Synthetic and negative control evaluation framework for large-scale propensity score survival analysis

Yuxi Tian

M.D./Ph.D candidate
Department of Biomathematics, UCLA

Joint work with: Marc Suchard - University of California, Los Angeles
Martijn Schuemie - Janssen Research and Development

OHDSI Community Call; September 5, 2017

Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?

Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?

Logistic Regression

Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?

Logistic Regression

How are Covariates Selected?

Propensity Score Adjustment

- PS = estimated probability of treatment assignment address confounding in observational studies

How is the PS Estimated?

Logistic Regression

How are Covariates Selected?

Thousands of potential confounders

PS Model Selection

- Traditionally: Investigator Selection
- high-dimensional Propensity Score algorithm (hdPS)
  univariate screen for significant covariates
  based on exposure or outcome association

  “exposure-based” : relative risk with treatment exposure
  “bias-based” : relative risk with outcome of interest

- L1-regularization (LASSO)
  multivariate model selection via penalized likelihood
  coefficients of unimportant covariates shrunk to zero

Study Goals

- Detail framework to evaluate propensity score estimation method performance

  - simulations

  - negative control experiments

- Use evaluation to compare:

  - hdPS Algorithm : “exposure-based” and “bias-based”

  - L1-regularization (LASSO)

PS Details

- hdPS Algorithm prescribes a certain set of data pre-processing:
  - aggregate covariates by coding
  - limit considered covariates to most prevalent
  - augment covariates by individual level frequency
  - 180 day lookback windows

- FeatureExtraction default uses more expansive set of covariates
  - eras, exposures, observations, measurements, scores
  - 30 day, 365 day, all day lookback windows

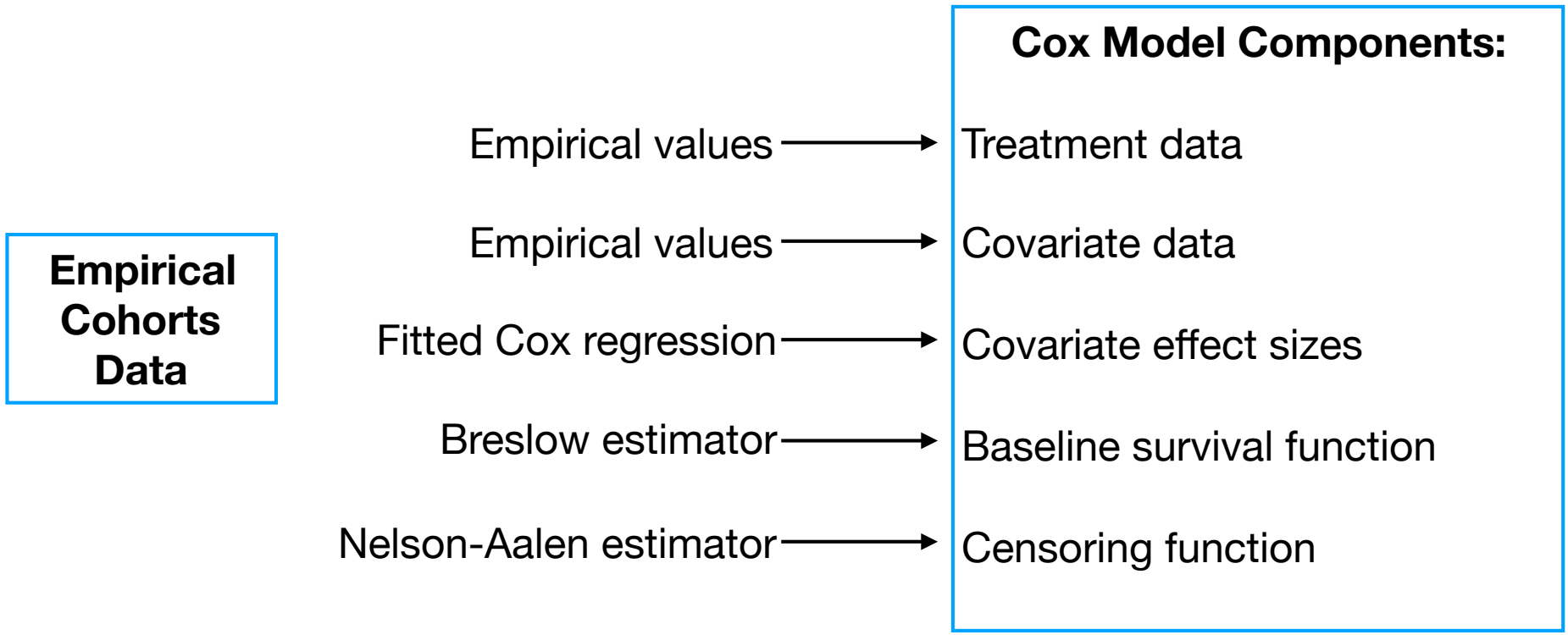
- We used L1-regularization on both (hdPS and CDM)

Simulations

- Keep treatment exposure and covariates from real-world data
- Simulate outcomes times under a survival model
- Simulate under known hazard ratio and with different outcome prevalences
- Extends the “plasmode” framework by Franklin et al. (2014)

Simulations

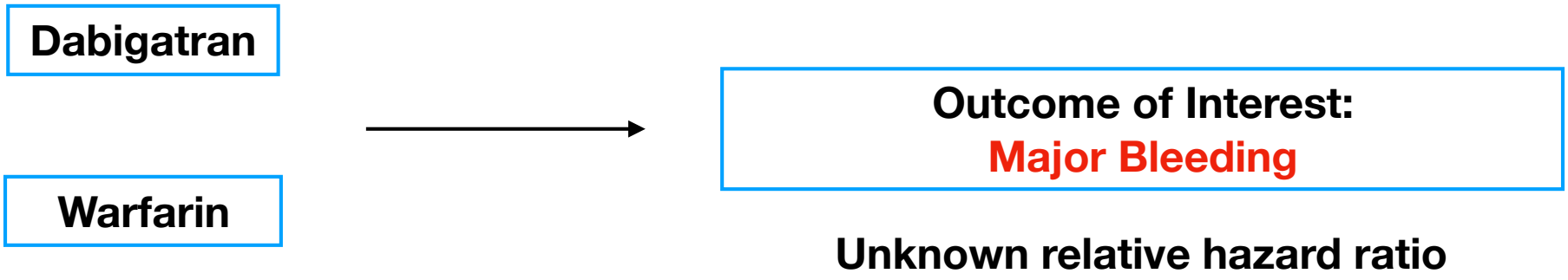
- Simulate realistic survival data under a **known hazard ratio** in Cox proportional hazards model



