Improving Heterogeneous Treatment Effect Estimation with Data Borrowing under Covariates Mismatch

Samhita Pal

Joint work with Dr. Amir Asiaee and Dr. Jared Huling

Vanderbilt University Medical Center

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Overview

Introduction

Motivation: Heterogeneous Treatment Effects in Trials

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- However, **most RCTs are powered for average effects** rather than the fine-grained heterogeneity that guides individualized decisions.
- **Integrating information from large observational studies (OS)** has the potential to sharpen HTE estimation in RCTs.
- **Problem:** Integration of RCT and OS is not straight forward since
  - OS are vulnerable to confounding;
  - OS and RCT often observe different (overlapping) sets of covariates.

RCT and OS integration

- **Goal:** Efficient and consistent estimation of the conditional average treatment effect (CATE) in the trial population,

$$\tau^r(\boldsymbol{x}) = \mathbb{E}\big\{ Y(1) - Y(-1) \mid \boldsymbol{X} = \boldsymbol{x},\ S = r \big\},$$

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  - **MR-OSCAR**: additionally leverages OS-only covariates under covariate mismatch to further improve on both RACER and R-OSCAR.

Innovation

- Prior work has mostly focused on borrowing **control arms** to reduce the variance of the treatment effect.
- Existing methods often assume that **CATEs are transportable** between populations.
- **Gap in the literature:** methods for efficient CATE estimation in an RCT that
  - reliably leverage **both treatment arms** from the OS, and
  - relax the **transportability** assumption.

RACER: a method for estimating the CATE from RCT data

Pseudo-outcomes: turning CATE into a regression problem

- Idea: construct a pseudo-outcome whose conditional mean is the CATE in the RCT, then estimate that conditional mean by regression.
- Given augmentation $m(X)$ and randomization probabilities $\pi_A(X)$, define

$$\tau_m(X, A, Y) = \frac{A\{Y - m(X)\}}{\pi_A(X)}.$$

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- **Key fact 3:** for any x, the true CATE $\tau(x)$ minimizes the following conditional risk: $\tau(x) = \arg\min_f E_{Y,A}[(\tau_m(x, A, Y) - f(x))^2 \mid X = x]$.

Estimation as Empirical Risk Minimizer.

$$\hat{\tau}^r(\cdot) = \arg\min_{f \in \mathcal{F}} \frac{1}{n^r} \sum_{i=1}^{n^r} \left\{ \tau_m(X_i^r, A_i^r, Y_i^r) - f(X_i^r) \right\}^2.$$

$$m(x) := \hat{\mu}^r(x) = \sum_a \pi^r_{-a}(x) \hat{\mu}^r_a(x), \quad \hat{\mu}^r_a(x) \in \mathcal{M}^r_a,$$

- At the population level the minimizer is $\tau^r(\cdot)$, so this is a standard regression of pseudo-outcomes on X.
- Crucially, the estimator's risk depends on the choice of augmentation function m.
- Our key insight is that the risk minimizing choice is the CMO.
- This shows that a more accurate estimation of the CMO (as m) reduces CATE estimation error.

R-OSCAR: A Method for Borrowing Data from an OS for CATE Estimation with Perfect Covariate Alignment

- Since the CMO is a weighted average of $\mu^r_{+1}(x)$ and $\mu^r_{-1}(x)$, improving its estimation requires accurate estimation of these per-arm outcomes.

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- A direct but potentially suboptimal approach would set $m(x) := \sum_a \pi^r_{-a}(x)\hat{\mu}^o(x, a)$, where $\hat{\mu}^o(x, a)$ is an outcome mean estimate derived from OS data and applied to RCT covariates.

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- But, $\forall a, x : \mu^r_a(x) \neq \mu^o(x,a)$.
- To account for this bias, we introduce an outcome mean discrepancy defined as $\delta_a(x) \equiv \mu^r_a(x) - \mu^o(x,a) \implies \mu^r_a(x) = \delta_a(x) + \mu^o(x,a)$.

R-OSCAR Stage 1: OS Outcome Model

Input: OS data $\{(\boldsymbol{X}_j, A_j, Y_j)\}_{j=1}^{n_o}$.

For each arm $a \in \{-1, +1\}$:

$$\underbrace{\hat{\mu}_a^o(\boldsymbol{x})}_{\text{estimate OS predictor}} = \arg\min_{\mu \in \mathcal{M}_a^o} \frac{1}{n_a^o} \sum_{\substack{i \in OS: \\ A_i = a}} \big(Y_i - \mu(\boldsymbol{X}_i)\big)^2$$

- Learns outcome-covariate relationship from the large OS
- May be biased for the RCT population due to distributional differences
- In practice: ridge regression, random forest, or neural network
- **Next:** Learn a discrepancy function from RCT data to correct the OS predictions.

