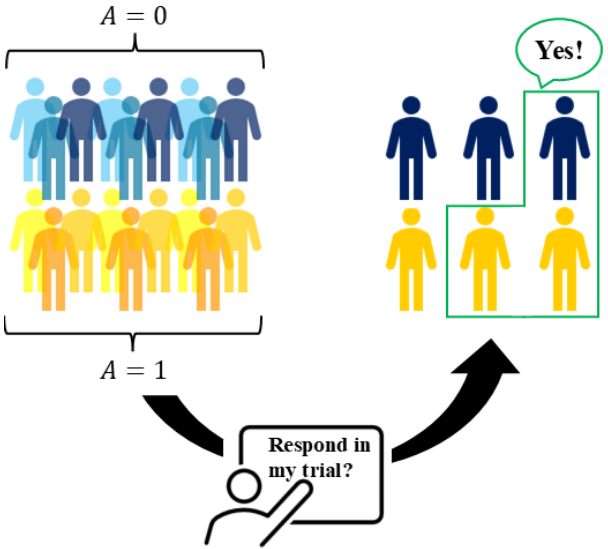

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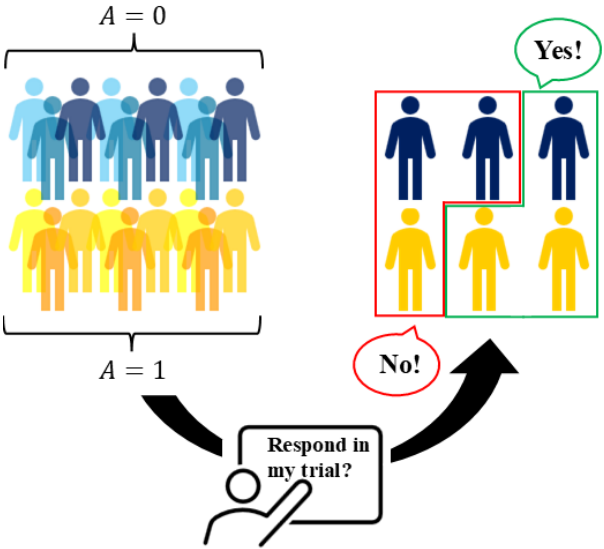

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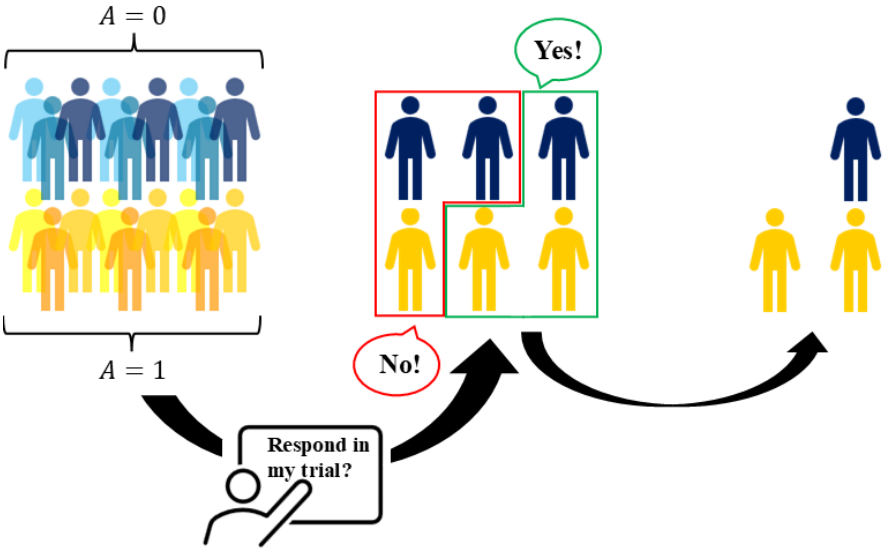

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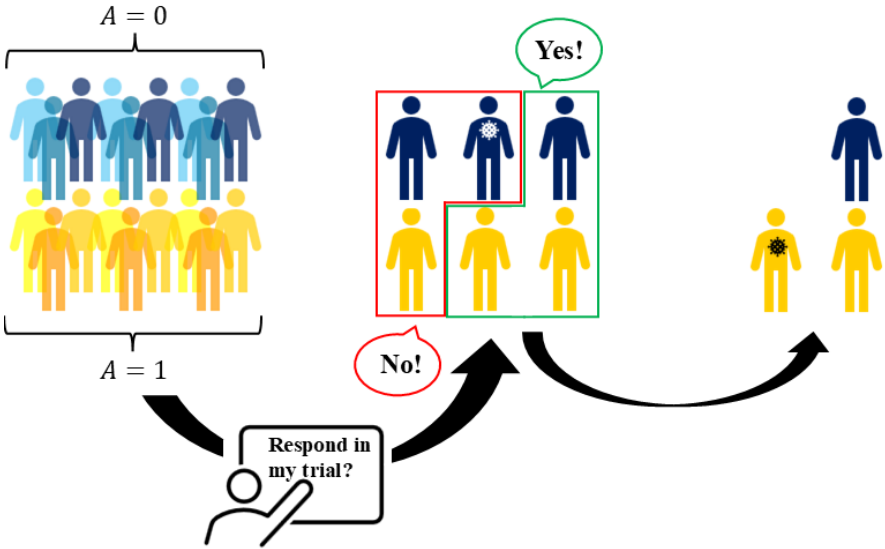

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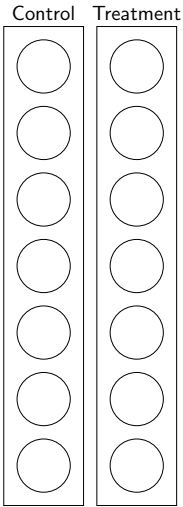

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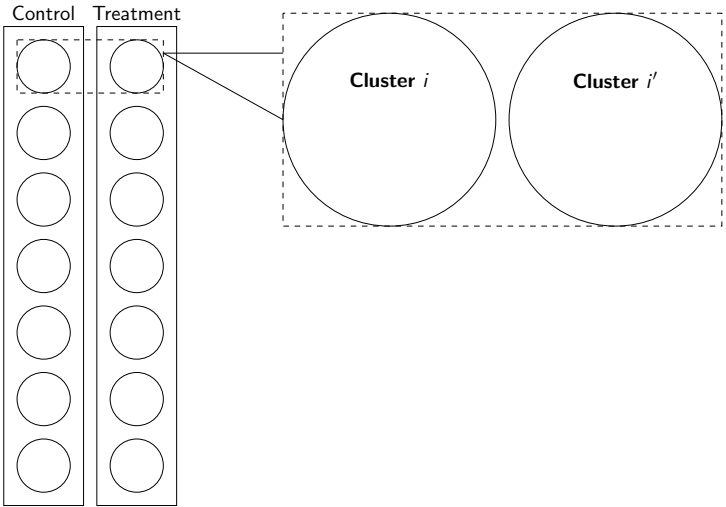

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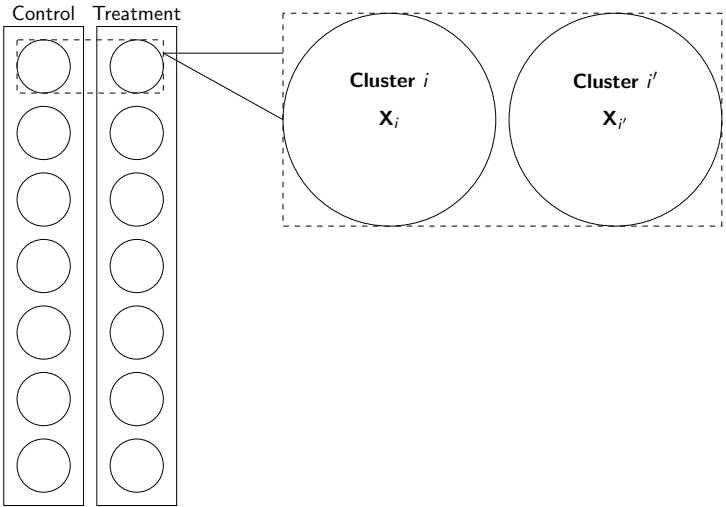

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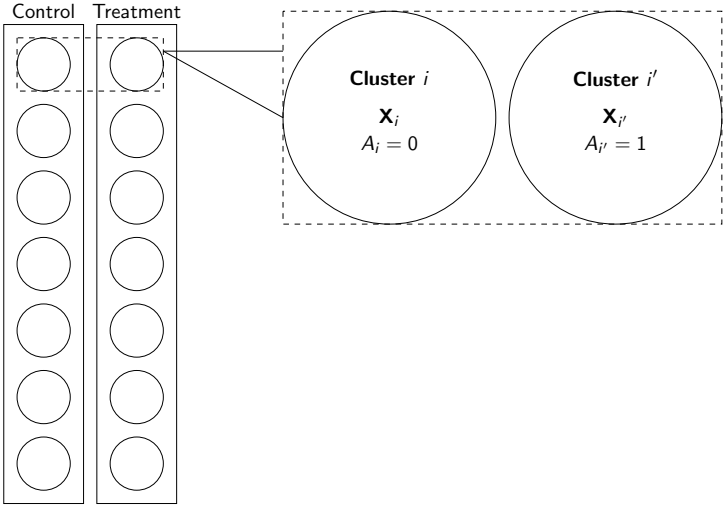

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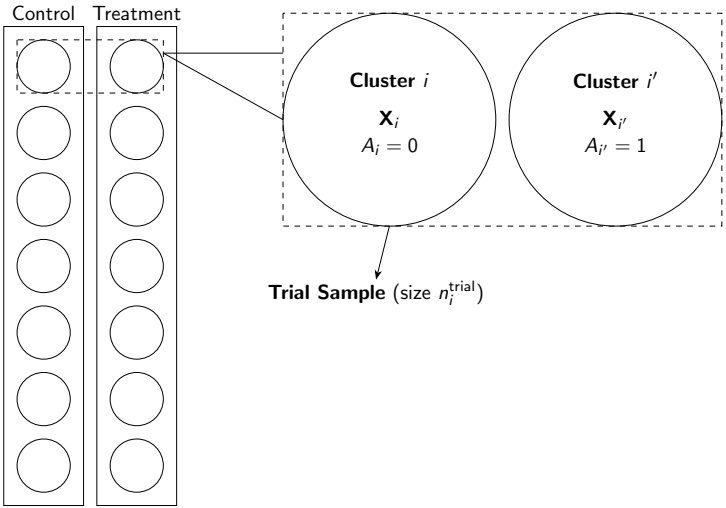

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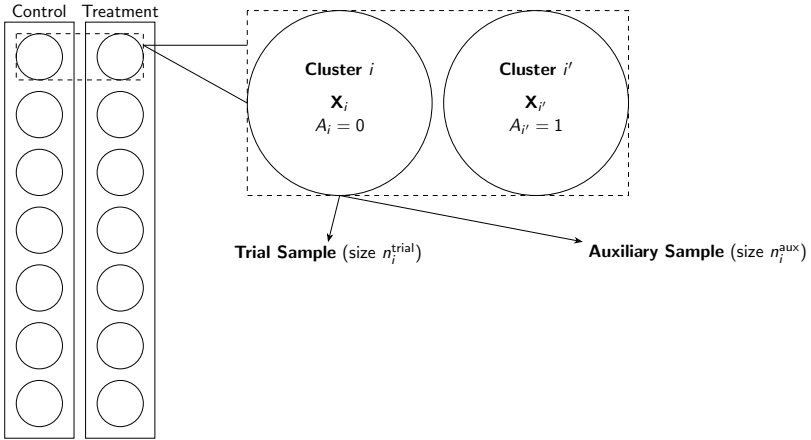

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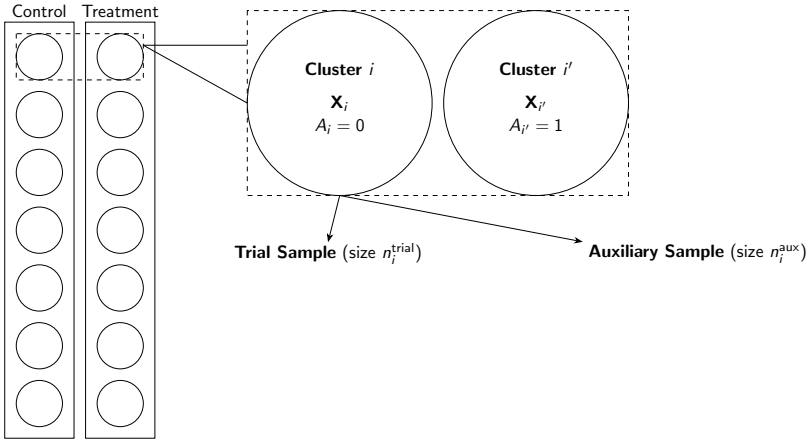

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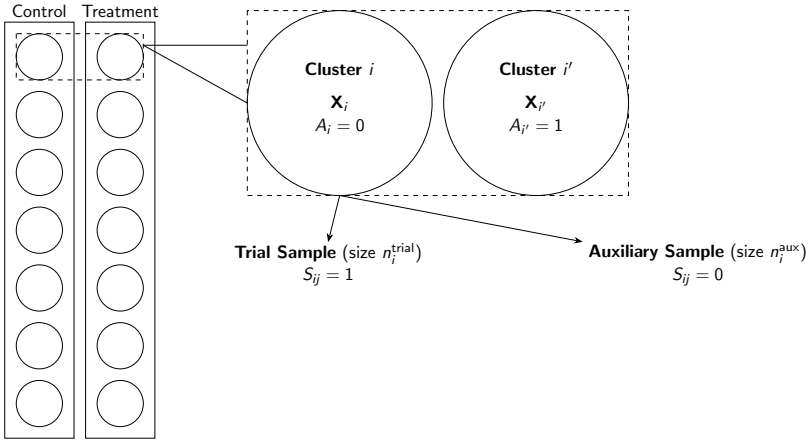

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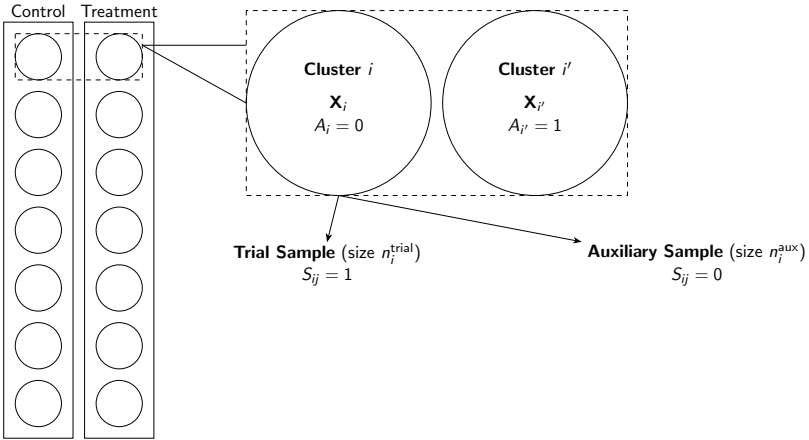

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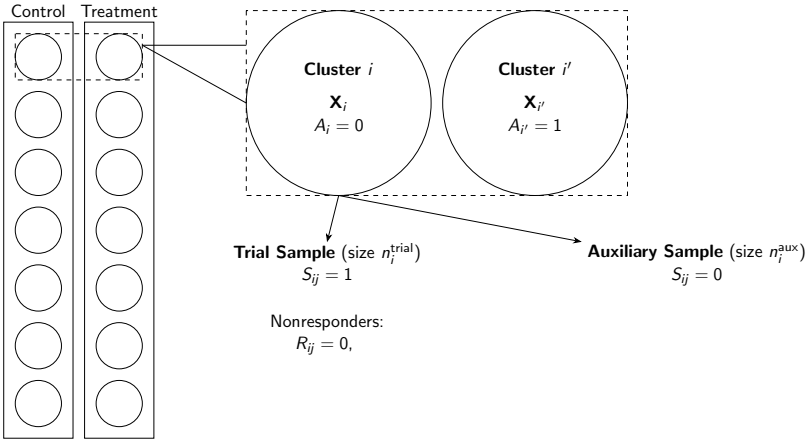
- R_{ij}: response indicator