Negative Control Experiments

- Downside to simulations:
  Do not capture full complexity of real-world data

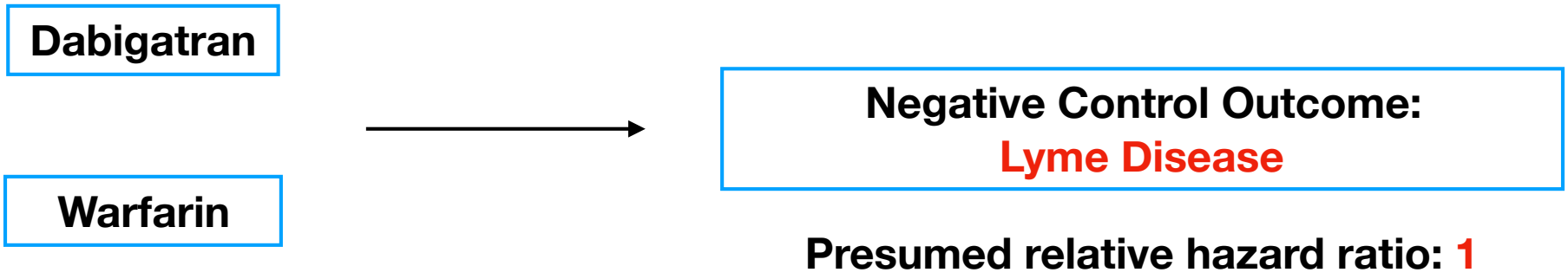
- Negative controls:
  Outcomes unaffected by the studied treatments



Negative Control Experiments

- Downside to simulations:
  Do not capture full complexity of real-world data

- Negative controls:
  Outcomes unaffected by the studied treatments



Empirical Data Used - Anticoagulants

- Replication of dabigatran vs warfarin observational study by Graham et al. (2014)

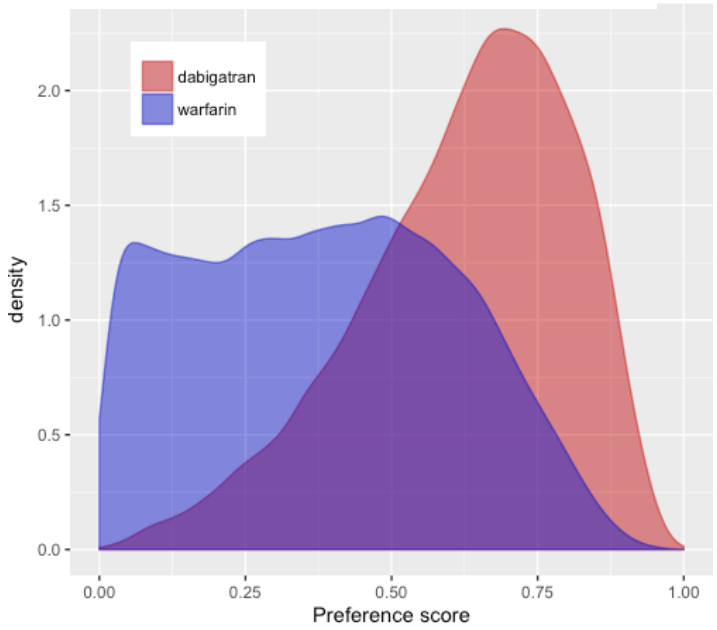
- Database: Truven Health Marketscan Medicare Supplemental and Coordination of Benefits Database

- Cohorts:
  19768 dabigatran users, 52721 warfarin users
  192 intracranial hemorrhage 0.26%
  98118 unique covariates

PS Distribution

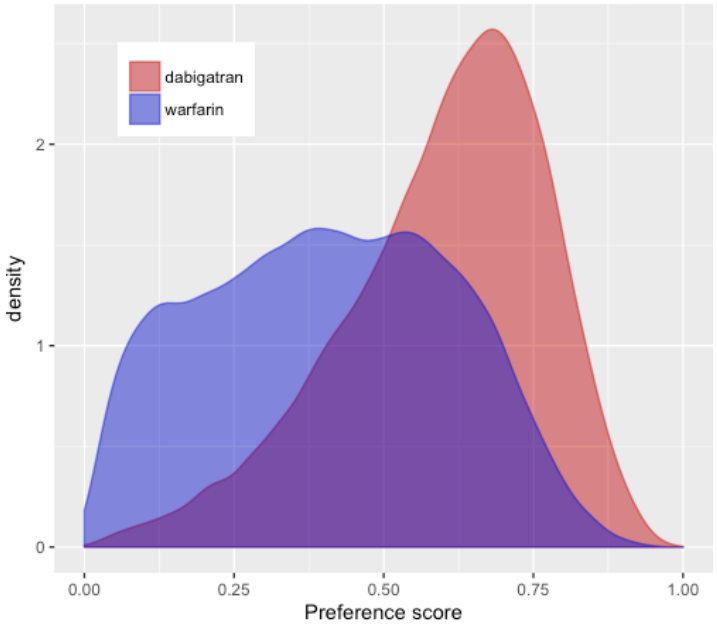
L1 Regularization (CDM)

AUC: 0.793



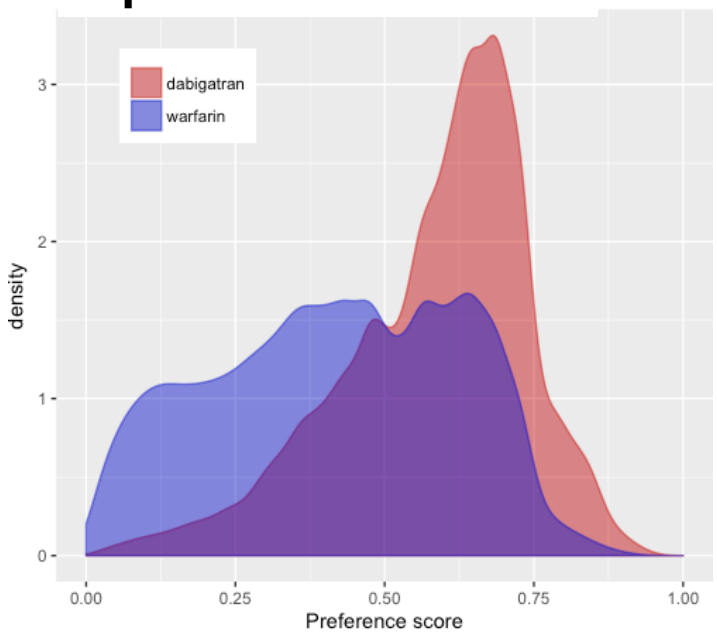
L1 Regularization (hdPS)

AUC: 0.760



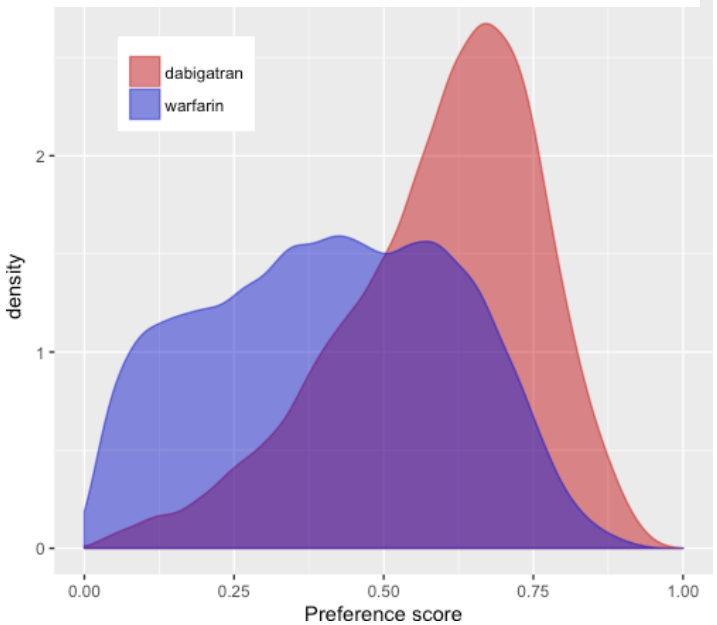
exposure-based hdPS

AUC: 0.737



bias-based hdPS (empirical)