R-OSCAR Stage 2: Outcome Calibration

$$\underbrace{\hat{\delta}_a^t}_{\text{RCT correction / transport}} \in \arg\min_{d \in \mathcal{D}_a} \frac{1}{n_a^r} \sum_{\substack{i \in RCT: \\ A_i = a}} \Big(Y_i - \underbrace{\hat{\mu}_a^o(\boldsymbol{X}_i)}_{\substack{\text{OS fit} \\ \text{evaluated on RCT X}}} - d(\boldsymbol{X}_i) \Big)^2 + \underbrace{\mathcal{P}_{\text{cal}}(d)}_{\substack{\text{shrink discrepancy} \\ \text{toward 0}}}$$

The calibrated prediction: $\underbrace{\hat{\mu}_a^{\text{cal}}(\boldsymbol{x})}_{\text{OS + correction}} = \hat{\mu}_a^o(\boldsymbol{x}) + \underbrace{\hat{\delta}_a^t(\boldsymbol{x})}_{\text{add discrepancy}}$

- If OS model is nearly correct for RCT: $\underbrace{\hat{\delta}_a^t \approx 0}_{\text{strong borrowing}}$
- If OS model is poor: $\underbrace{\hat{\delta}_a^t}_{\text{absorbs mismatch}}$

R-OSCAR Stages 3-4: CMO and CATE Calibration I

Stage 3: Form the calibrated CMO and pseudo-outcomes:

$$\underbrace{\hat{m}(\boldsymbol{x})}_{\text{baseline mean (CMO)}} = \sum_a \pi^r_{-a}(\boldsymbol{x})\, \hat{\mu}^{\text{cal}}_a(\boldsymbol{x})$$

$$\underbrace{\hat{\psi}_i}_{\text{RCT pseudo-outcome}} = \frac{A_i\big(Y_i - \hat{m}(\boldsymbol{X}_i)\big)}{\pi^r_{A_i}(\boldsymbol{X}_i)}$$

Stage 4: The preliminary CATE is

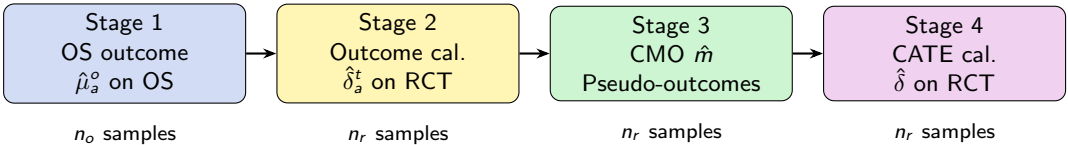
$$\underbrace{\tilde{\tau}(\boldsymbol{x})}_{\text{difference in calibrated means}} = \sum_a a\, \hat{\mu}^{\text{cal}}_a(\boldsymbol{x})$$

R-OSCAR Stages 3-4: CMO and CATE Calibration II

Estimate a CATE correction:

$$\underbrace{\hat{\delta}}_{\text{final RCT calibration}} \in \arg\min_{d \in \mathcal{D}} \frac{1}{n_r} \sum_{i \in RCT} \left(\hat{\psi}_i - \tilde{\tau}(\boldsymbol{X}_i) - d(\boldsymbol{X}_i)\right)^2 + \mathcal{P}_\tau(d)$$

$$\underbrace{\hat{\tau}_{\text{R-OSCAR}}(\boldsymbol{x})}_{\text{final CATE}} = \tilde{\tau}(\boldsymbol{x}) + \underbrace{\hat{\delta}(\boldsymbol{x})}_{\text{add correction}}$$



MR-OSCAR: A Method for Borrowing Data from an OS for CATE Estimation under Covariate Mismatch

Two Data Sources, Three Covariate Blocks

RCT ($S = r$, small n_r):

- Randomized treatment $A \in \{-1, +1\}$
- Observes $(\boldsymbol{U}, \boldsymbol{Z})$ but **not** $\boldsymbol{V}$

OS ($S = o$, large n_o):

- Confounded treatment assignment
- Observes $(\boldsymbol{Z}, \boldsymbol{V})$ but **not** $\boldsymbol{U}$

$\boldsymbol{U} \in \mathbb{R}^{p_u}$ RCT only

$\boldsymbol{Z} \in \mathbb{R}^{p_z}$ Shared

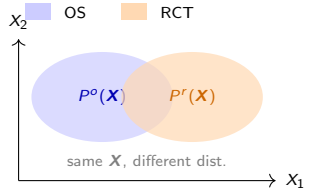
$\boldsymbol{V} \in \mathbb{R}^{p_v}$ OS only