PopART Observed Data



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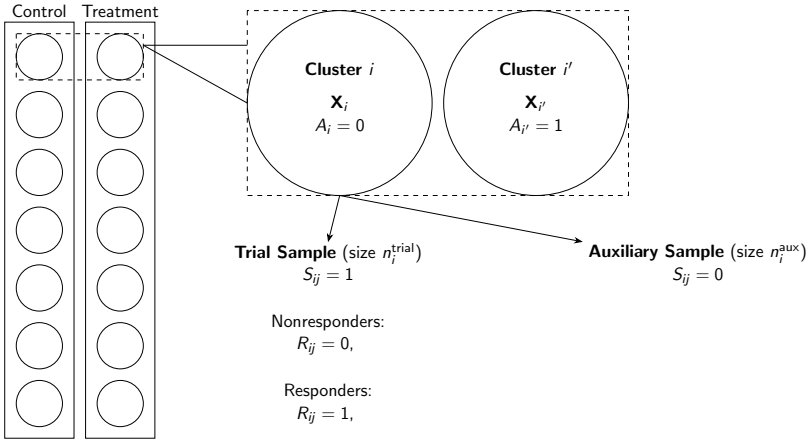

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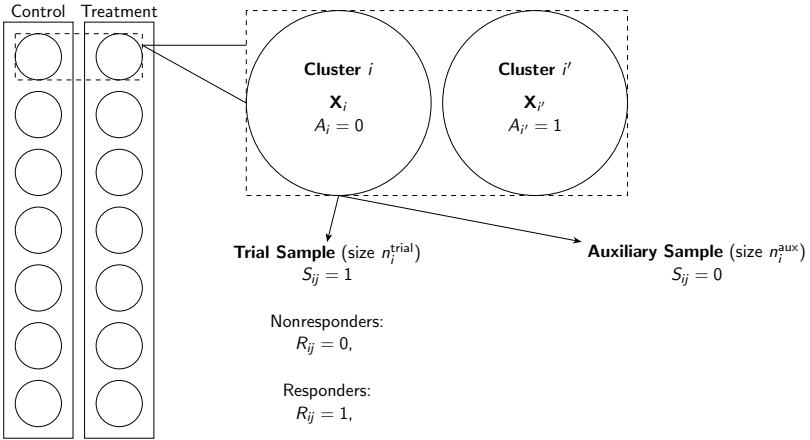

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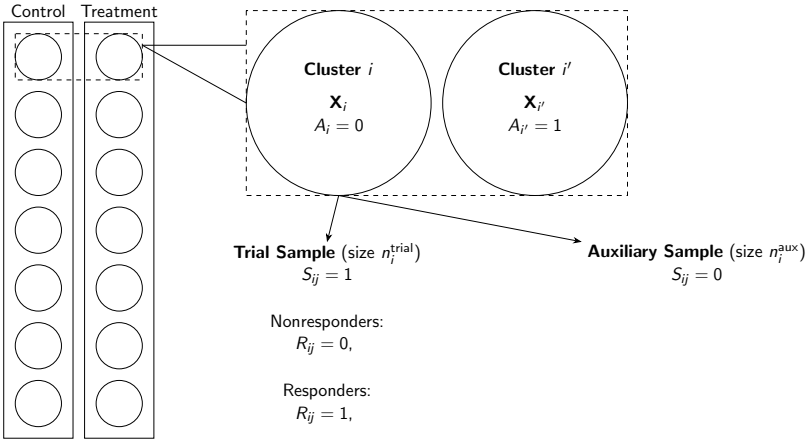
PopART Observed Data



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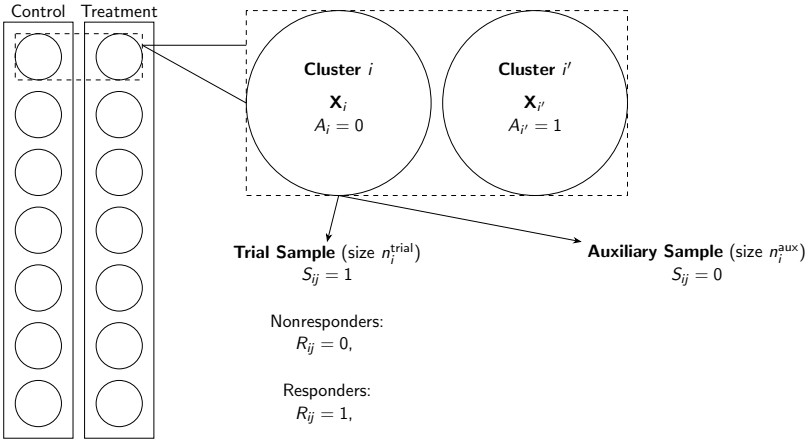

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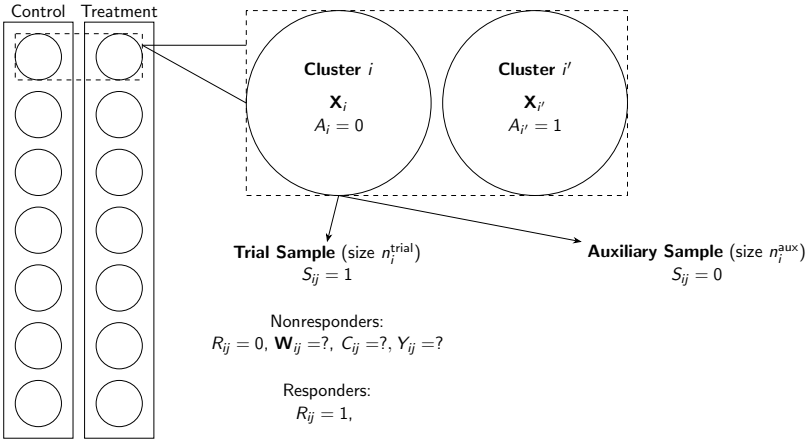

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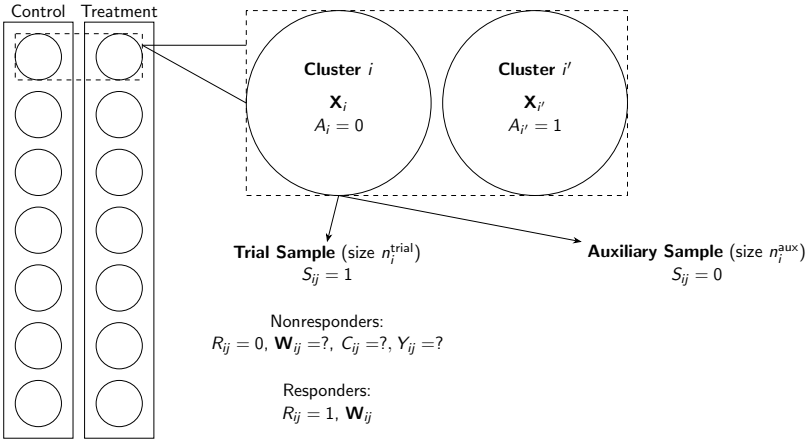

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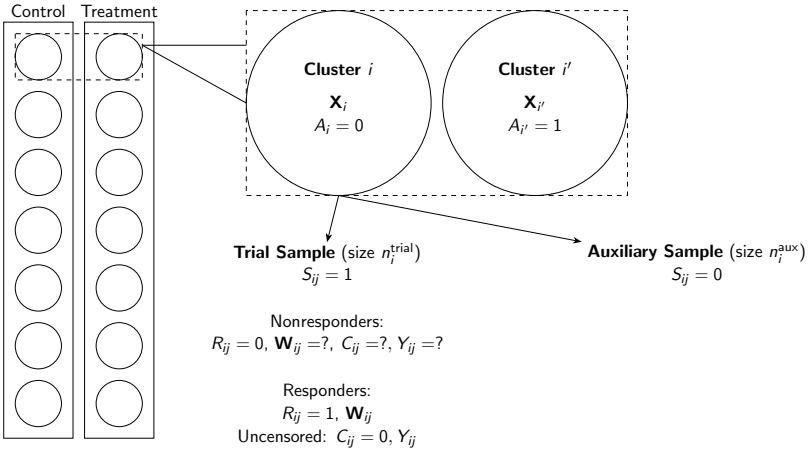

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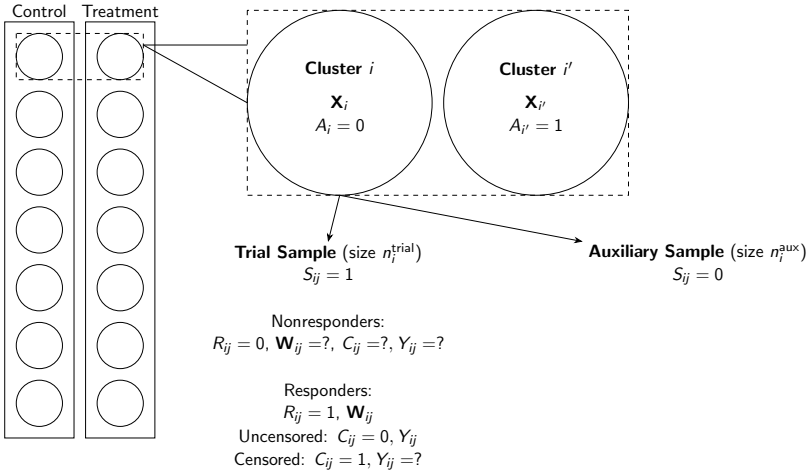

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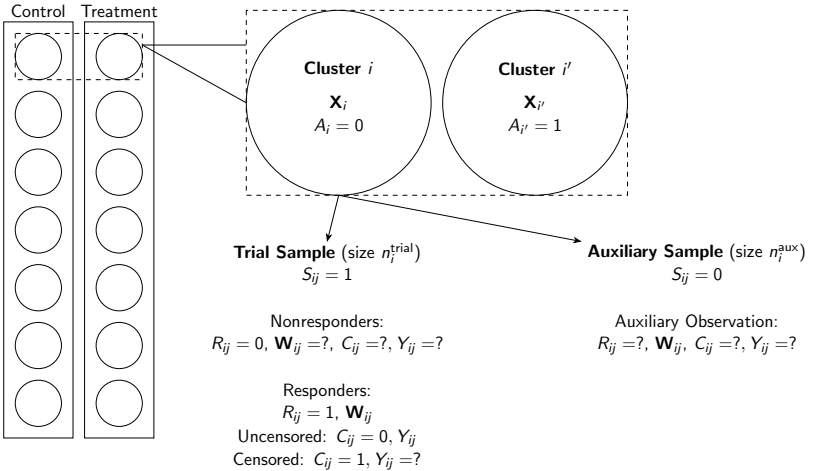

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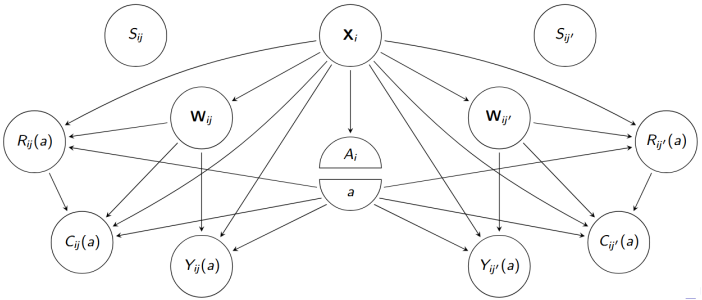
Identification

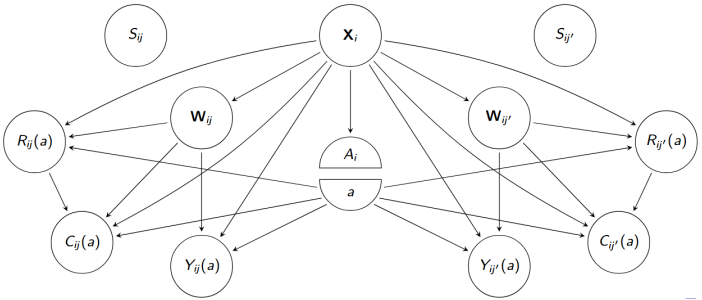
- Under assumptions*, the estimand $\eta(a)$ can be identified using either:



Identification

- Under assumptions*, the estimand $\eta(a)$ can be identified using either:
- G-formula:

$$\eta(a) = \mathrm{E}\left\{\mathrm{E}\left(Y_{ij} | A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0, \mathbf{X}_i, \mathbf{W}_{ij}\right) | S_{ij} = 0\right\}$$



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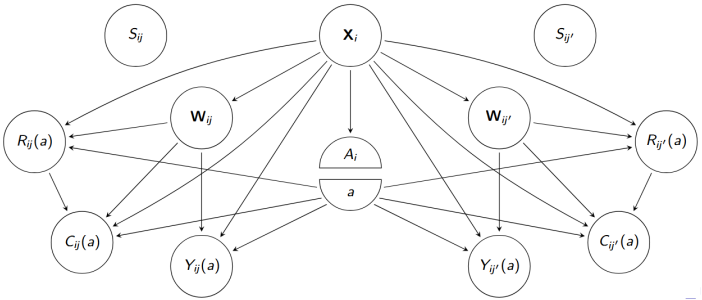
- Inverse Probability Weighting:

$$\eta(a) = \mathrm{E}\left\{\frac{\mathbb{1}(A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0) Y_{ij}}{\Pr(A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i, \mathbf{W}_{ij})}\right\}$$



Estimation: G-Formula

1. Fit the **outcome regression model** among **uncensored responders**

$$\mu_a(\mathbf{x}, \mathbf{w}) = \mathrm{E}(Y_{ij} | R_{ij} = 1, C_{ij} = 0, A_i = a, \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w})$$

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2. Marginalize the estimator $\widehat{\mu}_a(\mathbf{X}, \mathbf{W})$ over the distribution of covariates in the **auxiliary data**:

$$\widehat{\eta}^{GF}(a) = \underbrace{\frac{1}{n^{\text{aux}}} \sum_{i=1}^{m} \sum_{j=1}^{n_i} \mathbb{1}(S_{ij} = 0)}_{\text{sample mean in auxiliary data}} \widehat{\mu}_a(\mathbf{X}_i, \mathbf{W}_{ij})$$

Estimation: Inverse Probability Weighting

1. Fit the **joint propensity score model**

$$\pi_a(\mathbf{x}, \mathbf{w}) = \Pr(A_i = a, R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w})$$

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2. Take the **weighted mean outcome**

$$\widehat{\eta}^{IPW}(a) = \frac{1}{n^{\text{trial}}} \sum_{i=1}^{m} \sum_{j=1}^{n_i} \frac{\mathbb{1}(A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0) Y_{ij}}{\widehat{\pi}_a(\mathbf{X}_i, \mathbf{W}_{ij})}$$

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Joint Propensity Scores

$$\pi_a(\mathbf{x}, \mathbf{w}) = \Pr(A_i = a, R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w})$$

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$$\begin{aligned}\pi_a(\mathbf{x}, \mathbf{w}) &= \Pr(A_i = a, R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w}) \\ &= \Pr(A_i = a, R_{ij} = 1 | \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w}) \times \Pr(C_{ij} = 0 | A_i = a, R_{ij} = 1, \mathbf{X}_i = \mathbf{x}, \mathbf{W}_{ij} = \mathbf{w})\end{aligned}$$

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Response and Treatment Mechanism: $\pi_a^{AR}(\mathbf{x},\mathbf{w})$

$$= \Pr(A_i = a, R_{ij} = 1) \frac{f_{\mathbf{X},\mathbf{W}|A,R}(\mathbf{x},\mathbf{w}|a,1)}{f_{\mathbf{X},\mathbf{W}}(\mathbf{x},\mathbf{w})}$$

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- Estimate this ratio of densities following an approach in Sugiyama et al. (2010)

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Censoring Mechanism: $\pi_a^{C}(\mathbf{x},\mathbf{w})$

- Estimate using responders in the trial (for whom $A_i, \mathbf{X}_i, \mathbf{W}_{ij}, C_{ij}$ are available)

Estimation: Augmented Inverse Probability Weighting

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$$\sum_{i=1}^{m}\sum_{j=1}^{n_i}\left[\frac{\mathbb{1}(A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0)}{\widehat{n}^{\text{trial}}\widehat{\pi}_a(\mathbf{X}_i, \mathbf{W}_{ij})}\left\{Y_{ij} - \widehat{\mu}_a(\mathbf{X}_i, \mathbf{W}_{ij})\right\} + \frac{\mathbb{1}(S_{ij} = 0)}{n^{\text{aux}}}\widehat{\mu}_a(\mathbf{X}_i, \mathbf{W}_{ij})\right]$$

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$$\sum_{i=1}^{m}\sum_{j=1}^{n_i}\left[\frac{\mathbb{1}(A_i = a, S_{ij} = 1, R_{ij} = 1, C_{ij} = 0)}{\widehat{n}^{\text{trial}}\widehat{\pi}_a(\mathbf{X}_i, \mathbf{W}_{ij})}\left\{Y_{ij} - \widehat{\mu}_a(\mathbf{X}_i, \mathbf{W}_{ij})\right\} + \frac{\mathbb{1}(S_{ij} = 0)}{n^{\text{aux}}}\widehat{\mu}_a(\mathbf{X}_i, \mathbf{W}_{ij})\right]$$