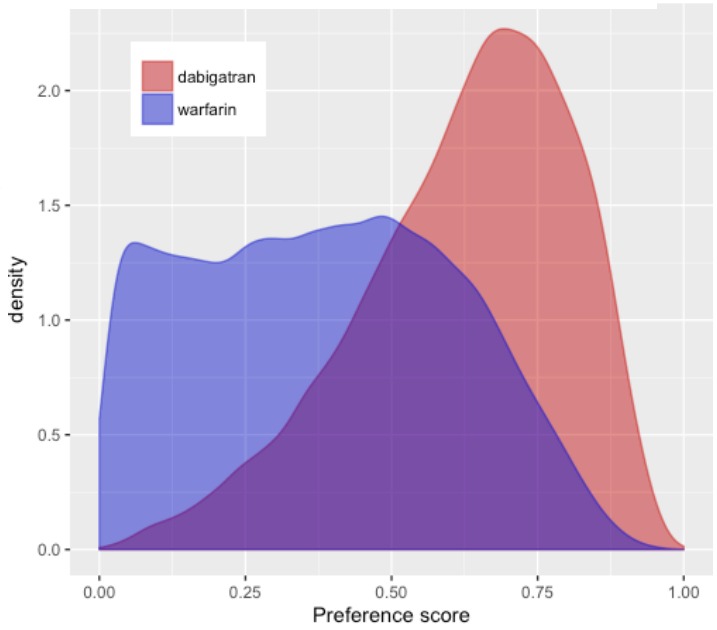
Empirical:
AUC: 0.747



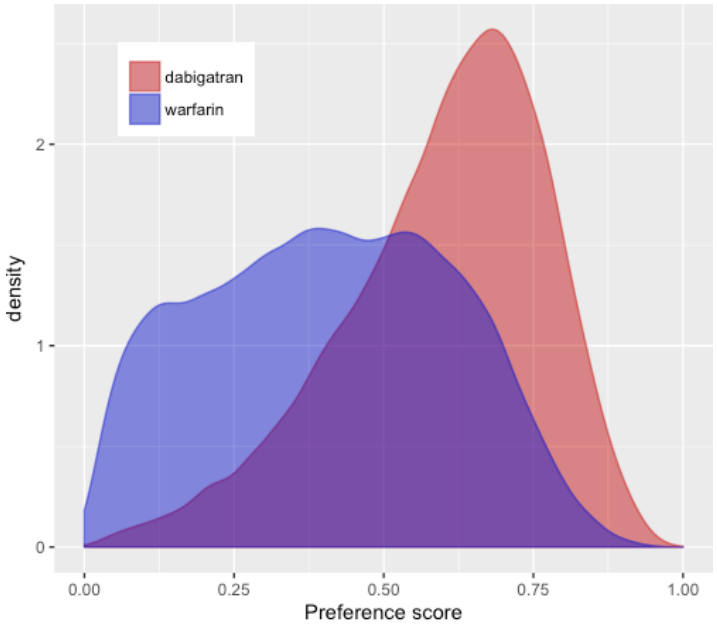
PS Distribution

L1 Regularization (CDM)

AUC: 0.793



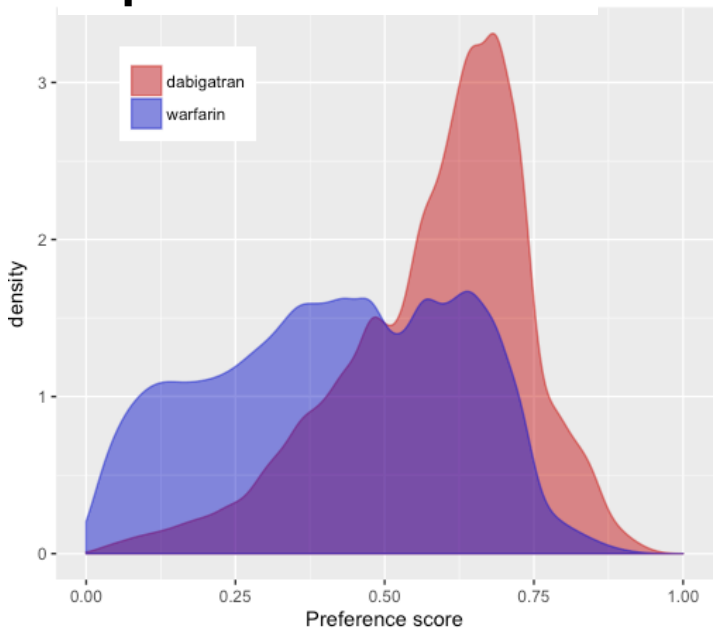
L1 Regularization (hdPS)



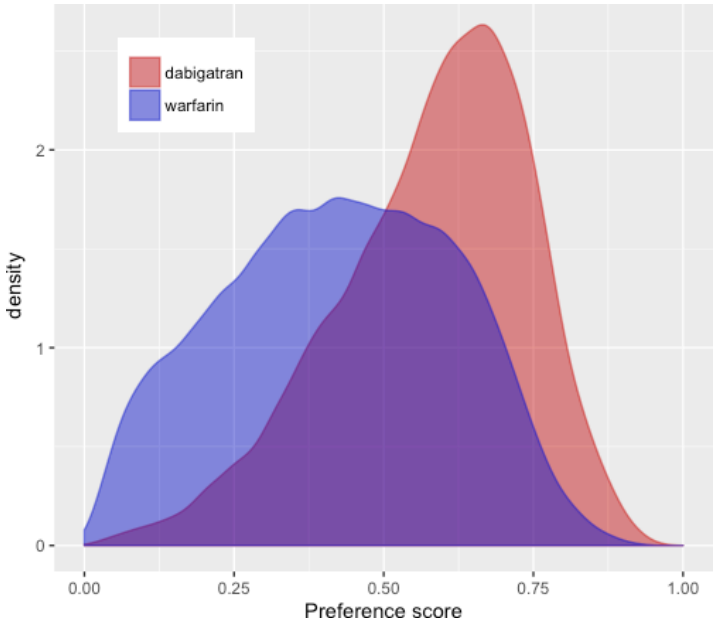
AUC: 0.760

exposure-based hdPS

AUC: 0.737



bias-based hdPS (simulation)