Observed Data

$$\text{RCT:} \quad \{(\boldsymbol{U}_i, \boldsymbol{Z}_i, A_i, Y_i)\}_{i=1}^{n_r}$$
$$\text{OS:} \quad \{(\boldsymbol{Z}_j, \boldsymbol{V}_j, A_j, Y_j)\}_{j=1}^{n_o}$$

Covariate Mismatch $\neq$ Covariate Shift

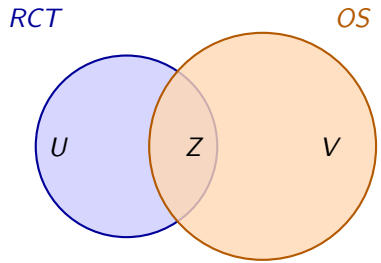
Covariate Shift



Same covariates observed in both sources;
$P^o(\boldsymbol{X}) \neq P^r(\boldsymbol{X})$

Issue: distribution changes, not variables.

Covariate Mismatch (our setting)



Issue: different feature spaces

The Core Challenge

Outcome models trained on $(\boldsymbol{Z}, \boldsymbol{V})$ in the OS cannot be evaluated on RCT units where $\boldsymbol{V}$ is missing.

The CATE Target

Our goal is to estimate the conditional average treatment effect in the RCT population:

CATE Definition

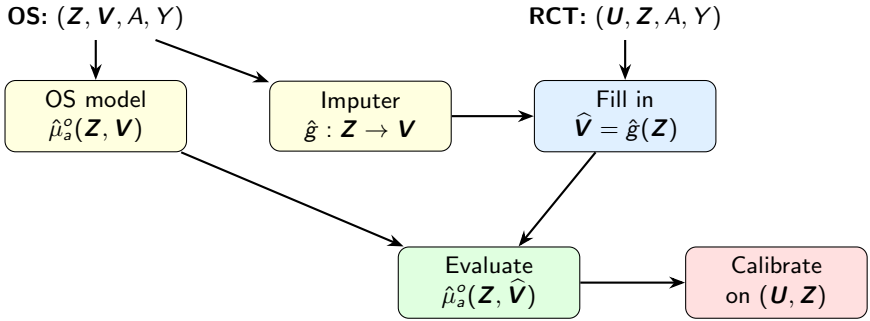
$$\tau^r(\boldsymbol{u}, \boldsymbol{z}) = \mathbb{E}\big[Y(1) - Y(-1) \mid \boldsymbol{U} = \boldsymbol{u}, \boldsymbol{Z} = \boldsymbol{z}, S = r\big]$$

Key points:

- The CATE is defined on $(\boldsymbol{U}, \boldsymbol{Z})$—the covariates available in the RCT
- It **marginalizes over $\boldsymbol{V}$**, since $\boldsymbol{V}$ is never observed in the trial
- Causal identification comes entirely from randomization $(A \perp\!\!\!\perp Y(a) \mid \boldsymbol{U}, \boldsymbol{Z}, S = r)$
- The OS enters only as an *auxiliary predictor*—it does not provide causal identification

MR-OSCAR: **M**ismatch-aware **R**obust **O**bservational **S**tudies for **C**MO-**A**ugmented **R**CT

Idea: Predict the missing $\boldsymbol{V}$ from the shared $\boldsymbol{Z}$, then run R-OSCAR as if $\boldsymbol{V}$ were observed.



Numerical Results

Simulation setup

- Two sources with partially overlapping covariates:
  $\boldsymbol{X}_{\text{RCT}} = (\boldsymbol{U}, \boldsymbol{Z}), \boldsymbol{X}_{\text{OS}} = (\boldsymbol{Z}, \boldsymbol{V}), p_{\text{tot}} = 100.$
- Sample sizes: $n_r = 300$ (RCT) and $n_o = 1000$ (OS), unless noted.
- Treatment:
  - RCT: completely randomized, $\Pr(A = 1) = 0.5$.
  - OS: logistic assignment using a subset of $\boldsymbol{Z}$; treated proportion $\approx 1/3$.
- Methods compared:
  - **RACER**: RCT-only CATE via outcome regression + calibration on $(\boldsymbol{U}, \boldsymbol{Z})$.
  - **SR-OSCAR**: borrows from OS using only shared covariates $\boldsymbol{Z}$.
  - **MR-OSCAR**: augments RCT with imputed $\widehat{\boldsymbol{V}}$ learned from $(\boldsymbol{Z}, \boldsymbol{V})$ in the OS and calibrates to the RCT.