$\implies$ **Double robustness** to parametric model specifications for μ_a, π_a

Estimation: Augmented Inverse Probability Weighting

1. Fit the **outcome regression model** μ_a
2. Fit the **joint propensity score model** π_a
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Crash Course on M-Estimation

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

$$\underbrace{\Psi}_{\text{score fun.}}(\quad ; \quad)$$

Crash Course on M-Estimation

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$$\underbrace{\boldsymbol{\Psi}}_{\text{score fun.}}\left(\underbrace{\mathbf{D}_{ij}}_{\text{data}};\quad\right)$$

Crash Course on M-Estimation

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that is **unbiased**, meaning

Crash Course on M-Estimation

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$$\mathrm{E}\{\boldsymbol{\Psi}(\mathbf{D}_{ij};\underbrace{\theta_0}_{\text{true}})\} = \mathbf{0}$$

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Crash Course on M-Estimation

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The M-estimator $\widehat{\theta}$ is the solution to

$$\sum_{i=1}^{m}\sum_{j=1}^{n_i}\boldsymbol{\Psi}(\mathbf{D}_{ij};\theta) = \mathbf{0}$$

$\widehat{\theta}$ is consistent and asymptotically normal and has a simple variance estimator (Stefanski and Boos, 2002)

Inference: Estimating Equations

Each of the proposed estimators can be expressed as an **M-estimator**:

Inference: Estimating Equations

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$\widehat{\eta}^{GF}$ has estimating function

$$\boldsymbol{\Psi}_{GF}(\mathbf{D}_{ij};\theta_{GF}) = \begin{bmatrix} \boldsymbol{\Psi}_{\mu}(\mathbf{D}_{ij},\beta) \\ \frac{1}{p^{\text{aux}}}\mathbb{1}(S_{ij}=0)\mu_0(\mathbf{X}_i,\mathbf{W}_{ij};\beta) - \eta(0) \\ \frac{1}{p^{\text{aux}}}\mathbb{1}(S_{ij}=0)\mu_1(\mathbf{X}_i,\mathbf{W}_{ij};\beta) - \eta(1) \end{bmatrix},$$

where

- $\boldsymbol{\Psi}_{\mu}$ is an estimating function for fitting the outcome model $\mu_a(\mathbf{x},\mathbf{w};\beta)$
- $\theta_{GF} = [\beta, \eta(0), \eta(1)]$
- $p^{\text{aux}} = n^{\text{aux}}/n$

Inference: Estimating Equations

Each of the proposed estimators can be expressed as an **M-estimator**:

$\widehat{\eta}^{IPW}$ has estimating function

$$\boldsymbol{\Psi}_{IPW}(\mathbf{D}_{ij};\theta_{IPW}) = \begin{bmatrix} \boldsymbol{\Psi}_{\pi}(\mathbf{D}_{ij},\gamma) \\ \frac{1}{p^{\text{trial}}} \frac{\mathbb{1}(A_i=0,S_{ij}=1,R_{ij}=1,C_{ij}=0)Y_{ij}}{\widehat{\pi}_0(\mathbf{X}_i,\mathbf{W}_{ij};\gamma)} - \eta(0) \\ \frac{1}{p^{\text{trial}}} \frac{\mathbb{1}(A_i=1,S_{ij}=1,R_{ij}=1,C_{ij}=0)Y_{ij}}{\widehat{\pi}_1(\mathbf{X}_i,\mathbf{W}_{ij};\gamma)} - \eta(1) \end{bmatrix},$$

where

- $\boldsymbol{\Psi}_{\pi}$ is an estimating function for fitting the joint propensity score model $\pi_a(\mathbf{x},\mathbf{w};\gamma)$
- $\theta_{IPW} = [\gamma, \eta(0), \eta(1)]$
- $p^{\text{trial}} = n^{\text{trial}}/n$

Inference: Estimating Equations

Each of the proposed estimators can be expressed as an **M-estimator**:

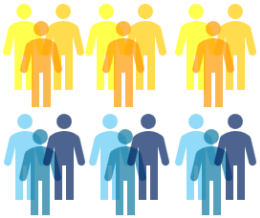
$\widehat{\eta}^{AIPW}$ has estimating function

$$\boldsymbol{\Psi}_{AIPW}(\mathbf{D}_{ij};\theta_{AIPW}) = \begin{bmatrix} \boldsymbol{\Psi}_{\mu}(\mathbf{D}_{ij},\beta) \\ \boldsymbol{\Psi}_{\pi}(\mathbf{D}_{ij},\gamma) \\ \frac{\mathbb{1}(A_i=0,S_{ij}=1,R_{ij}=1,C_{ij}=0)}{p^{\text{trial}}\pi_0(\mathbf{X}_i,\mathbf{W}_{ij};\gamma)}\{Y_{ij}-\mu_0(\mathbf{X}_i,\mathbf{W}_{ij};\beta)\}+\frac{\mathbb{1}(S_{ij}=0)}{p^{\text{aux}}}\mu_0(\mathbf{X}_i,\mathbf{W}_{ij};\beta)-\eta(0) \\ \frac{\mathbb{1}(A_i=1,S_{ij}=1,R_{ij}=1,C_{ij}=0)}{p^{\text{trial}}\pi_1(\mathbf{X}_i,\mathbf{W}_{ij};\gamma)}\{Y_{ij}-\mu_1(\mathbf{X}_i,\mathbf{W}_{ij};\beta)\}+\frac{\mathbb{1}(S_{ij}=0)}{p^{\text{aux}}}\mu_1(\mathbf{X}_i,\mathbf{W}_{ij};\beta)-\eta(1) \end{bmatrix},$$

where

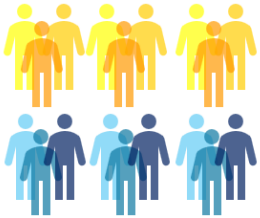
- $\theta_{AIPW} = [\beta, \gamma, \eta(0), \eta(1)]$

Simulation Study



Simulation Study

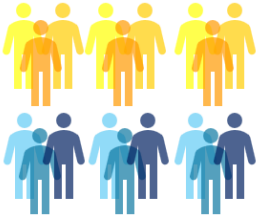
$X \sim N(0,1)$



Simulation Study

$X \sim N(0,1)$

$W_1 \sim Bernoulli(0.5)$
$W_2 \sim N(0,1)$



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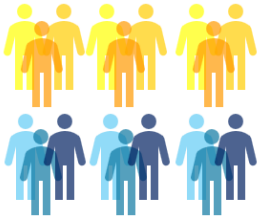

Treatment marginally protective, but harmful when $W_1 = 1$

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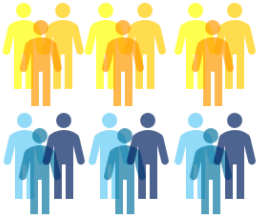

Treatment marginally protective, but harmful when $W_1 = 1$

Invited Trial Sample, size $n^{trial} \in \{500, 5000\}$

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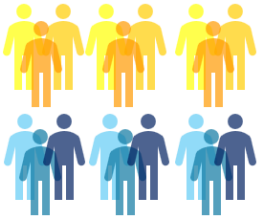

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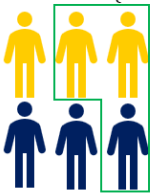

Marginal response rate: 50%

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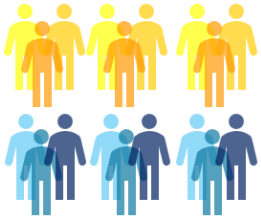

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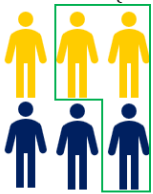

Marginal response rate: 50%

More nonresponse when $W_1 = 1, A = 1$

Simulation Study

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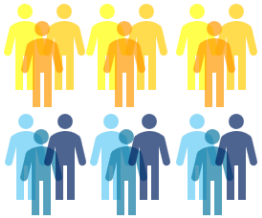

Treatment marginally protective, but harmful when $W_1 = 1$

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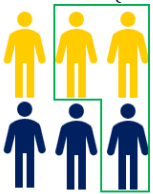
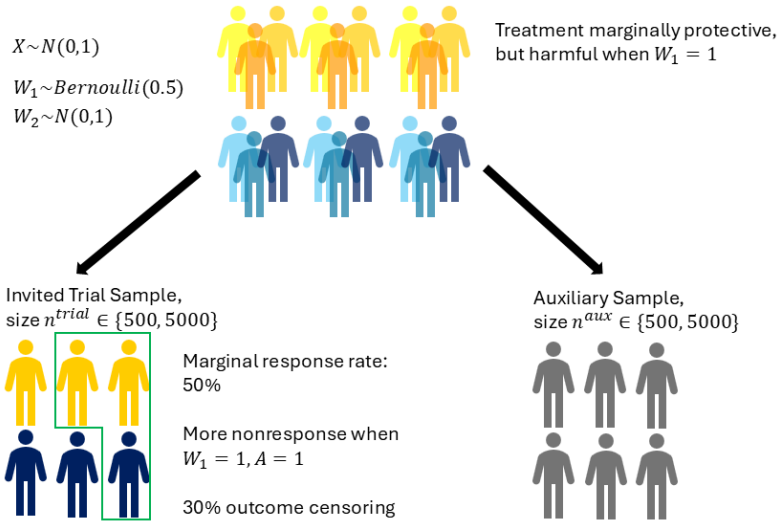


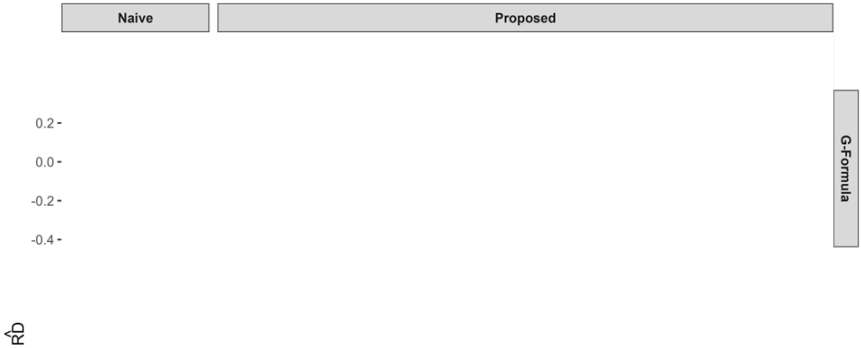
Marginal response rate: 50%

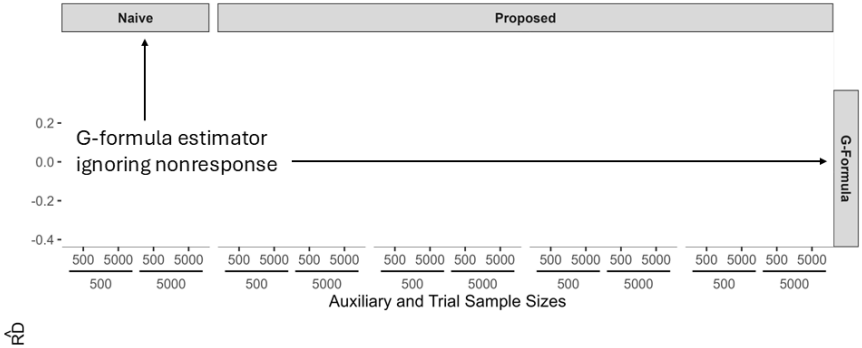
More nonresponse when $W_1 = 1, A = 1$

30% outcome censoring

Simulation Study




Naive
Proposed
G-Formula
0.2
0.0
-0.2
-0.4
RD


Naive
Proposed
G-formula estimator
ignoring nonresponse
G-Formula
0.2
0.0
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-0.4
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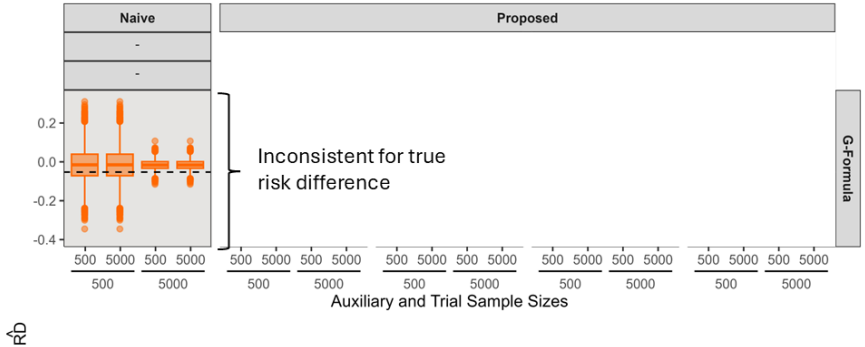
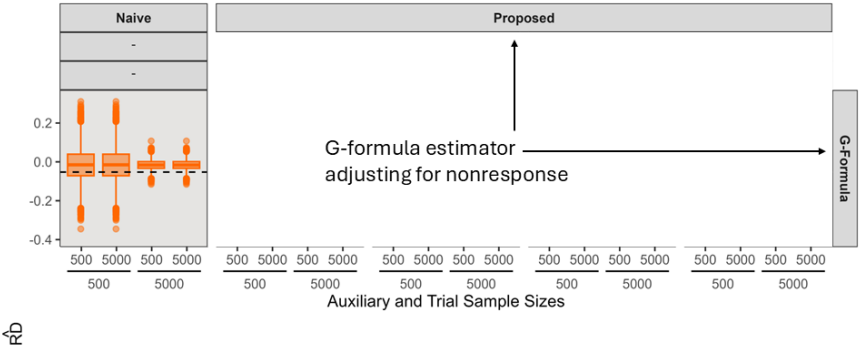
500 5000 500 5000 500 5000 500 5000
Auxiliary and Trial Sample Sizes
RD


Naive
Proposed
-
-
G-Formula
0.2
0.0
-0.2
-0.4
Inconsistent for true
risk difference
500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000
500 5000 500 5000 500 5000 500 5000 500 5000
Auxiliary and Trial Sample Sizes
$\widehat{RD}$


Naive
Proposed
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-
G-formula estimator
adjusting for nonresponse
G-Formula
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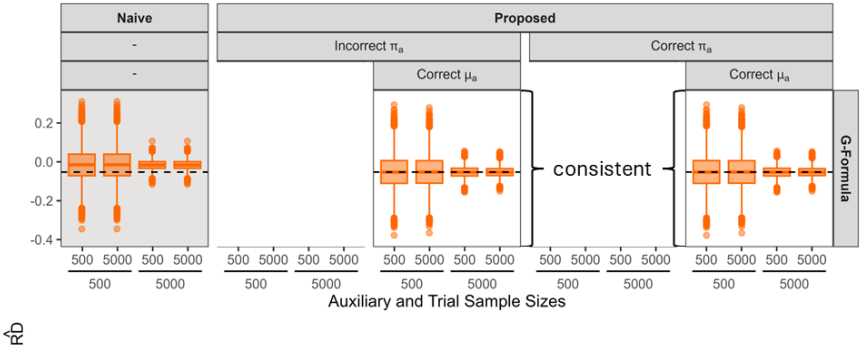
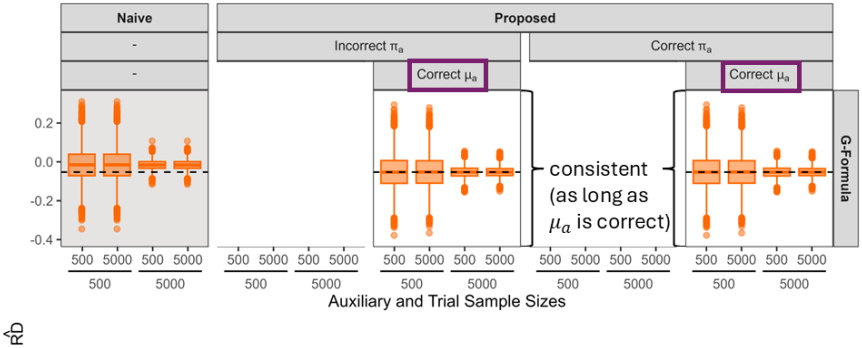
Auxiliary and Trial Sample Sizes
RD


Naive
Proposed
-
-
Incorrect π_a
Correct π_a
Correct μ_a
Correct μ_a
G-Formula
consistent
0.2
0.0
-0.2
-0.4
500 5000 500 5000
500
5000
Auxiliary and Trial Sample Sizes
$\widehat{RD}$