Empirical:
AUC: 0.747

Simulation:
AUC: 0.742

Covariate Balance

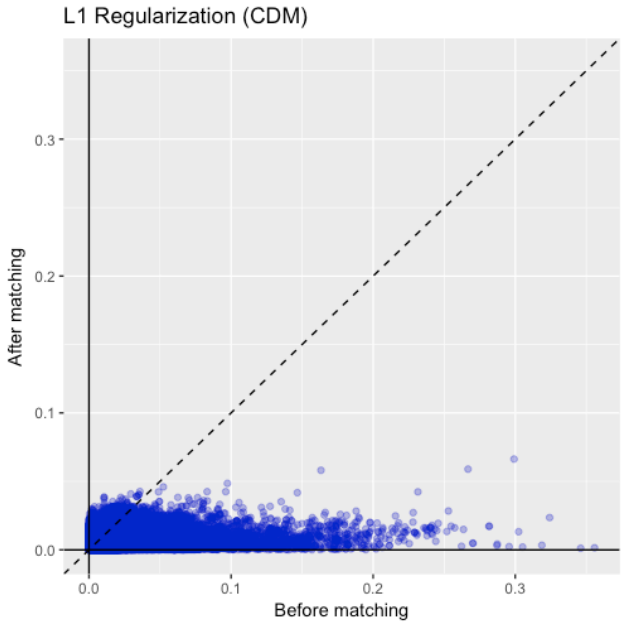
- standardized difference of covariates before and after propensity score matching

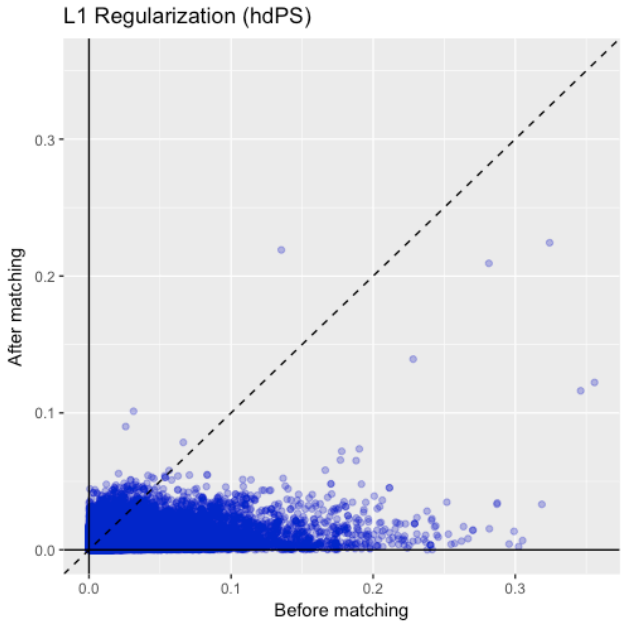
Which covariates to consider?

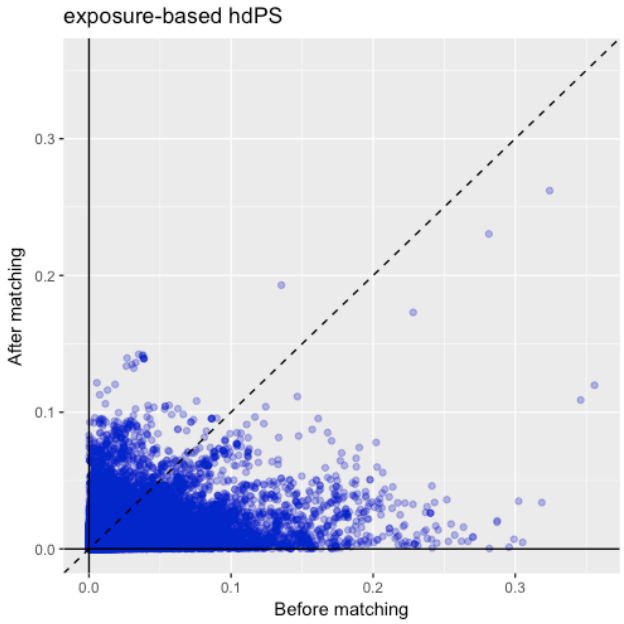
- All covariates

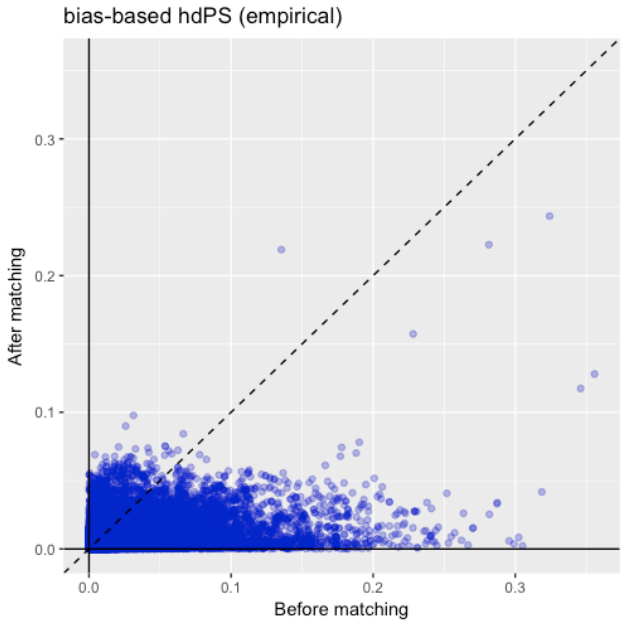
- “true confounders”
  - approximated by simulation model covariates
  - note: these include “hdPS Algorithm Covariates” and “CDM Covariates”