Simulation results: when is borrowing helpful?

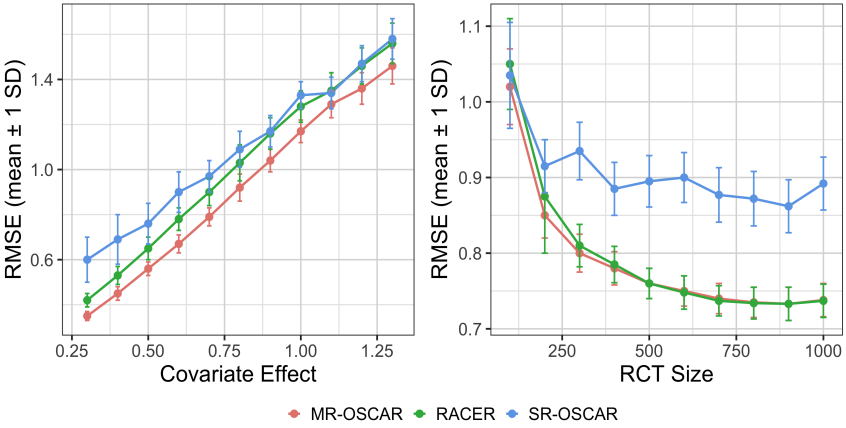
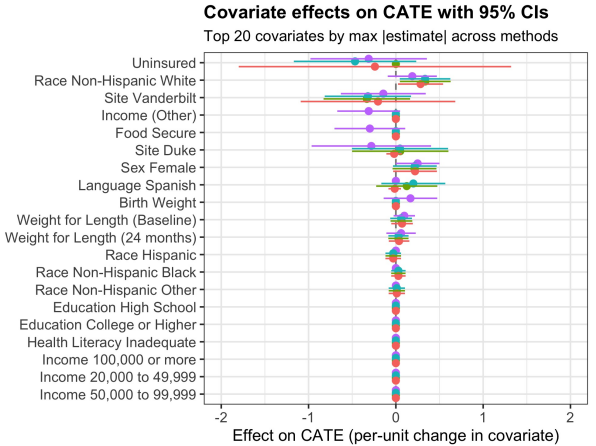


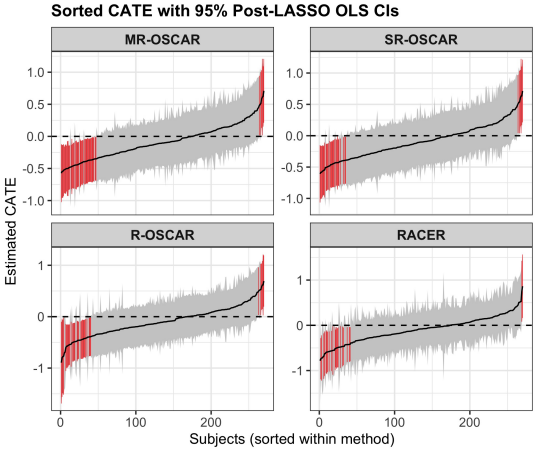
Figure: **Left:** *Mean RMSE (points) with* ± 1 *SD (bars) versus the effect size of the OS-only covariates* $\boldsymbol{V}$. **Right:** *Mean RMSE versus RCT sample size* n_r *(OS fixed at* $n_o = 1000$*).*

Greenlight Plus study: design and covariate mismatch

- Pediatric obesity prevention trial (**Greenlight Plus**):
  - Outcome: weight-for-length z-score at 12 months.
  - Trial covariates include demographics, baseline anthropometrics, socioeconomic and literacy measures.
- External EHR dataset:
  - Control patients only ($A = 0$); rich baseline covariates including **insurance status** V.
- We deliberately impose covariate mismatch:
  - Mask binary insurance V in the RCT and treat it as OS-only.
  - Use EHR controls to learn $\Pr(V = 1 \mid Z)$ and impute $\widehat{V}$ in the trial (MR-OSCAR).
- Methods compared on these data:
  - **RACER**: RCT-only baseline using all observed trial covariates.
  - **SR-OSCAR**: R-OSCAR applied using only shared covariates Z.
  - **MR-OSCAR**: imputation-augmented version using $(Z, \widehat{V})$ in the RCT.
  - **R-OSCAR (oracle)**: uses (Z, V) in both EHR and RCT; represents a gold-standard scenario where insurance is observed in the trial.

Greenlight Plus: CATE uncertainty and covariate effects





Conclusion

Papers

ArXiv R-OSCAR paper

Google Scholar profile