Naive
Proposed
-
-
Incorrect π_a
Correct π_a
Correct μ_a
Correct μ_a
G-Formula
consistent
(as long as
μ_a is correct)
0.2
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-0.2
-0.4
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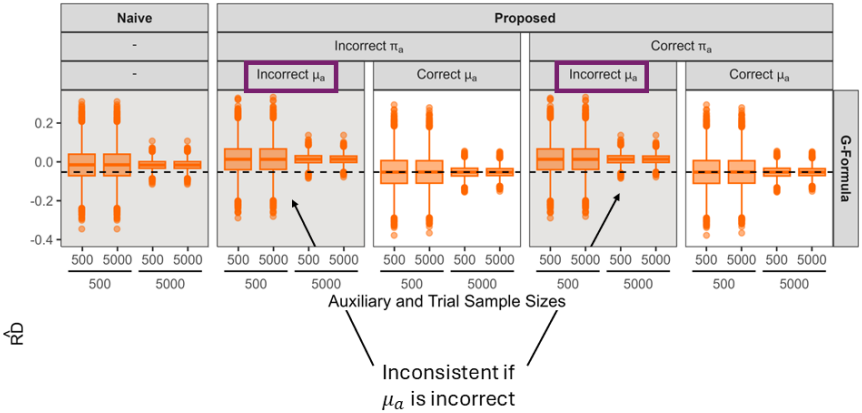
Auxiliary and Trial Sample Sizes
$\widehat{RD}$


Naive
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Incorrect π_a
Correct π_a
Incorrect μ_a
Correct μ_a
G-Formula
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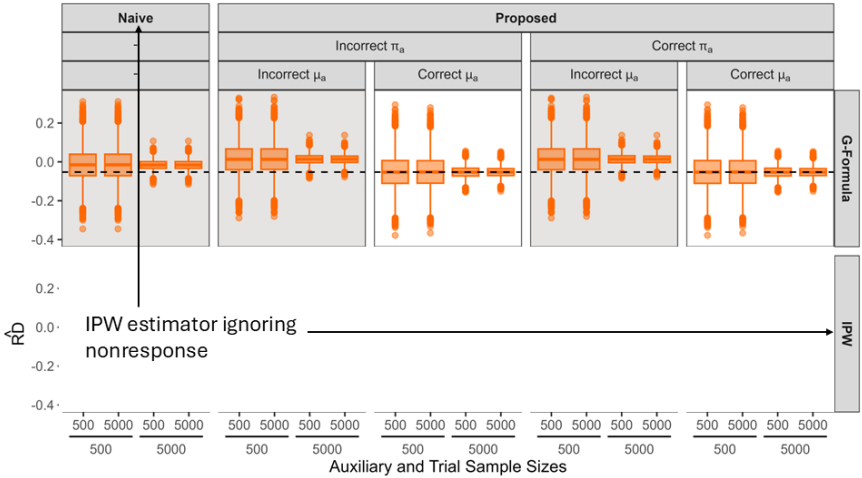
0.0
-0.2
-0.4
500 5000 500 5000
500 5000
Auxiliary and Trial Sample Sizes
$\widehat{RD}$
Inconsistent if
μ_a is incorrect


Naive
Proposed
Incorrect π_a
Correct π_a
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
$\hat{RD}$
0.2
0.0
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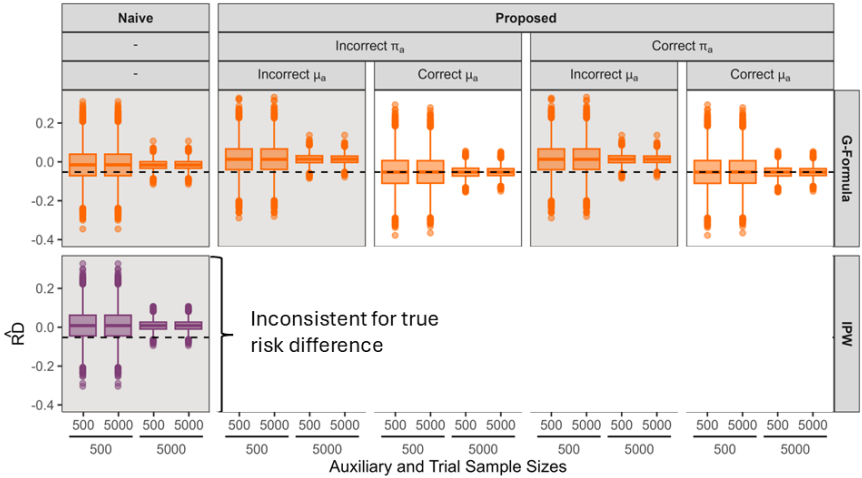
-0.4
IPW estimator ignoring nonresponse
500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000
500 5000 500 5000 500 5000 500 5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
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Inconsistent for true
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500 5000 500 5000
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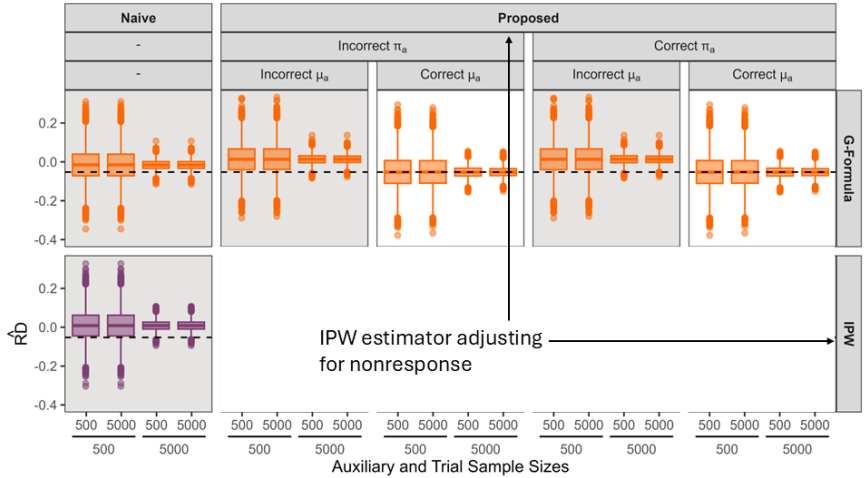
500
5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
$\hat{RD}$
0.2
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-0.2
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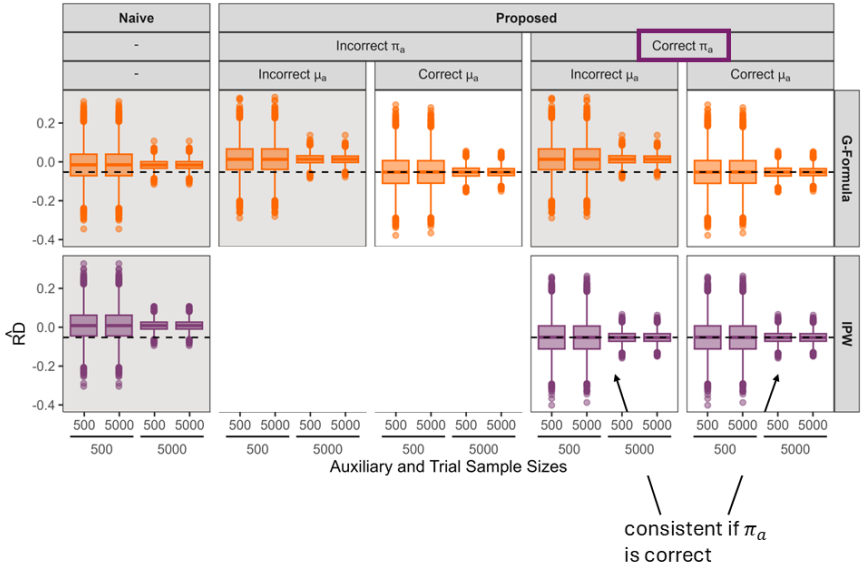
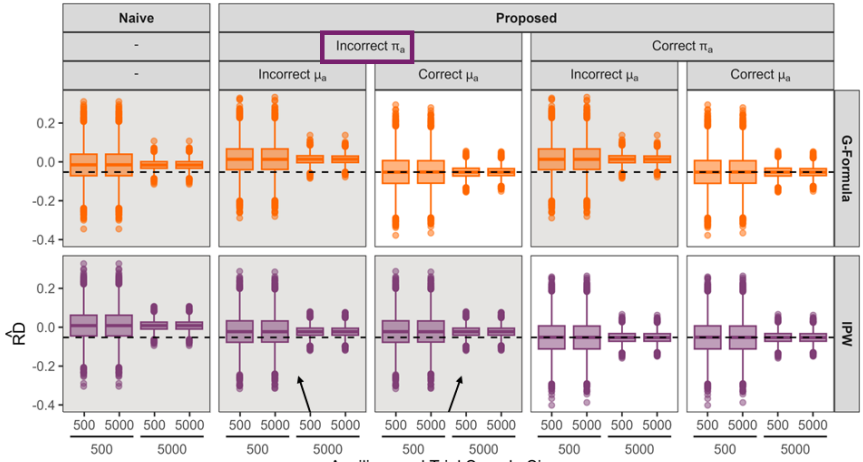
IPW estimator adjusting
for nonresponse
500 5000 500 5000
500
5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
$\hat{RD}$
0.2
0.0
-0.2
-0.4
500 5000 500 5000
500 5000
Auxiliary and Trial Sample Sizes
consistent if π_a is correct


Naive
Proposed
-
Incorrect π_a
Correct π_a
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Correct μ_a
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G-Formula
IPW
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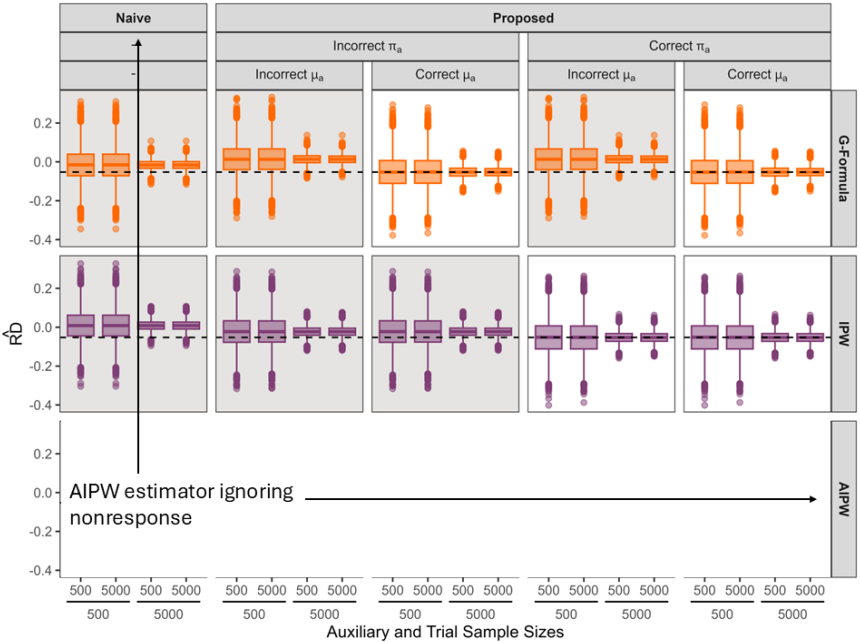
0.2
0.0
-0.2
-0.4
500 5000 500 5000
500 5000
Auxiliary and Trial Sample Sizes
inconsistent if
π_a is incorrect


Naive
Proposed
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
AIPW
$\widehat{RD}$
0.2
0.0
-0.2
-0.4
AIPW estimator ignoring nonresponse
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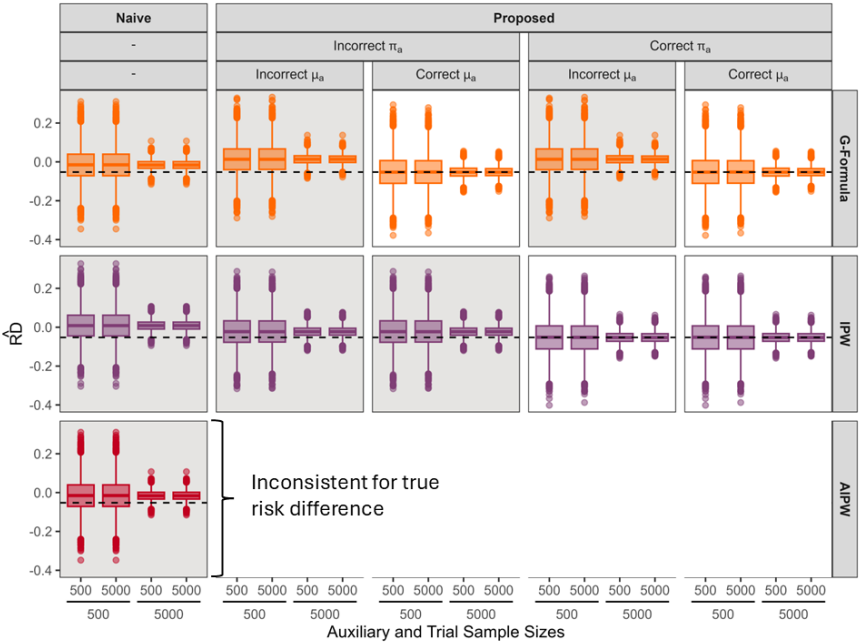
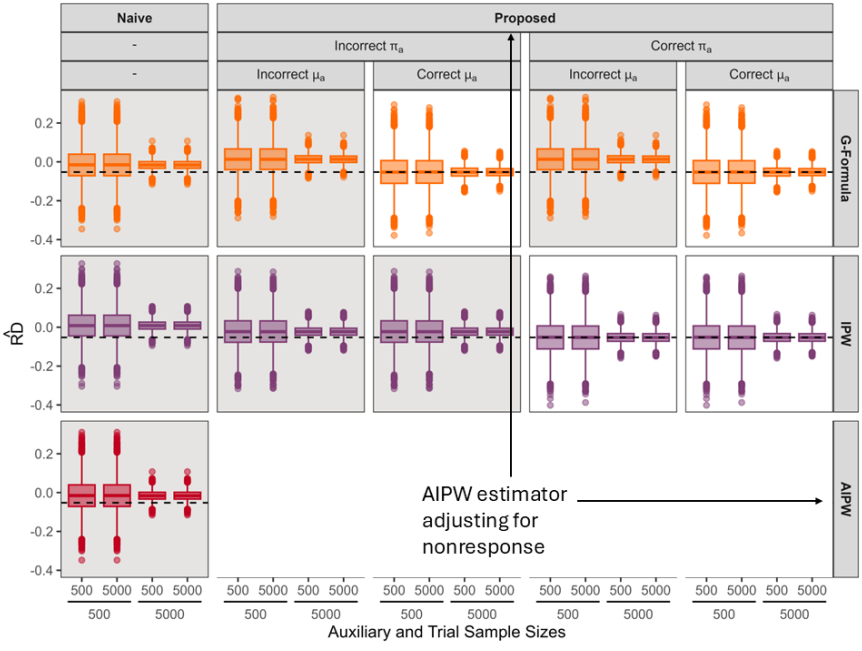
500 5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
AIPW
$\hat{RD}$
0.2
0.0
-0.2
-0.4
Inconsistent for true risk difference
500
5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
AIPW
RD
0.2
0.0
-0.2
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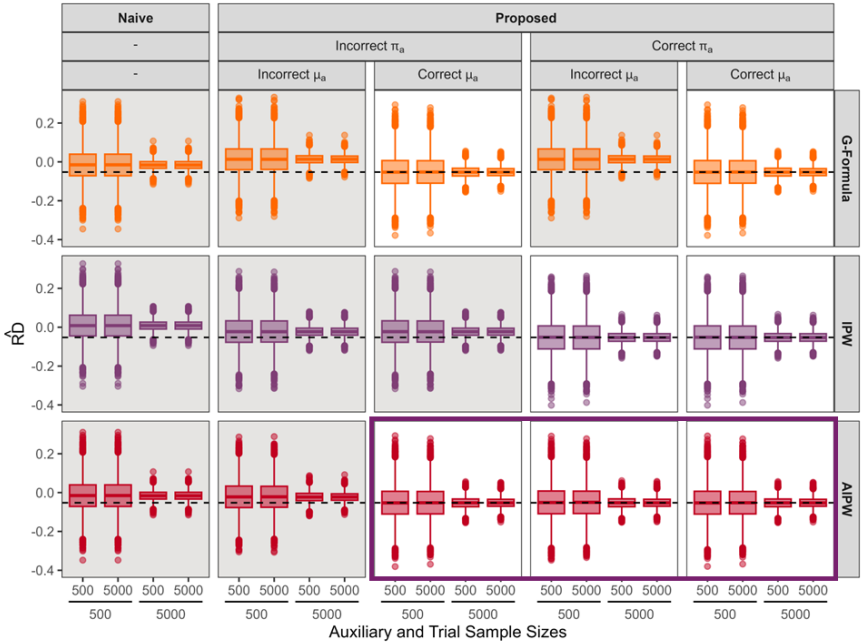
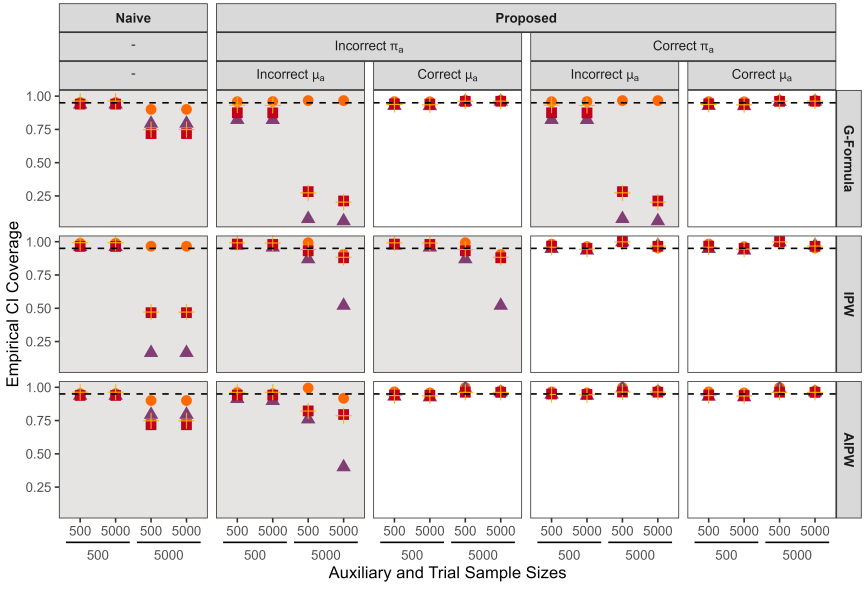
AIPW estimator adjusting for nonresponse
500 5000 500 5000
500 5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
AIPW
$\widehat{RD}$
0.2
0.0
-0.2
-0.4
500 5000 500 5000
500 5000
Auxiliary and Trial Sample Sizes