All Covariates





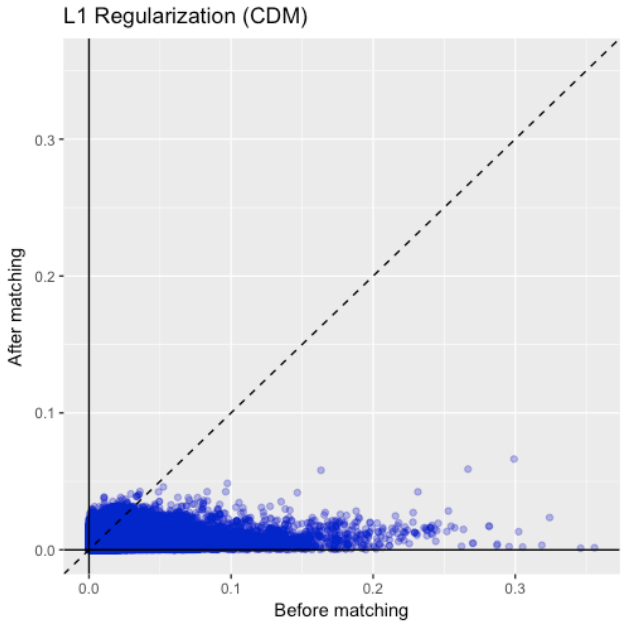


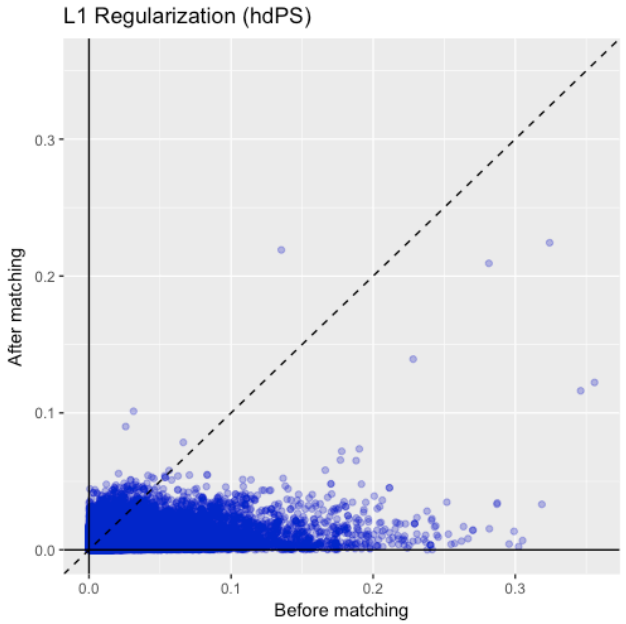


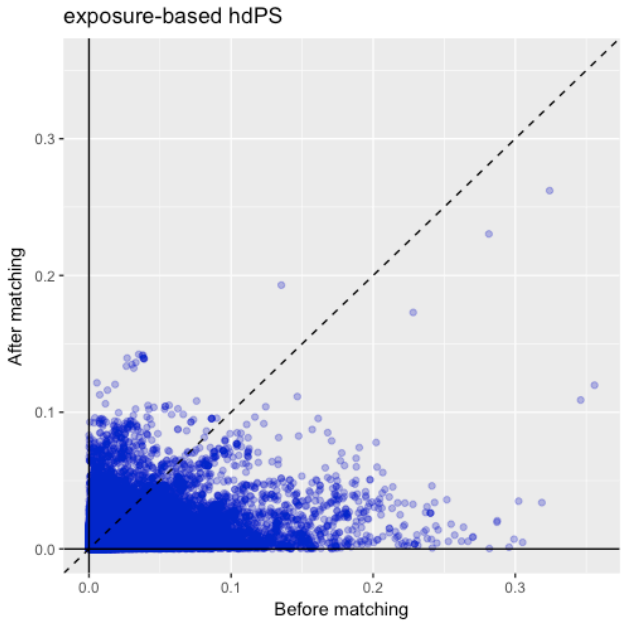
10:1 variable ratio matching

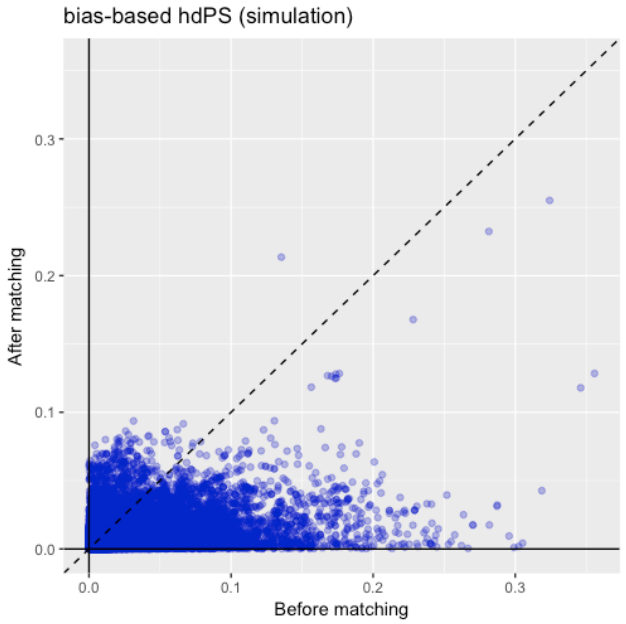
Outcome Independent Metric

All Covariates





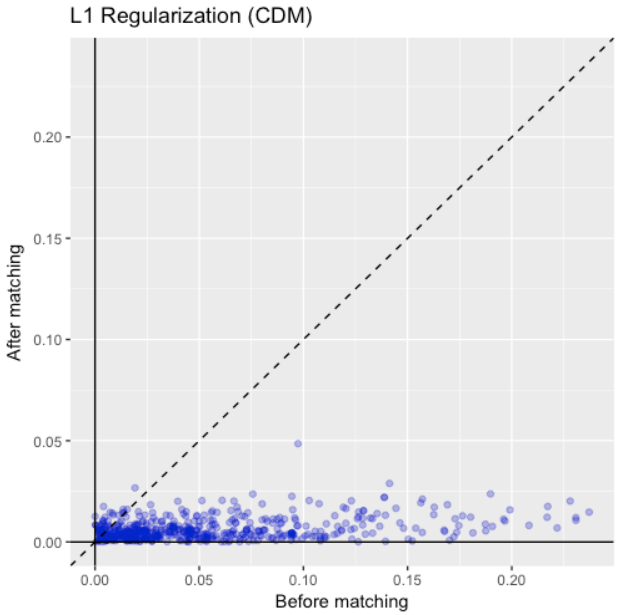


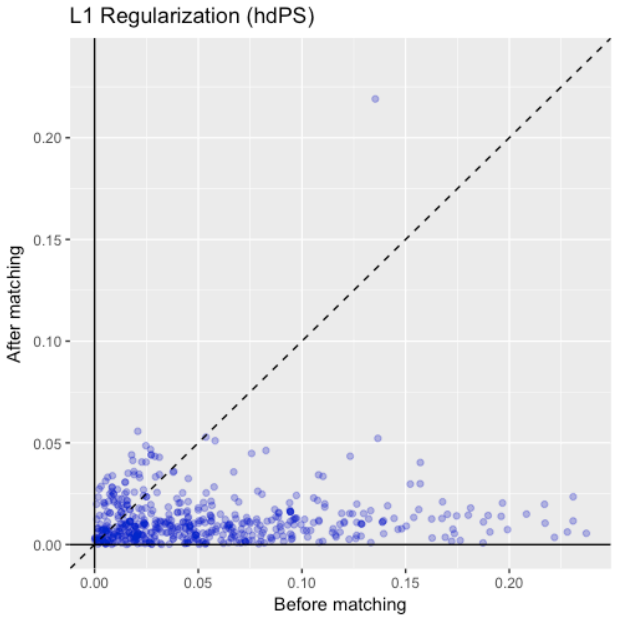


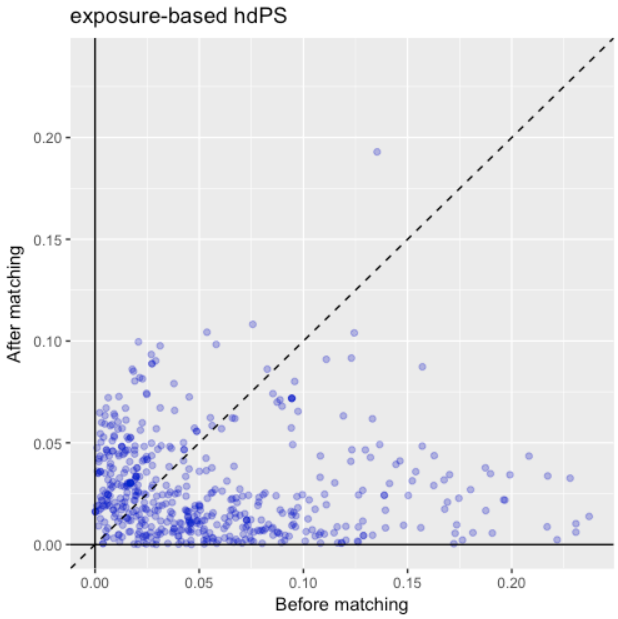
10:1 variable ratio matching

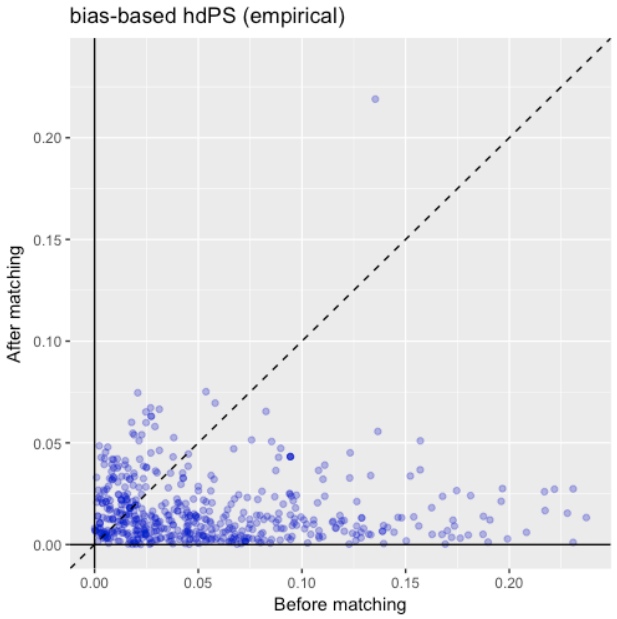
Outcome Independent Metric

Simulation Model Covariates





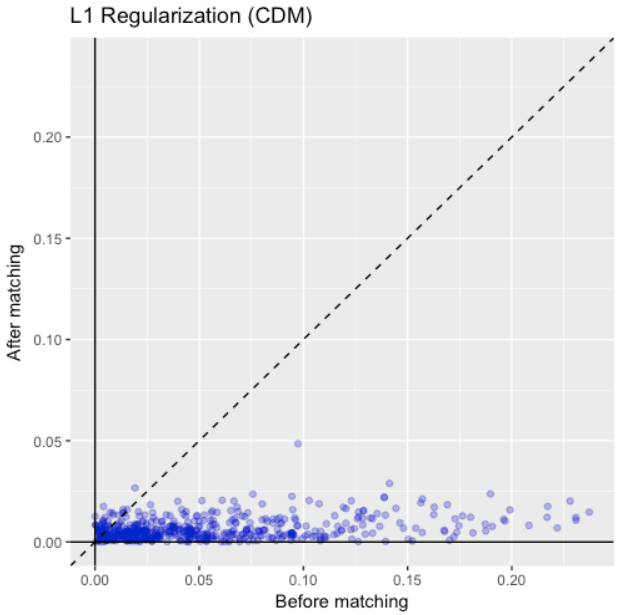


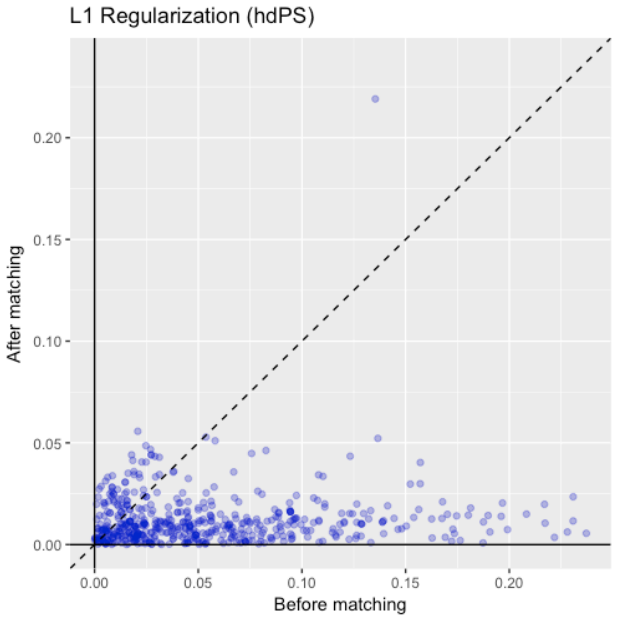