Naive
Proposed
-
Incorrect π_a
Correct π_a
-
Incorrect μ_a
Correct μ_a
Incorrect μ_a
Correct μ_a
G-Formula
IPW
AIPW
Empirical CI Coverage
1.00
0.75
0.50
0.25
500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000 500 5000
500 5000 500 5000
Auxiliary and Trial Sample Sizes
Estimand
$\eta(0)$
$\eta(1)$
RD
RR

PopART Application

- Trial data: PopART trial (Hayes et al., 2014, 2019)

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- Auxiliary data:

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	PopART Trial Responders				**Auxiliary Data**
	Overall $N = 29,130$	**A** $N = 9,594$	**B** $N = 10,235$	**C (Control)** $N = 9,301$	$N = 5,076$
Sex and Male Circumcision					
Female	19,494 (68%)	6,547 (69%)	6,828 (68%)	6,119 (68%)	54%
Male (Circumcised)	4,190 (15%)	1,403 (15%)	1,516 (15%)	1,271 (14%)	22%
Male (Uncircumcised)	4,847 (17%)	1,474 (16%)	1,725 (17%)	1,648 (18%)	24%

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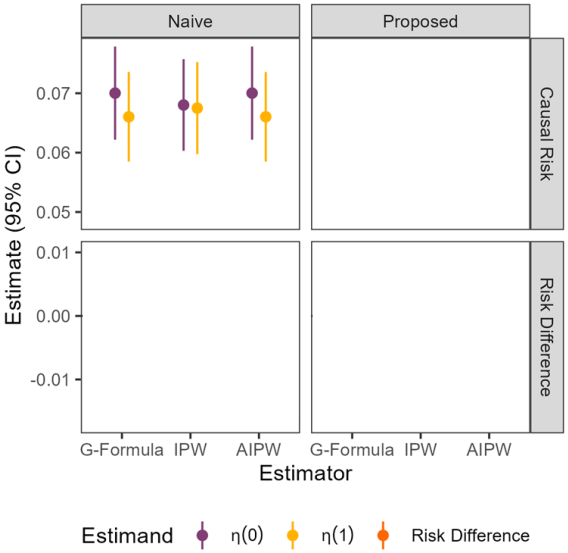
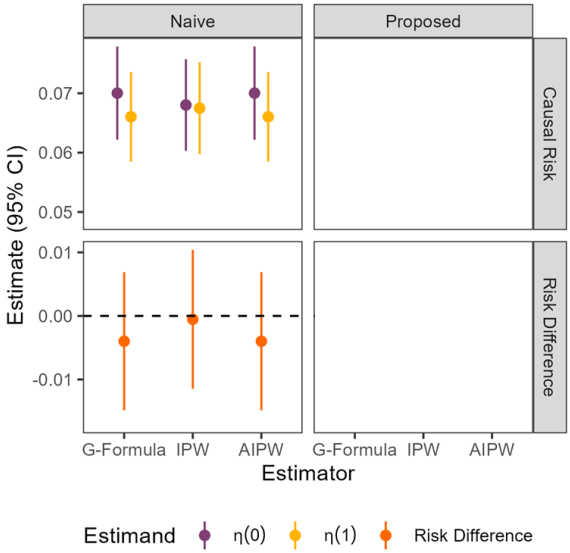
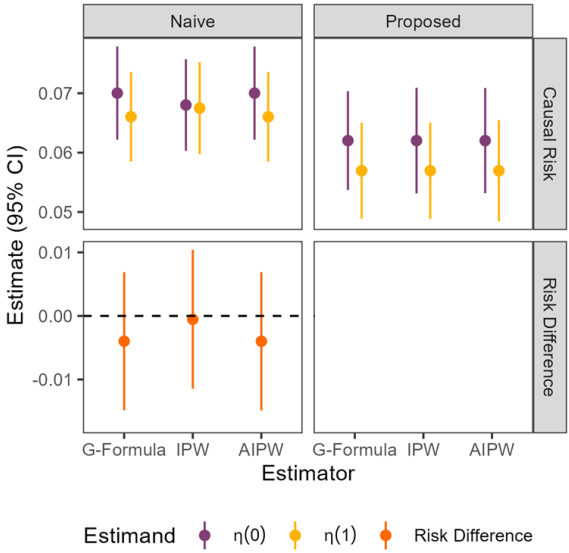
PopART Results



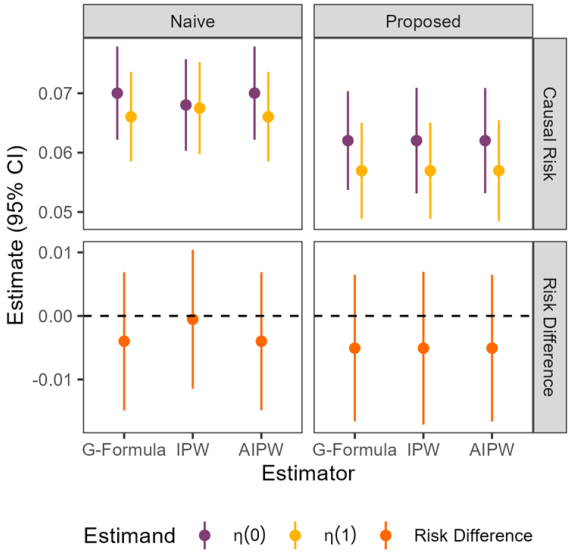
PopART Results



PopART Results



PopART Results



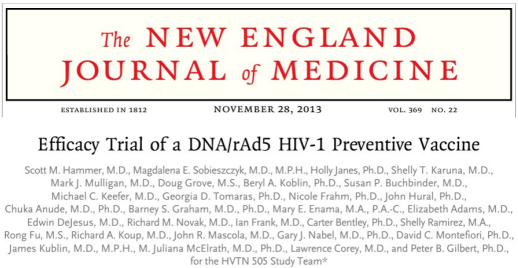
Summary of Project 3

- Developed estimators to adjust for differential nonresponse and outcome censoring in a cluster RCT
  - Established theoretical properties (consistency, asymptotic normality, double robustness of AIPW)
  - Demonstrated empirical performance through simulations
- Applied the method to the **PopART trial**, along with auxilary data from national surveys
- **Future Directions**:
  - show semiparametric efficiency of AIPW estimator
  - derive asymptotic results for AIPW estimator under nonparametric estimators of μ_a, π_a
- **Status**: in preparation to submit to *Annals of Applied Statistics*

Project 1 : Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

Brian Richardson, Brian Blette, Peter Gilbert, Michael Hudgens (2025)

Motivation: HVTN 505 trial



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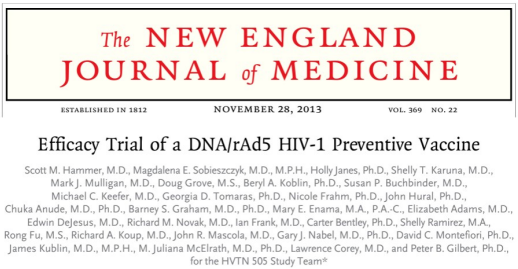
ESTABLISHED IN 1812 NOVEMBER 28, 2013 VOL. 369 NO. 22

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

Scott M. Hammer, M.D., Magdalena E. Sobieszczyk, M.D., M.P.H., Holly Janes, Ph.D., Shelly T. Karuna, M.D., Mark J. Mulligan, M.D., Doug Grove, M.S., Beryl A. Koblin, Ph.D., Susan P. Buchbinder, M.D., Michael C. Keefer, M.D., Georgia D. Tomaras, Ph.D., Nicole Frahm, Ph.D., John Hural, Ph.D., Chuka Anude, M.D., Ph.D., Barney S. Graham, M.D., Ph.D., Mary E. Enama, M.A., P.A.-C., Elizabeth Adams, M.D., Edwin DeJesus, M.D., Richard M. Novak, M.D., Ian Frank, M.D., Carter Bentley, Ph.D., Shelly Ramirez, M.A., Rong Fu, M.S., Richard A. Koup, M.D., John R. Mascola, M.D., Gary J. Nabel, M.D., Ph.D., David C. Montefiori, Ph.D., James Kublin, M.D., M.P.H., M. Juliana McElrath, M.D., Ph.D., Lawrence Corey, M.D., and Peter B. Gilbert, Ph.D., for the HVTN 505 Study Team*

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

Motivation: HVTN 505 trial



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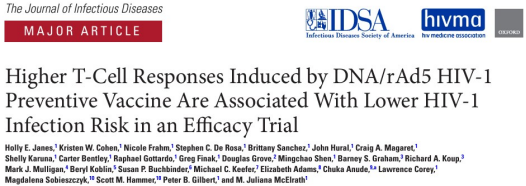
- **HVTN 505 trial**: trial of a preventive HIV vaccine
- Stopped early after reaching predetermined cutoffs for efficacy futility (Hammer et al., 2013)

Motivation: HVTN 505 trial


The Journal of Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

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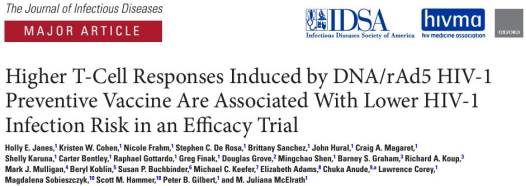
- Several biomarkers correlated with HIV among vaccine recipients (Janes et al., 2017; Fong et al., 2018; Neidich et al., 2019)

Motivation: HVTN 505 trial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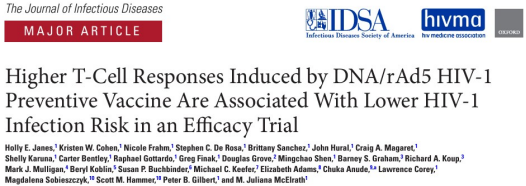
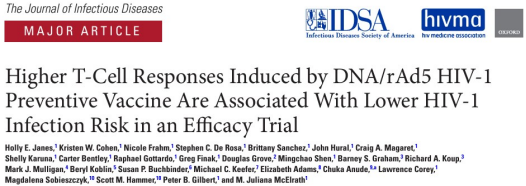


- Several biomarkers correlated with HIV among vaccine recipients (Janes et al., 2017; Fong et al., 2018; Neidich et al., 2019)
- Is there a **causal** relationship between these biomarkers and HIV?
- Biomarker-HIV relationship is **confounded**

Motivation: HVTN 505 trial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- Is there a **causal** relationship between these biomarkers and HIV?
- Biomarker-HIV relationship is **confounded**
- Biomarkers are **measured with error**

Goal

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

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(i) The exposure-outcome relationship is potentially **confounded**

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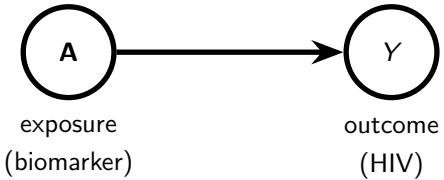
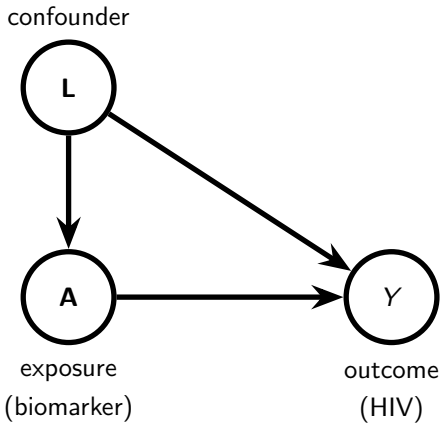
(i) The exposure-outcome relationship is potentially **confounded**

(ii) The exposure is **measured with error**

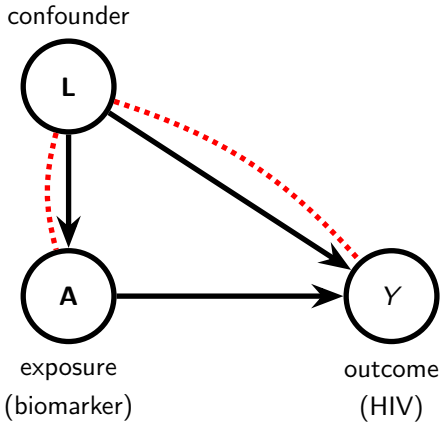
Confounding



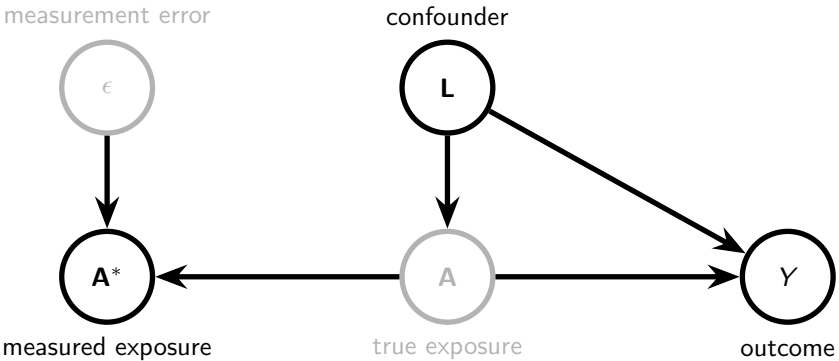
Confounding



Confounding



Measurement Error



Addressing Confounding Alone

- G-Formula
- IPW
- Doubly Robust Estimator

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- G-Formula

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

- IPW
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- IPW

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

- Doubly Robust Estimator

Addressing Confounding Alone

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- Doubly Robust Estimator

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

Addressing Confounding and Measurement Error

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

$$\sum_{i=1}^{n} \boldsymbol{\Psi}_0(Y_i, \mathbf{L}_i, \underbrace{\mathbf{A}_i^*}_{\text{mismeasured}}; \theta) = \mathbf{0}?$$

Addressing Confounding and Measurement Error

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

$$\sum_{i=1}^{n} \boldsymbol{\Psi}_0(Y_i, \mathbf{L}_i, \underbrace{\mathbf{A}_i^*}_{\text{mismeasured}}; \theta) = \mathbf{0}?$$

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

$$\mathrm{E}\{\boldsymbol{\Psi}_0(Y, \mathbf{L}, \mathbf{A}^*; \theta_0)\} \neq \mathbf{0}.$$

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

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

$$\mathrm{E}\{\underbrace{\boldsymbol{\Psi}_{CS}}_{\text{new score fun.}}(Y, \mathbf{L}, \underbrace{\mathbf{A}^*}_{\text{mismeasured}}; \theta_0)\} = \mathbf{0}.$$

Corrected Score Functions

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

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The G-Formula, IPW, and DR score functions can all be corrected in this way

$$\begin{aligned}
\boldsymbol{\Psi}_{0-GF} &\longrightarrow \boldsymbol{\Psi}_{CS-GF} \\
\boldsymbol{\Psi}_{0-IPW} &\longrightarrow \boldsymbol{\Psi}_{CS-IPW} \\
\boldsymbol{\Psi}_{0-DR} &\longrightarrow \boldsymbol{\Psi}_{CS-DR}
\end{aligned}$$

Summary of Project 1

Paper in *Biometrics* (2025)

GitHub R package

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

Acknowledgments

- add photos

Thank you! Questions?

References I

Allison E. Aiello, Amanda M. Simanek, Marisa C. Eisenberg, Alison R. Walsh, Brian Davis, Erik Volz, Caroline Cheng, Jeanette J. Rainey, Amra Uzicanin, Hongjiang Gao, Nathaniel Osgood, Dylan Knowles, Kevin Stanley, Kara Tarter, and Arnold S. Monto. Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial. *Epidemics*, 15:38–55, June 2016. ISSN 17554365. doi: 10.1016/j.epidem.2016.01.001. URL https://linkinghub.elsevier.com/retrieve/pii/S1755436516000025.

Shaina J. Alexandria, Michael G. Hudgens, and Allison E. Aiello. Assessing Intervention Effects in a Randomized Trial Within a Social Network. *Biometrics*, 79(2):1409–1419, June 2023. ISSN 0006-341X, 1541-0420. doi: 10.1111/biom.13606. URL https://academic.oup.com/biometrics/article/79/2/1409-1419/7513977.

R. A. Fisher. The design of experiments. *Nature*, 137(3459):252–254, February 1936. ISSN 0028-0836, 1476-4687. doi: 10.1038/137252a0.

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.

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.

Richard Hayes, Helen Ayles, Nulda Beyers, Kalpana Sabapathy, Sian Floyd, Kwame Shanaube, Peter Bock, Sam Griffith, Ayana Moore, Deborah Watson-Jones, Christophe Fraser, Sten H Vermund, Sarah Fidler, and The HPTN 071 (PopART) Study Team. Hptn 071 (popart): Rationale and design of a cluster-randomised trial of the population impact of an hiv combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial. *Trials*, 15(1):57, December 2014. ISSN 1745-6215. doi: 10.1186/1745-6215-15-57.

References II

Richard J. Hayes, Deborah Donnell, Sian Floyd, Nomtha Mandla, Justin Bwalya, Kalpana Sabapathy, Blia Yang, Mwelwa Phiri, Ab Schaap, Susan H. Eshleman, Estelle Piwowar-Manning, Barry Kosloff, Anelet James, Timothy Skalland, Ethan Wilson, Lynda Emel, David Macleod, Rory Dunbar, Musonda Simwinga, Nozizwe Makola, Virginia Bond, Graeme Hoddinott, Ayana Moore, Sam Griffith, Nirupama Deshmane Sista, Sten H. Vermund, Wafaa El-Sadr, David N. Burns, James R. Hargreaves, Katharina Hauck, Christophe Fraser, Kwame Shanaube, Peter Bock, Nulda Beyers, Helen Ayles, and Sarah Fidler. Effect of universal testing and treatment on hiv incidence — hptn 071 (popart). *New England Journal of Medicine*, 381(3):207–218, 2019. ISSN 0028-4793, 1533-4406. doi: 10.1056/NEJMoa1814556.

Michael G Hudgens and M. Elizabeth Halloran. Toward causal inference with interference. *Journal of the American Statistical Association*, 103(482):832–842, 2008. ISSN 0162-1459, 1537-274X. doi: 10.1198/016214508000000292.

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.

Ministry of Health Zambia. Zambia population-based hiv impact assessment (zamphia) 2016. *Lusaka: Ministry of Health*, 2019.

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.

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.

David M. Ritzwoller, Joseph P. Romano, and Azeem M. Shaikh. Randomization inference: Theory and applications, 2024.

References III

Bonnie E. Shook-Sa, Paul N. Zivich, Stephen R. Cole, Nora E. Rosenberg, Michael G. Hudgens, Deborah J. Donnell, Sizulu Moyo, Khangelani Zuma, Helen Ayles, Peter Bock, Joseph J. Eron, Richard J. Hayes, and Jessie K. Edwards. Examining the effect of universal testing and treatment strategies for hiv prevention in zambia and south africa: generalizing the results of the hptn 071 (popart) trial. *Journal of the International AIDS Society*, 28(12):e70062, December 2025. ISSN 1758-2652, 1758-2652. doi: 10.1002/jia2.70062.

L. Simbayi, Khangelani Zuma, S. Moyo, E. Marinda, M. Mabaso, S. Ramlagan, A. North, N. Mohlabane, C. Dietrich, and I. Naidoo. South african national hiv prevalence, incidence, behaviour and communication survey, 2017. *Cape Town: HSRC Press*, 2021.

Leonard A Stefanski and Dennis D Boos. The calculus of m-estimation. *The American Statistician*, 56(1):29–38, February 2002. ISSN 0003-1305, 1537-2731. doi: 10.1198/000313002753631330.

M. Sugiyama, T. Suzuki, and Takafumi Kanamori. Density ratio estimation: A comprehensive review. *RIMS Kokyuroku*, pages 10–31, 01 2010.

Yao Zhang and Qingyuan Zhao. What is a randomization test? *Journal of the American Statistical Association*, 118(544):2928–2942, October 2023. ISSN 0162-1459, 1537-274X. doi: 10.1080/01621459.2023.2199814.

P.N. Zivich, M.C. Eisenberg, A.S. Monto, A. Uzicanin, R. S. Baric, T. P. Sheahan, J. J. Rainey, H. Gao, and A. E. Aiello. Transmission of viral pathogens in a social network of university students: the eX-FLU study. *Epidemiology and Infection*, 148:e267, 2020. ISSN 0950-2688, 1469-4409. doi: 10.1017/S0950268820001806. URL https://www.cambridge.org/core/product/identifier/S0950268820001806/type/journal_article.

Supplement to Project 2: Physical Distancing to Reduce Transmission of Influenza-Like-Illness on College Campuses: the eX-FLU Trial

Brian Richardson, Allison Aiello, Michael Hudgens

Choice of Test Statistic

Test statistics: "proportion of possible transmission events attributable to students in the intervention group:"

$$T^{**}(\mathbf{Z}, \overline{\mathbf{A}}, \overline{\mathbf{Y}}) = \frac{\sum_{k=2}^{\tau} \sum_{i=1}^{n} \sum_{j>i} Z_i E_{ijk}^{**}}{\sum_{k=2}^{\tau} \sum_{i=1}^{n} \sum_{j>i} E_{ijk}^{**}}.$$

	From Infected to Infected	**From Infected**
Contact at $k-1$	$E_{ijk}^{11} = Y_i^{k-1} A_{ij}^{k-1} Y_j^k$	$E_{ijk}^{12} = Y_i^{k-1} A_{ij}^{k-1}$
Contact at k	$E_{ijk}^{21} = Y_i^{k-1} A_{ij}^{k} Y_j^k$	$E_{ijk}^{22} = Y_i^{k-1} A_{ij}^{k}$
Contact at $k-1$ **or** k	$E_{ijk}^{31} = Y_i^{k-1} (A_{ij}^{k-1} \vee A_{ij}^{k}) Y_j^k$	$E_{ijk}^{32} = Y_i^{k-1} (A_{ij}^{k-1} \vee A_{ij}^{k})$
Contact at $k-1$ **and** k	$E_{ijk}^{41} = Y_i^{k-1} (A_{ij}^{k-1} * A_{ij}^{k}) Y_j^k$	$E_{ijk}^{42} = Y_i^{k-1} (A_{ij}^{k-1} * A_{ij}^{k})$

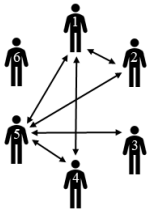
Table: Definitions of a possible transmission event E_{ijk} from student i to student j at time k. Y_i^k is an indicator for student i being infected at week k, A_{ij}^k is an indicator for students i and j being in contact at week k, and $a \vee b$ denotes the maximum of a and b.

Exponential Family Random Graph Models

Goal: model a network ($\mathbf{A}$) given covariates ($\mathbf{X}$)

Exponential Family Random Graph Models

Goal: model a network (**A**) given covariates (**X**)



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3	0	0	0	0	1	0
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6	0	0	0	0	0	0

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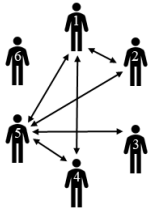
An **ERGM** assumes:

$$\Pr_{\theta}(\mathbf{A} = \mathbf{a} | \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}}{\kappa(\theta, \mathcal{A}, \mathbf{x})}$$



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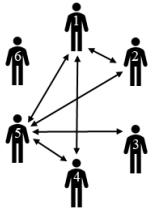

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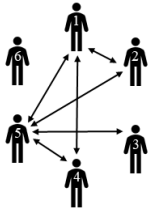

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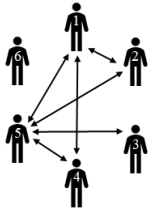

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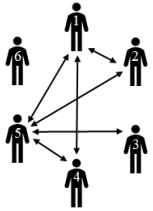

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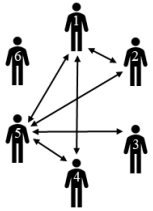
  - number of edges



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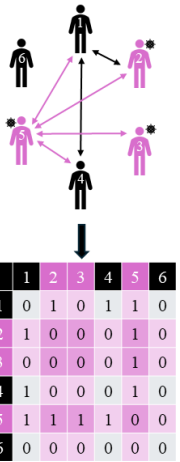
- $\mathbf{g}(\mathbf{a}, \mathbf{x})$: sufficient statistics
  - number of edges
  - number of edges touching treated students



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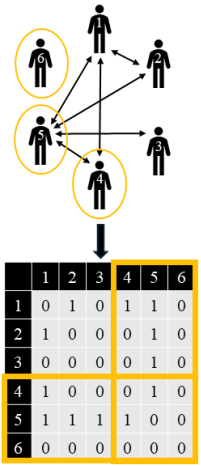
  - number of edges touching treated students
  - number of edges touching infected students



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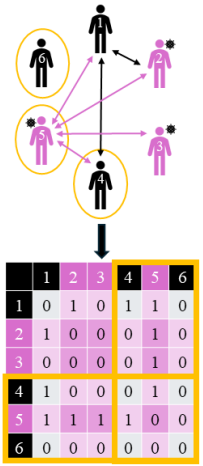
  - number of edges touching infected students
  - number of edges touching treated $\times$ infected students



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ERGM Model Formulation

$$\Pr_{\theta}(\mathbf{A} = \mathbf{a} | \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}}{\kappa(\theta, \mathcal{A}, \mathbf{x})},$$

$$\kappa(\theta, \mathcal{A}, \mathbf{x}) = \sum_{\mathbf{a} \in \mathcal{A}} \exp\{\theta \cdot \mathbf{g}(\mathbf{a}, \mathbf{x})\}$$

For example, in the simulation study and eX-FLU application,

$$\mathbf{g}(\mathbf{a}, \mathbf{x}) = \begin{bmatrix} \text{\# edges} \\ \text{\# edges touching a treated node} \\ \text{\# edges touching an infected node} \\ \text{\# edges touching a treated and infected node} \\ \text{\# edges between roommate pairs} \end{bmatrix} = \begin{bmatrix} \sum_{i,j} a_{ij} \\ \sum_{i,j} a_{ij}(z_i + z_j) \\ \sum_{i,j} a_{ij}(y_i + y_j) \\ \sum_{i,j} a_{ij}(z_i y_i + z_j y_j) \\ \sum_{i,j} a_{ij} \mathbb{1}(i, j \text{ roomates}) \end{bmatrix}$$

ERGM Change Statistic Model Formulation

- **Change statistic**: $\delta_{\mathbf{g}}(\mathbf{a}, \mathbf{x})_{ij} = \mathbf{g}(\mathbf{a}_{ij}^{+}, \mathbf{x}) - \mathbf{g}(\mathbf{a}_{ij}^{-}, \mathbf{x})$ is the change in network statistic that would occur if a_{ij} were changed from 0 to 1
  - where $\mathbf{a}_{ij}^{+}$ and $\mathbf{a}_{ij}^{-}$ represent the network $\mathbf{a}$ with dyad a_{ij} set to 1 or 0, respectively
- Then the equivalent ERGM specification is

$$\text{logit}\{\Pr_{\theta}(A_{ij} = 1 | \mathbf{A}_{ij}^{C} = \mathbf{a}_{ij}^{C}, \mathbf{X} = \mathbf{x})\} = \theta^{k} \delta_{\mathbf{g}}(\mathbf{a}, \mathbf{x})_{ij}$$

  - where $\mathbf{A}_{ij}^{C}$ represents all dyads in $\mathbf{A}$ except A_{ij}
- **Interpretation of** θ: the change in conditional log-odds of the network associated with a one-unit increase in the corresponding component of $\mathbf{g}(\mathbf{a}, \mathbf{x})$ resulting from switching a particular dyad A_{ij} from 0 to 1 and leaving the rest of the network fixed at $\mathbf{A}_{ij}^{C}$

Dyadic Independence EGRMs

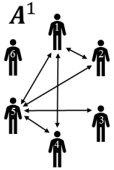
- **Dyadic independence term**: a component g of $\mathbf{g}$ in an ERGM for which the corresponding change statistic $\delta_g(\mathbf{a}, \mathbf{x})_{ij}$ can be calculated for any i, j without knowing $\mathbf{a}$
  - For example, if $g(\mathbf{a}, \mathbf{x}) = \sum_{i,j} a_{ij}(Z_i + Z_j)$ counts the number of edges touching treated nodes, then $\delta_g(\mathbf{a}, \mathbf{x})_{ij} = z_i + z_j$ doesn't depend on $\mathbf{a}$
- **Dyadic independence ERGM**: an ERGM with only dyadic independence terms
  - replace $\delta_g(\mathbf{a}, \mathbf{x})_{ij}$ with $\delta_g(\mathbf{x})_{ij}$ and write the model as

$$\text{logit}\{\Pr(A_{ij} = 1 | \mathbf{X} = \mathbf{x})\} = \theta \cdot \delta_g(\mathbf{x})_{ij}$$

- **Interpretation of** θ: the change in log-odds of the network associated with a one-unit increase in the corresponding component of $\mathbf{g}(\mathbf{a}, \mathbf{x})$ resulting from switching a particular dyad A_{ij} from 0 to 1

Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:



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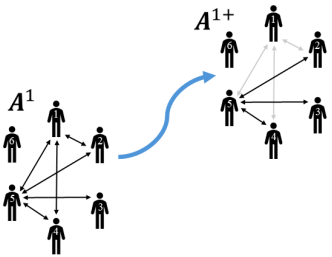
- New edges form according to a **formation** ERGM

$$\Pr_{\theta^+}(\mathbf{A}^{k+} = \mathbf{a}^{k+} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^+ \cdot \mathbf{g}^+(\mathbf{a}^{k+}, \mathbf{x})\}}{\kappa\{\theta^+, \mathcal{A}^+(\mathbf{a}^k), \mathbf{x}\}}$$

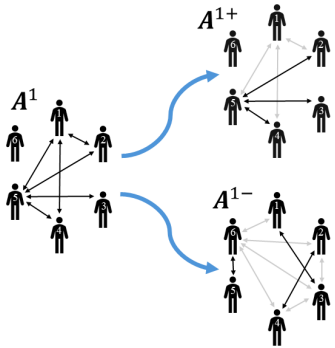


Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:

- New edges form according to a **formation** ERGM
- Old edges persist according to a **persistence** ERGM

$$\Pr_{\theta^-}(\mathbf{A}^{k-} = \mathbf{a}^{k-} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^- \cdot \mathbf{g}^-(\mathbf{a}^{k-}, \mathbf{x})\}}{\kappa\{\theta^-, \mathcal{A}^-(\mathbf{a}^k), \mathbf{x}\}}.$$

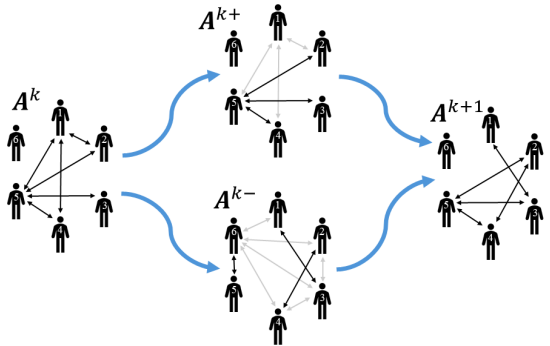


Separable Temporal Exponential Family Random Graph Models

A **STERGM** assumes that, at each time step $k = 1, \ldots, \tau - 1$:

- New edges form according to a **formation** ERGM
- Old edges persist according to a **persistence** ERGM
- The network at time step $k + 1$ is the result of formation and persistence

$$\mathbf{A}^{k+1} = \underbrace{\mathbf{A}^k}_{\text{previous network}} \cup \underbrace{(\mathbf{A}^{k+} - \mathbf{A}^k)}_{\text{new edges formed}} - \underbrace{(\mathbf{A}^k - \mathbf{A}^{k-})}_{\text{old edges not persisting}}$$