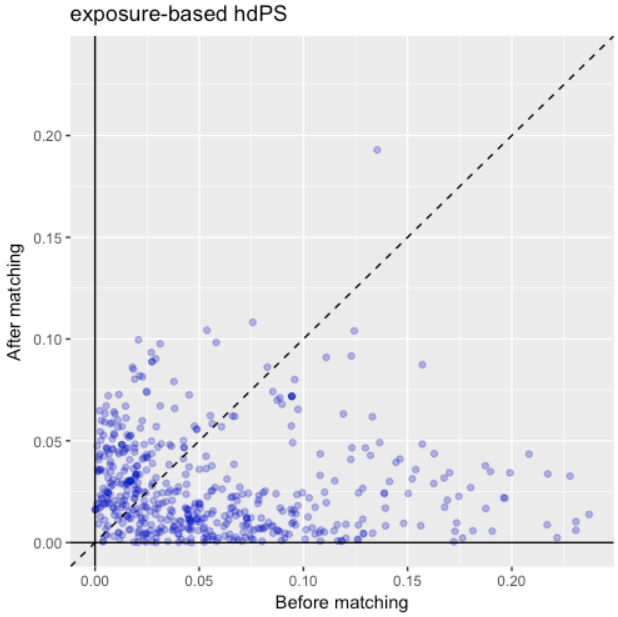
10:1 variable ratio matching

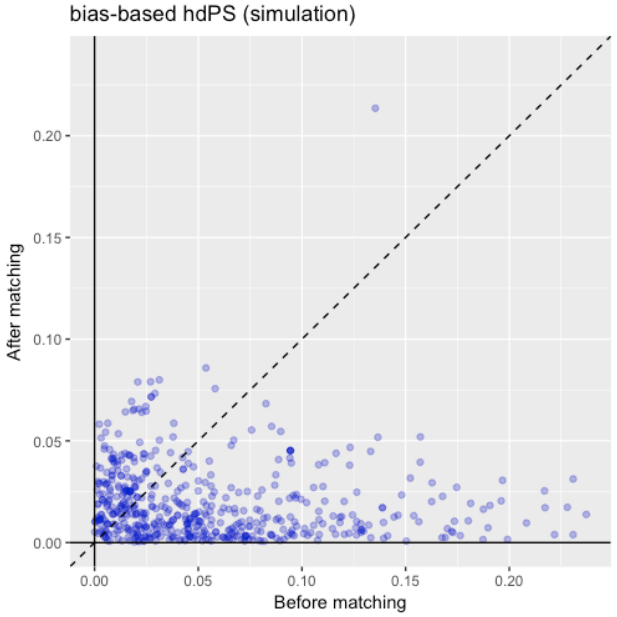
Outcome Independent Metric

Simulation Model Covariates









10:1 variable ratio matching

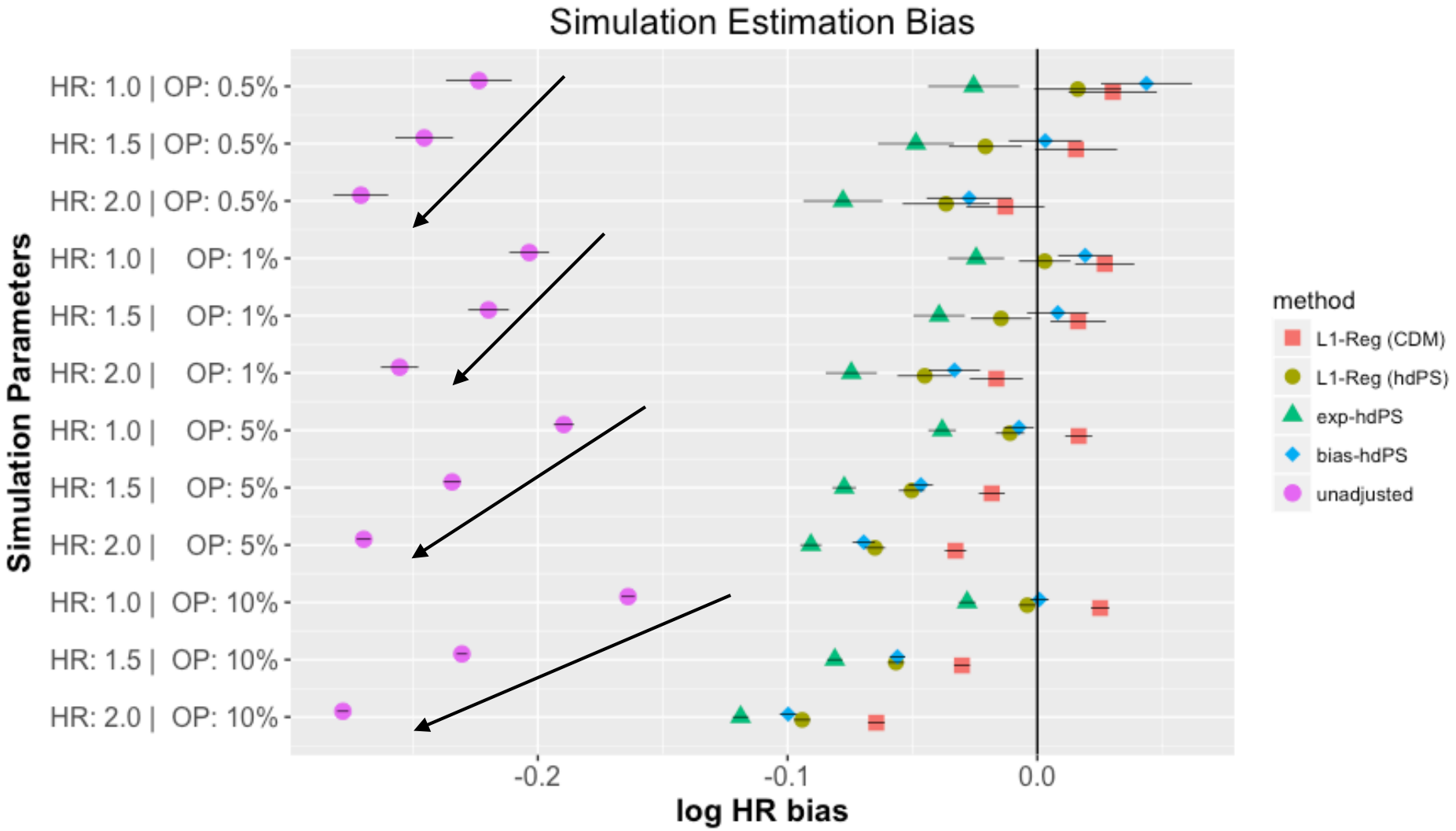
Outcome Independent Metric

Bias Reduction: Simulations

10:1 variable ratio matching

Outcome Dependent Metric

Bias Reduction: Simulations



10:1 variable ratio matching

Outcome Dependent Metric

Simulation Bias

Survival Simulation; consider 1:1 matching

$$\hat{\eta} = \log N_1 - \log N_0$$

N_1 : exposed has event, time before unexposed

N_0 : unexposed has event, time before exposed

$$\Pr(\text{set in } N_1) = \int_0^\infty (\frac{\partial}{\partial t} S(t)^{\exp\{\theta_{1,k}\}}) S(t)^{\exp\{\theta_{0,k}\}} C(t) C(t) \mathrm{d}t$$

survival function

exposed hazard
contains true effect size

unexposed hazard

censoring function

Simulation Bias

Survival Simulation; consider 1:1 matching

$$\hat{\eta} = \log N_1 - \log N_0$$

N_1 : exposed has event, time before unexposed

N_0 : unexposed has event, time before exposed

$$\Pr(\text{set in } N_1) = \int_0^\infty (\frac{\partial}{\partial t} S(t)^{\exp\{\theta_{1,k}\}}) S(t)^{\exp\{\theta_{0,k}\}} C(t) C(t) \mathrm{d}t$$