STERGM Model Formulation

- **Formation model** is an ERGM conditional on only adding edges:

$$\Pr_{\theta^+}(\mathbf{A}^{k+} = \mathbf{a}^{k+} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^+ \cdot \mathbf{g}^+(\mathbf{a}^{k+}, \mathbf{x})\}}{\kappa\{\theta^+, \mathcal{A}^+(\mathbf{a}^k), \mathbf{x}\}}$$

  - $\mathcal{A}^+(\mathbf{a})$: space of possible networks that can be formed by adding edges to $\mathbf{a}$

- **Persistence model** is an ERGM conditional on only removing edges:

$$\Pr_{\theta^-}(\mathbf{A}^{k-} = \mathbf{a}^{k-} | \mathbf{A}^k = \mathbf{a}^k, \mathbf{X} = \mathbf{x}) = \frac{\exp\{\theta^- \cdot \mathbf{g}^-(\mathbf{a}^{k-}, \mathbf{x})\}}{\kappa\{\theta^-, \mathcal{A}^-(\mathbf{a}^k), \mathbf{x}\}}$$

  - $\mathcal{A}^-(\mathbf{a})$: space of possible networks that can be formed by removing edges to $\mathbf{a}$

- A **STERGM** assumes the network at time $k+1$ is then the result of applying the changes in $\mathbf{A}^{k+}$ and $\mathbf{A}^{k-}$ to $\mathbf{A}^k$:

$$\mathbf{A}^{k+1} = \underbrace{\mathbf{A}^k}_{\text{previous network}} \cup \underbrace{(\mathbf{A}^{k+} - \mathbf{A}^k)}_{\text{new edges formed}} - \underbrace{(\mathbf{A}^k - \mathbf{A}^{k-})}_{\text{old edges not persisting}}$$

Separability of STERGMs

1. $\mathbf{A}^{k+} \perp\!\!\!\perp \mathbf{A}^{k-} | \mathbf{A}^{k}$, i.e., the formation and persistence processes are conditionally independent give the network at time k

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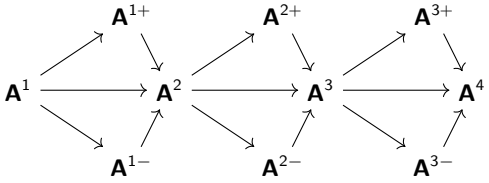
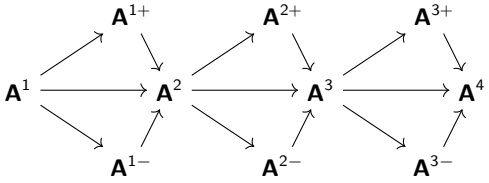


Separability of STERGMs

1. $\mathbf{A}^{k+} \perp\!\!\!\perp \mathbf{A}^{k-} | \mathbf{A}^{k}$, i.e., the formation and persistence processes are conditionally independent give the network at time k
2. the parameter space for $\theta = (\theta^{+}, \theta^{-})$ is the product of the parameter spaces for θ^{+} and θ^{-}



Simulation Setup

- $n \in \{24, 48\}$ students were equally divided into two residence halls, each with six clusters of equal size
- Within each residence hall group, the clusters were randomized using a 50:50 allocation to either the intervention group or the control group
- Five pairs of students were randomly selected to be roommates, meaning they had contact with each other each week
- Baseline ($k = 1$) face-to-face contacts were simulated between each pair of students with probability 0.5
- Baseline infection statuses were simulated for each student with probability 0.5
- Social networks were simulated over the remaining $\tau \in \{5, 10\}$ weeks according to a STERGM with both formation and persistence models including edge count, intervention assignment Z, infection status Y, $Z \times Y$ interaction, and an offset to force constant edges between roommates
- Infection statuses were simulated for each student i at each week $k \in \{2, \ldots, \tau\}$ with probability $\Pr\left(Y_i^k = 1 | \overline{\mathbf{A}}^{k-1}, \overline{\mathbf{Y}}^{k-1}\right) = h_i(\mathbf{S}^{k-1})$ depending on the vector $\mathbf{S}^{k-1} = \mathbf{A}^{k-1}\mathbf{Y}^{k-1}$ of counts of infected contacts for each student at week $k - 1$.

Simulation Setup

Three scenarios:

Null Hypothesis	Formation Model Parameters θ^+	Persistence Model Parameters θ^-	Infection Probability Function h_i
$H_0^\sharp$	$(-0.5, 0, 0, 0)$	$(-0.5, 0, 0, 0)$	$h_i(\mathbf{s}) = 0.5$
$\overline{H_0^A} \cap H_0^Y$	$(-0.2, 0, 0, -1)$	$(-0.2, 0, 0, -1)$	$h_i(\mathbf{s}) = 0.5$
$\overline{H_0^A} \cap \overline{H_0^Y}$	$(-0.2, 0, 0, -1)$	$(-0.2, 0, 0, -1)$	$h_i(\mathbf{s}) = \frac{n}{2}\text{expit}(s_i - \bar{s}) / \sum_{j=1}^n \text{expit}(s_j - \bar{s})$

Table: The null hypothesis refers to the null hypothesis that is true under the data generating process, formation model parameters are $\theta^+ = (\theta^+_{\text{edges}}, \theta^+_Z, \theta^+_Y, \theta^+_{ZY})$, persistence model parameters are $\theta^- = (\theta^-_{\text{edges}}, \theta^-_Z, \theta^-_Y, \theta^-_{ZY})$, the infection probability function $h_i(\mathbf{s})$ gives the probability of student i being infected at week k given the vector $\mathbf{S}^{k-1} = \mathbf{s} = (s_1, \ldots, s_n)$ of infected contact counts for each student at week $k-1$, and $\bar{s} = n^{-1} \sum_{i=1}^n s_i$.

Three p-values:

- $\rho_B^\sharp$: testing the sharp null
- ρ_B^Y: testing H_0^Y using known q
- $\widehat{\rho}_B^Y$: testing H_0^Y using estimated q

Simulation Study

Goal: use simulated data to investigate the performance of our testing procedure

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- $n \in \{24, 48\}$ students
- $\tau \in \{5, 10\}$ weeks
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- $n \in \{24, 48\}$ students
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- Three scenarios:
  1. $H_0^\sharp$: no effect of intervention on networks or infection
  2. $\overline{H}_0^A \cap H_0^Y$: no effect of intervention on infection
  3. $\overline{H}_0^A \cap \overline{H}_0^Y$: effect of intervention on both networks and infection

Simulation Study

Goal: use simulated data to investigate the performance of our testing procedure

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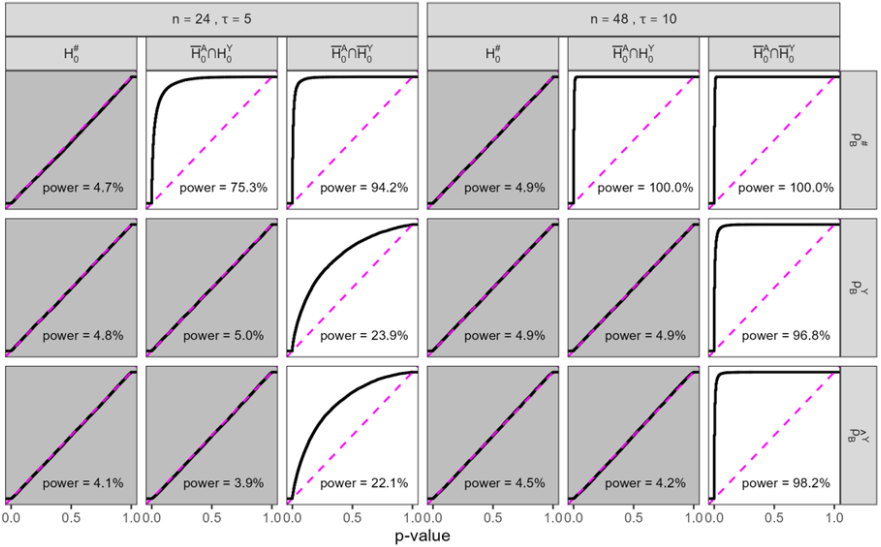
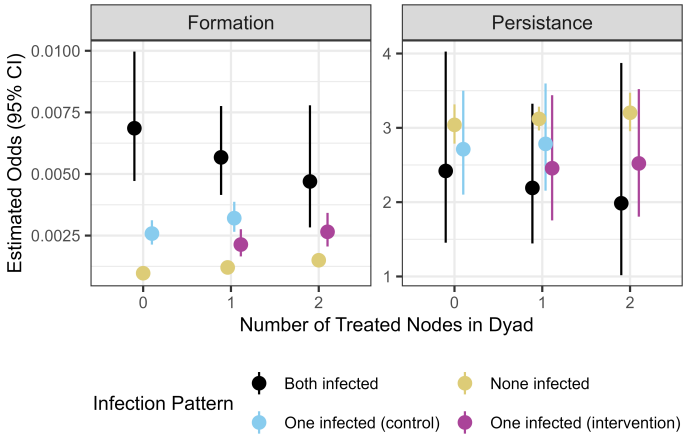
  3. $\overline{H}_0^A \cap \overline{H}_0^Y$: effect of intervention on both networks and infection
- Three testing procedures:
  1. $\rho_B^\sharp$: testing $H_0^\sharp$
  2. ρ_B^Y: testing H_0^Y using known q
  3. $\widehat{\rho}_B^Y$: testing H_0^Y using estimated q

Simulation Results: Empirical CDF of P-Values



eX-FLU: STERGM Results



Type I Error Control

- **Proposition 2.1**: Let T_N be a test statistic with CDF F_N under H_0.
  1. Under H_0, $F_N(T_N)$ stochastically dominates a Uniform$(0,1)$ distribution for any N.
  2. If the test statistic T_N has a continuous limiting distribution, then $F_N(T_N) \to^d$ Uniform$(0,1)$.
- **Corollary 2.2**:
  1. Under $H_0^\sharp$, the sharp null p-value $\rho_N^\sharp$ stochastically dominates a Uniform$(0,1)$ distribution for any N.
  2. Under H_0^Y, the oracle p-value ρ_N^Y stochastically dominates a Uniform$(0,1)$ distribution for any N.
  3. If the test statistic T_N has a continuous limiting distribution, then $\rho_N^\sharp \to^d$ Uniform$(0,1)$ under $H_0^\sharp$ and $\rho_N^Y \to^d$ Uniform$(0,1)$ under H_0^Y.

Type I Error Control

- **Proposition 2.3**: Let $q(\mathbf{a}, \mathbf{z}, \theta) \equiv \Pr\{\mathbf{A}(\mathbf{z}) = \mathbf{a}; \theta\}$ denote the PMF of the distribution of stochastic potential networks $\mathbf{A}(\mathbf{z})$ at parameter value θ, let $\widehat{\theta}_N$ denote the estimator of θ, and let $F_N(\cdot; \theta)$ denote the CDF of the test statistic T_N at θ, with limiting CDF $F(\cdot; \theta)$. Let θ_0 denote the true value of θ. Assume the following:

(A1) $\widehat{\theta}_N \to^p \theta_0$

(A2) $F(t; \theta_0)$ is continuous in t on $\mathbb{R}$

(A3) there exists a $\delta_0 > 0$ such that

$$\sup_{\theta \in B_{\delta_0}(\theta_0)} \sup_{t \in \mathbb{R}} |F_N(t; \theta) - F(t; \theta)| \to 0$$

(A4) $F(t; \theta)$ is continuous in θ at θ_0 uniformly in t, i.e.,

$$\lim_{\theta \to \theta_0} \sup_{t \in \mathbb{R}} |F(t; \theta) - F(t; \theta_0)| = 0$$

Then the plug-in p-value $\widehat{\rho}_N^Y$ converges in distribution to Uniform$(0, 1)$.

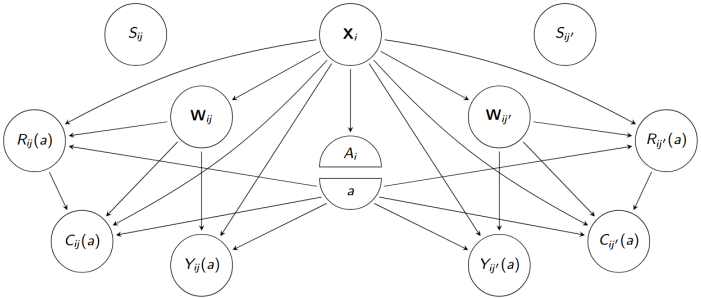
Type I Error Control

- **Proposition 2.4**: Let $\rho_N = F_N(T_N)$ for test statistic T_N and CDF F_N (not necessarily the true CDF of T_N). Let $T_N^* = h_N(T_N)$ for a sequence of deterministic, strictly increasing functions h_N. Define $F_N^*(t) = F_N\{h_N^{-1}(t)\}$, the (not necessarily true) CDF of the transformed test statistic, and let $\rho_N^* = F_N^*(T_N^*)$. Then $\rho_N^* = \rho_N$.
- **Corollary 2.5**: Let h_N be a sequence of deterministic, strictly increasing functions.
  1. If the hypotheses of Proposition 2.1 are met for a test statistic T_N, then the results also hold for $T_N^* = h_N(T_N)$.
  2. If the hypotheses of Proposition 2.3 are met for $T_N, F_N(\cdot;\theta)$, then the results also hold for $T_N^* = h_N(T_N), F_N^*(\cdot;\theta) = F_N\{h_N^{-1}(\cdot);\theta\}$.

Supplement to Project 3 : Causal Inference from Cluster Randomized Trials with Differential Nonresponse

Brian Richardson, Bonnie Shook-Sa, Michael Hudgens

Assumptions



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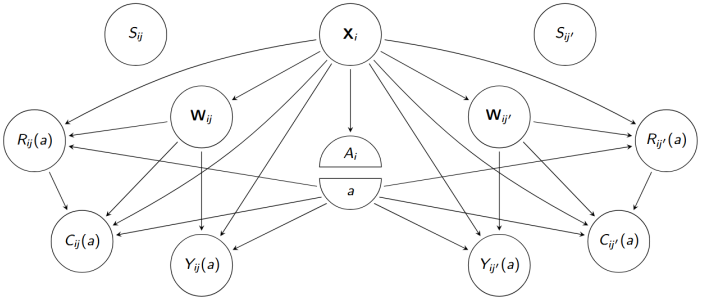

Assumptions

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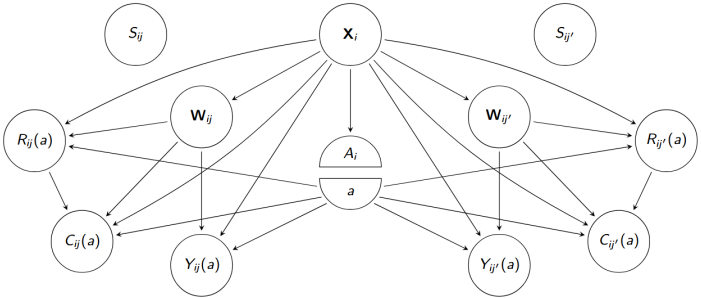
  - **Cluster-randomization**: $A_i \perp\!\!\!\perp (\mathbf{W}_{ij}, \ldots, \mathbf{W}_{in_i}) | \mathbf{X}_i$



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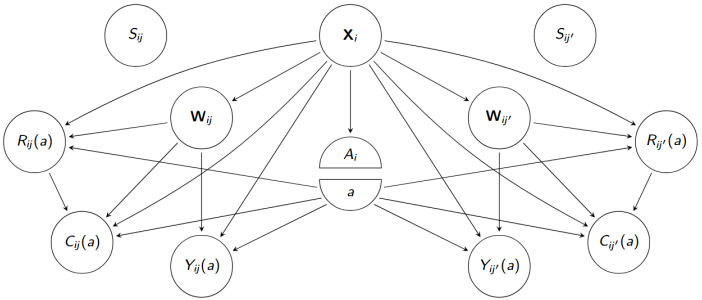
  - **Independent random sampling of trial and auxiliary data**: $S_{ij} \perp\!\!\!\perp (A_i, \mathbf{X}_i, \mathbf{W}_{ij}, R_{ij}, C_{ij}, Y_{ij})$



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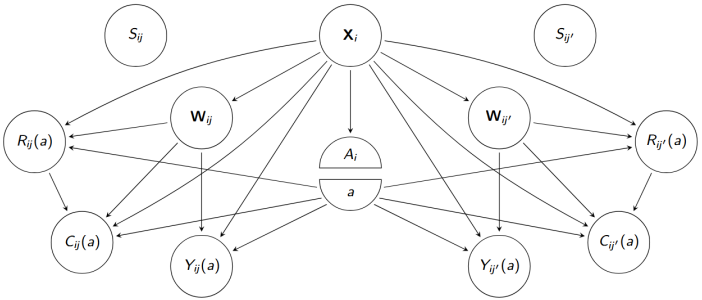

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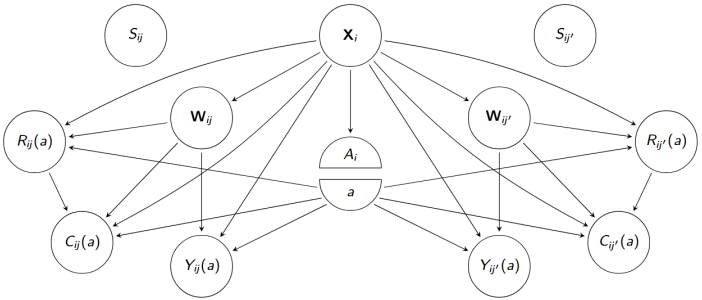

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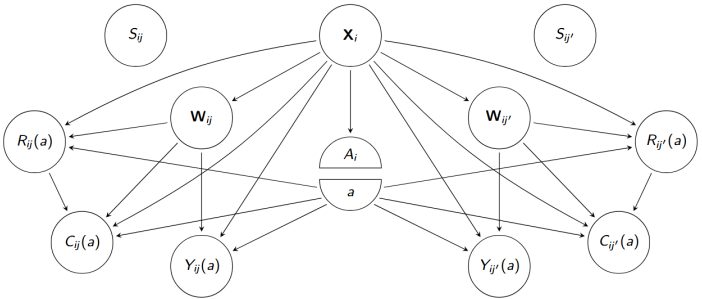
  - **Conditional exchangeability**: $Y_{ij}(a) \perp\!\!\!\perp A_i | \mathbf{X}_i, \mathbf{W}_{ij}$



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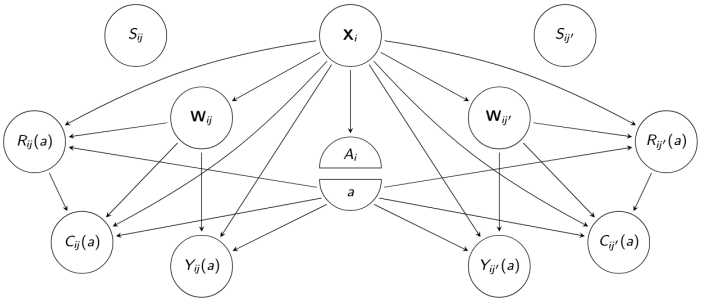
  - **Conditional exchangeability**: $Y_{ij}(a) \perp\!\!\!\perp A_i | \mathbf{X}_i, \mathbf{W}_{ij}$
  - **Positivity of treatment assignment**: $\Pr(A_i = a | \mathbf{X}_i = \mathbf{x}) > 0 \; \forall \, \mathbf{x}$ with positive density $f_{\mathbf{X}}(\mathbf{x}) > 0$.



Assumptions

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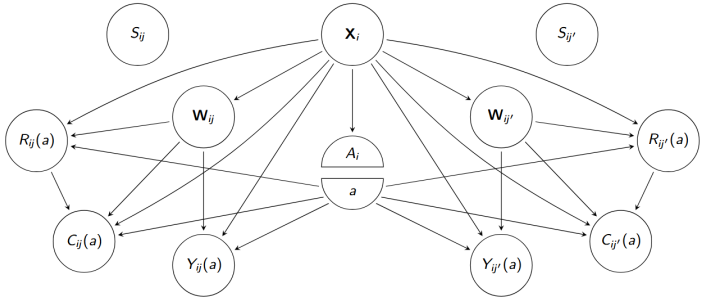
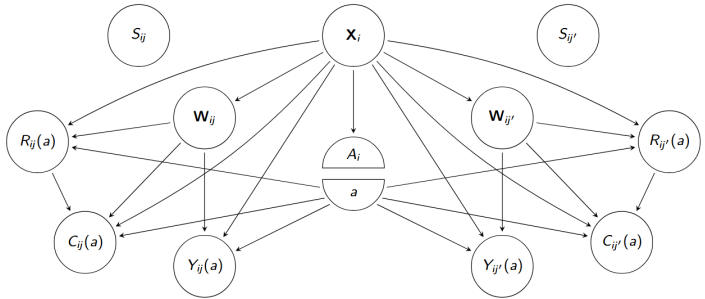


Assumptions

- Additional assumptions
  - **Positivity of uncensored response**:
    $\Pr(R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, A_i = a, \mathbf{W}_{ij} = \mathbf{w}) > 0 \; \forall \, \mathbf{x}, \mathbf{w}$ with $f_{\mathbf{X},\mathbf{W}}(\mathbf{x}, \mathbf{w}) > 0$



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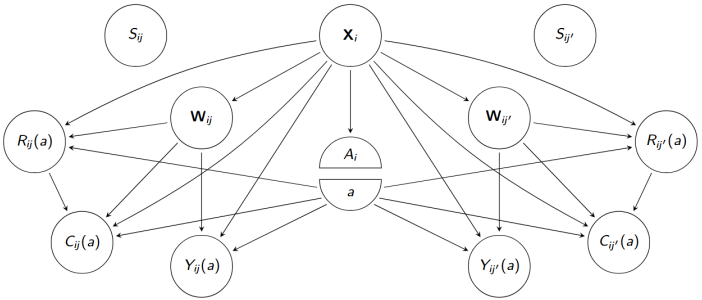
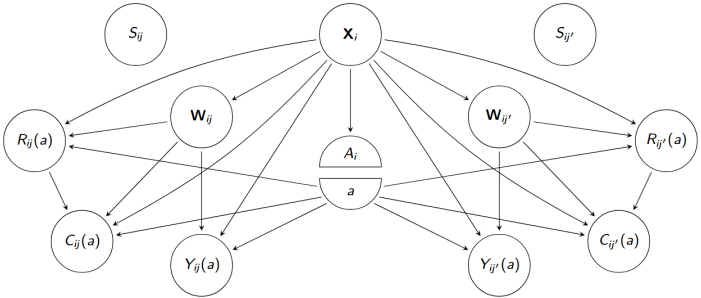
- Additional assumptions
  - **Positivity of uncensored response**:
    $\Pr(R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, A_i = a, \mathbf{W}_{ij} = \mathbf{w}) > 0 \; \forall \, \mathbf{x}, \mathbf{w}$ with $f_{\mathbf{X},\mathbf{W}}(\mathbf{x}, \mathbf{w}) > 0$
  - **Conditional independence of potential outcome and response**: $Y_{ij}(a) \perp\!\!\!\perp R_{ij}(a) | A_i, \mathbf{X}_i, \mathbf{W}_{ij}$



Assumptions

- Additional assumptions
  - **Positivity of uncensored response**:
    $\Pr(R_{ij} = 1, C_{ij} = 0 | \mathbf{X}_i = \mathbf{x}, A_i = a, \mathbf{W}_{ij} = \mathbf{w}) > 0 \; \forall \, \mathbf{x}, \mathbf{w}$ with $f_{\mathbf{X},\mathbf{W}}(\mathbf{x}, \mathbf{w}) > 0$
  - **Conditional independence of potential outcome and response**: $Y_{ij}(a) \perp\!\!\!\perp R_{ij}(a) | A_i, \mathbf{X}_i, \mathbf{W}_{ij}$
  - **Conditional independence of potential outcome and censoring among responders**:
    $Y_{ij}(a) \perp\!\!\!\perp C_{ij}(a) | A_i, \mathbf{X}_i, \mathbf{W}_{ij}, R_{ij} = 1$



Simulation Details

- $m = 20$ clusters
  - cluster treatment $\Pr(A = 1) = 0.5$
  - cluster covariate $X \sim N(0, 1)$
- invited trial sample of size $n^{\text{trial}} \in \{500, 5000\}$
- individual covariates $W_1 \sim \text{Bernoulli}(0.5)$, $W_2 \sim N(0, 1)$
- potential outcomes

$$Y(0) \sim \text{Bernoulli}\{\text{expit}(-0.5 + 0.25X_1 + 0.5W_1 + 0.5W_2)\},$$
$$Y(1) \sim \text{Bernoulli}\{\text{expit}(0 - 1W_1 - 0.5W_2)\}$$
$$\implies \text{treatment is marginally protective, but harmful when } W_1 = 0$$

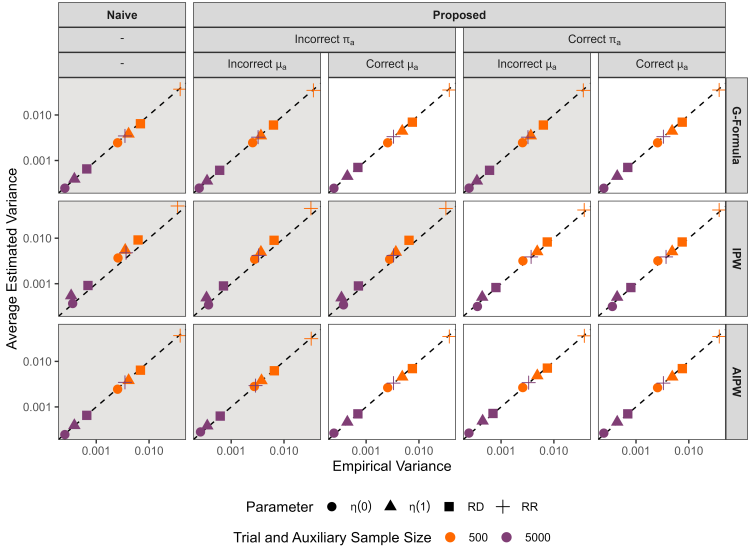
- observed outcomes $Y = (1 - A)Y(0) + AY(1)$
- response $R \sim \text{Bernoulli}\{\text{expit}(\alpha_0 - 2AW_1)\}$

  $\implies$ marginal $\Pr(R = 1) = 0.5$, but higher response rate if $W_1 = 0$
- auxiliary sample of size $n^{\text{aux}} \in \{500, 5000\}$
  - same covariates W_1, W_2

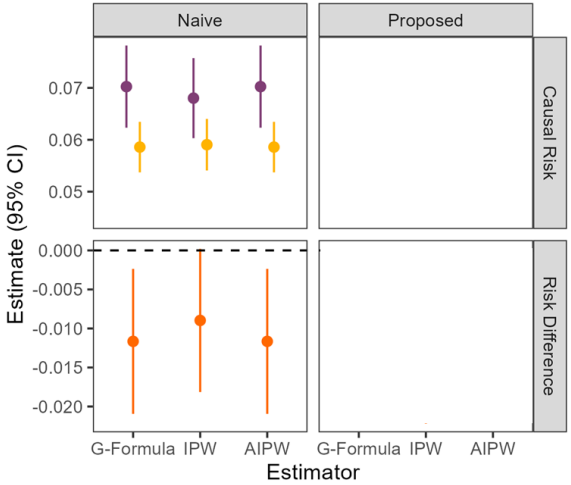
Simulation Details

- naive and proposed versions of the g-formula, IPW, and AIPW estimators of $\eta(a)$
  - naive versions used trial data only, and ignored nonresponse
- Estimand: $RD = \eta(1) - \eta(0)$
- Estimator: $\widehat{RD} = \widehat{\eta}(1) - \widehat{\eta}(0)$
  - variance estimated using the delta method
- Outcome model specification
  - μ_a correctly modeled with logistic regression with covariates X, W_1, W_2 and their interaction with treatment A
  - μ_a mis-specified by excluding the covariate W_1 and its interaction with A
- Joint propensity score model specification
  - censoring mechanism π_a^C always correctly specified as logistic regression with covariates X, W_1, W_2 and their interaction with treatment A
  - response mechanism π_a^{AR} possibly mis-specified by incorrectly assuming $R_{ij} \perp\!\!\!\perp A_i | \mathbf{X}_i, \mathbf{W}_{ij}$

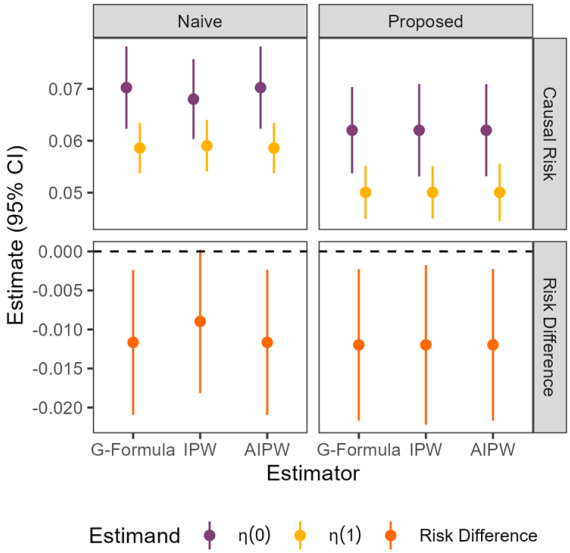
Simulation: Variance Estimation



Supplemental Analysis: Arms A/B vs Standard of Care



Supplemental Analysis: Arms A/B vs Standard of Care



Supplement to Project 1 : Addressing Confounding and Continuous Exposure Measurement Error Using Corrected Score Functions

Brian Richardson, Brian Blette, Peter Gilbert, Michael Hudgens

Corrected Score Functions: What?

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

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

- Define the corrected score function as

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

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

- Then

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

Corrected Score Functions: Why?

The key result (Novick and Stefanski, 2002) for corrected score functions is that, for a smooth enough function $\mathbf{f}$, the function $\widetilde{\mathbf{f}}$ defined by

$$\widetilde{\mathbf{f}}(\mathbf{A}^*) \equiv \mathrm{E}[\mathrm{Re}\{\mathbf{f}(\mathbf{A}^* + i\widetilde{\epsilon})\}|\mathbf{A}, \mathbf{A}^*]$$

does not depend on $\mathbf{A}$ and satisfies

$$\mathrm{E}\{\widetilde{\mathbf{f}}(\mathbf{A}^*)|\mathbf{A}\} = \mathbf{f}(\mathbf{A}).$$

The proof of this for the special case $f(\mathbf{A}) = \exp(\mathbf{c}\mathbf{A}^T)$ is illustrative.

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp(\mathbf{c}\mathbf{A}^T)$.

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp\left(\mathbf{c}\mathbf{A}^T\right)$.

$$\begin{aligned}\widetilde{f}(\mathbf{A}^*) &\equiv \mathrm{E}(\mathrm{Re}[\exp\{\mathbf{c}(\mathbf{A}^* + i\widetilde{\epsilon})^T\}]|\mathbf{A}, \mathbf{A}^*) \\ &= \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\mathrm{Re}[\underbrace{\mathrm{E}\{\exp\left(i\mathbf{c}\widetilde{\epsilon}^T\right)\}}_{\text{normal c.f.}}] = \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\exp\left(-\frac{1}{2}\mathbf{c}\boldsymbol{\Sigma}_{me}\mathbf{c}^T\right)\end{aligned}$$

Corrected Score Functions: Why?

CLAIM: $\mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} = f(\mathbf{A})$ for $f(\mathbf{A}) = \exp\left(\mathbf{c}\mathbf{A}^T\right)$.

$$\begin{aligned}
\widetilde{f}(\mathbf{A}^*) &\equiv \mathrm{E}(\mathrm{Re}[\exp\{\mathbf{c}(\mathbf{A}^* + i\widetilde{\epsilon})^T\}]|\mathbf{A}, \mathbf{A}^*) \\
&= \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\mathrm{Re}[\underbrace{\mathrm{E}\{\exp\left(ic\widetilde{\epsilon}^T\right)\}}_{\text{normal c.f.}}] = \exp\left(\mathbf{c}\mathbf{A}^{*T}\right)\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
\implies \mathrm{E}\{\widetilde{f}(\mathbf{A}^*)|\mathbf{A}\} &= \mathrm{E}\{\exp\left(\mathbf{c}\mathbf{A}^{*T}\right)|\mathbf{A}\}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \mathrm{E}\{\exp\{\mathbf{c}(\mathbf{A}^T + \epsilon^T)\}|\mathbf{A}\}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right)\underbrace{\mathrm{E}\{\exp\left(\mathbf{c}\epsilon^T\right)\}}_{\text{normal m.g.f.}}\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right)\exp\left(\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right)\exp\left(-\frac{1}{2}\mathbf{c}\mathbf{\Sigma}_{me}\mathbf{c}^T\right) \\
&= \exp\left(\mathbf{c}\mathbf{A}^T\right) = f(\mathbf{A})
\end{aligned}$$