survival function

exposed hazard
contains true effect size

unexposed hazard

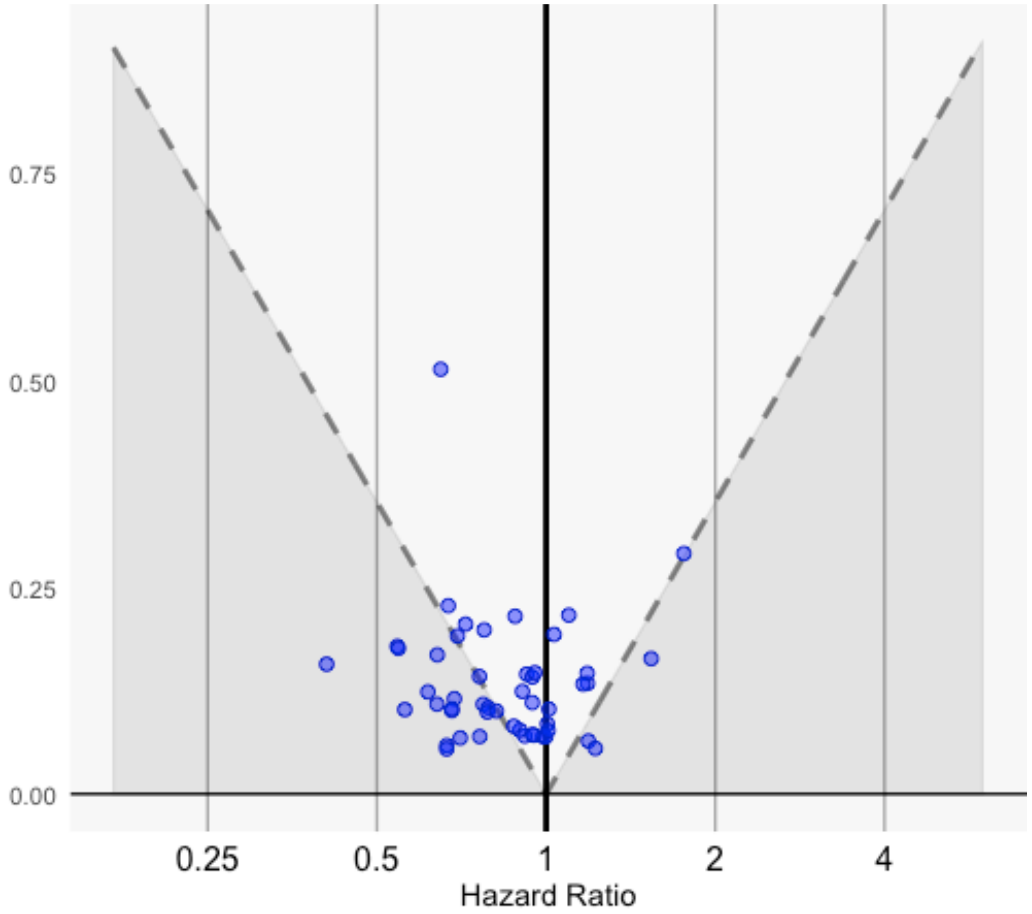
censoring function

Not unbiased when there is variance in baseline hazards

Negative Controls

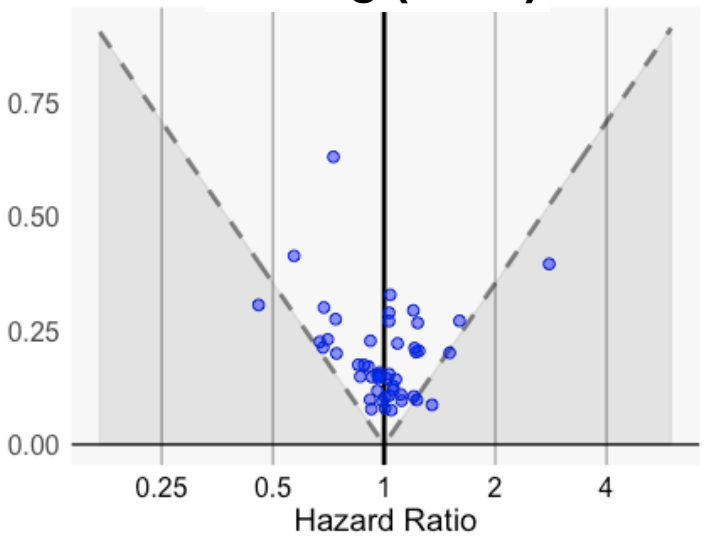
Coverage:
0.53±0.07

Unadjusted



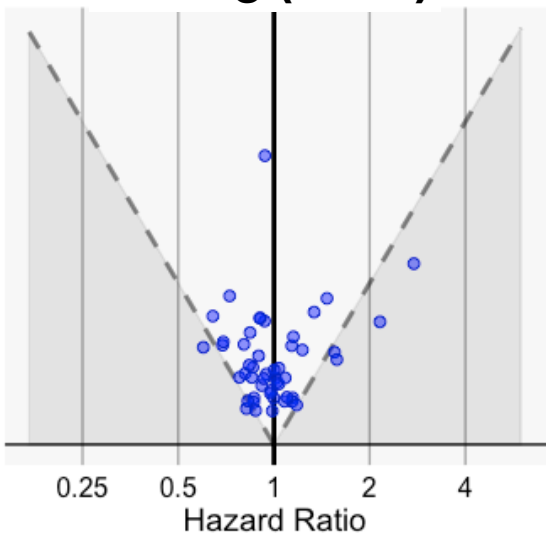
Bias Reduction: Negative Outcomes

L1 Reg (CDM)



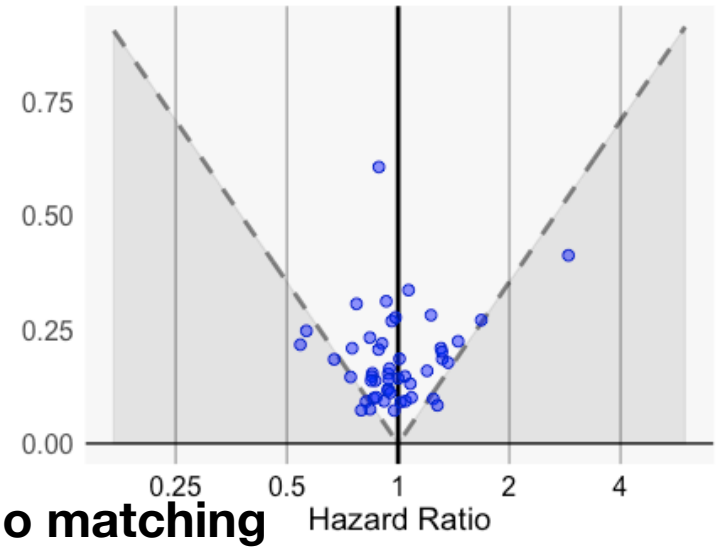
Coverage: 0.90±0.04

L1 Reg (hdPS)



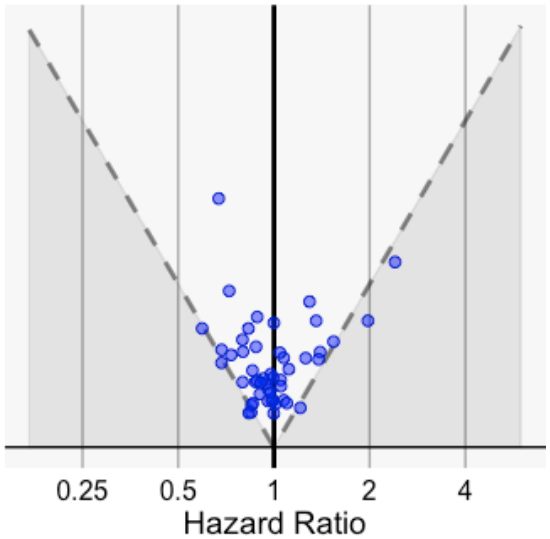
Coverage: 0.86±0.05

exposure-based hdPS



Coverage: 0.80±0.06

bias-based hdPS



Coverage: 0.86±0.05

10:1 variable ratio matching

Outcome Dependent Metric

Outcome Dependent Metrics

Outcome Dependent Metrics

- Susceptible to bias:

  - PS adjustment techniques
  - simulation design choices
  - negative control misspecification

Outcome Dependent Metrics

- Susceptible to bias:

  - PS adjustment techniques
  - simulation design choices
  - negative control misspecification

- Different outcomes can yield different results

Outcome Dependent Metrics

- Susceptible to bias:

  - PS adjustment techniques
  - simulation design choices
  - negative control misspecification

- Different outcomes can yield different results

- Outcome independent metrics more generalizable

Instrument Variables

- Variables that predict treatment exposure but has no effect on outcome (or correlation with any confounder)

- Inclusion in PS can increase bias and variance of estimate

Suppose:

- eye color perfectly separates treatment groups (all blue eyed receive A, all brown eyed receive B)
- eye color does not influence outcome
- no power in experiment

Instrument Variables

- Variables that predict treatment exposure but has no effect on outcome (or correlation with any confounder)

- Inclusion in PS can increase bias and variance of estimate

Suppose:

- absent of IV, PS correlated with outcome hazard, PS matches patients with similar baseline outcome hazard
- add in IV, PS of many exposed people increases
- exposed people now matched with higher hazard
- negative bias results

Instrument Variables

- True IV are rare, impact on real-world data unproven
- IV only problematic if uncorrelated with any confounders - unlikely situation in real-world data
- Identifying IV's is difficult
- bias-based hdPS uses outcome information in PS to avoid IV's, but breaks Rubin's unconfoundedness assumption

Instrument Variables - Solution?

- If certain IV's are suspected, stratify on them in the PS logistic regression -> conditional logistic regression (CLR)
- CLR avoids estimating any effect size from IVs
- Keeps unconfoundedness while eliminates effects on PS
- Issue:
  CLR computationally expensive for large strata
  CLR approximations can be very inaccurate
- Future direction:
  Efficient CLR implementation, apply to PS

Take Away Points

- L1 Regularization favorable over hdPS Algorithm
- Simulations and negative controls provided useful evidence
- Regularization solves PS “convergence” problem
  (no MLE for regression exists)