Experiences using the CohortMethod

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15 December 2015

Agenda

- Overview of CohortMethod
- Recent clinical applications
- OHDSI community collaboration
  - Methods research
  - Open-source development
  - MORE clinical applications!

What is CohortMethod?

- R package developed by the OHDSI community, led by Martijn Schuemie and Marc Suchard (http://github.com/OHDSI/CohortMethod)
- Open-source implementation of the new user cohort design for OMOP Common Data Model v5
- User input specification allows execution of standardized analysis and reporting, including cohort and feature construction, model fitting and diagnostics, and summary outputs

Drug Saf (2013) 36 (Suppl 1):S59–S72
DOI 10.1007/s40264-013-0099-6

ORIGINAL RESEARCH ARTICLE

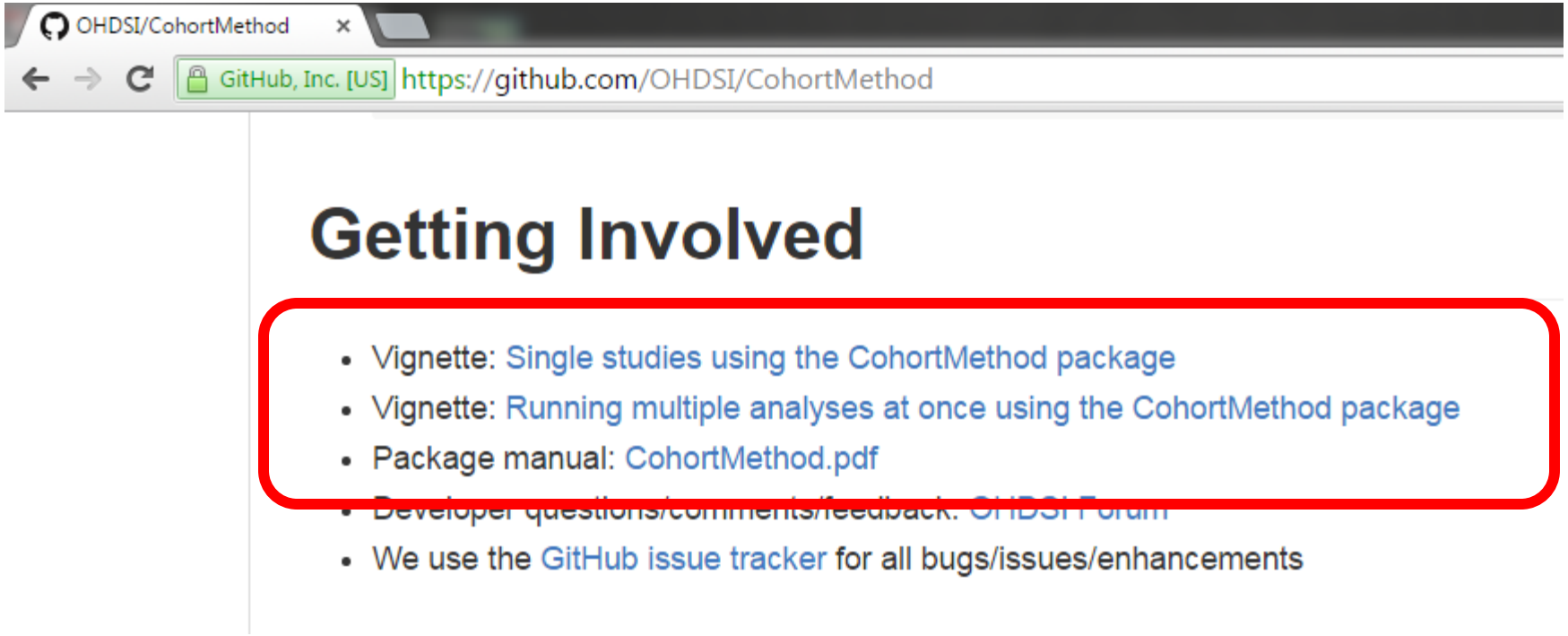
Incident user cohort design parameters:

1. **Required observation time prior to exposure:** 180d, None
2. **Nesting within population with the indication of the target drug:** Yes, No
3. **Comparator population:** Patients with exposure to most prevalent comparator drug which shares the same indication as the target drug but is not in the same pharmacologic class, Patients with exposure to any comparator drug which shares the same indication as the target drug but is not in the same pharmacologic class, Patients with a diagnosis for the indication of the target drug, Patients with a diagnosis for the indication of the target drug and at least one exposure to a drug known to be not associated with the outcome
4. **Time-at-risk:** *Length of exposure + 30d*, 30d from exposure start, All time post-exposure start
5. **Propensity score covariate selection strategy:** Bayesian logistic regression using all available covariates, High-dimensional propensity score covariate selection algorithm by Schneeweiss et al, Exposure-specific covariate selection algorithm identified by Brookhart et al, No covariate adjustment
6. **Covariate eligibility window:** 30d prior to exposure, 180d prior to exposure, All time prior to exposure
7. **Dimensions to include as potential covariates:** Drugs only, drugs and conditions, drugs and conditions and procedures
8. **Additional covariates in propensity score model:** Age, sex, index year, Charlson index, number of drugs, number of visits, number of procedures
9. **Propensity score trimming:** None, Trim lower 5% from the comparator group and the upper 5% from the target group
10. **Metric:** Propensity score stratification using Mantel Haenszel adjustment over 5 strata, Propensity score stratification using Mantel Haenszel adjustment over 20 strata, Propensity score adjustment using 5 strata as indicator variables in logistic regression outcome model, Propensity score adjustment using 20 strata as indicator variables in logistic regression outcome model, Propensity score adjustment using propensity score as continuous variable in logistic regression outcome model, Unadjusted odds ratio from univariate logistic regression predicting outcome from exposure

Person record

CohortMethod Manuals, vignettes

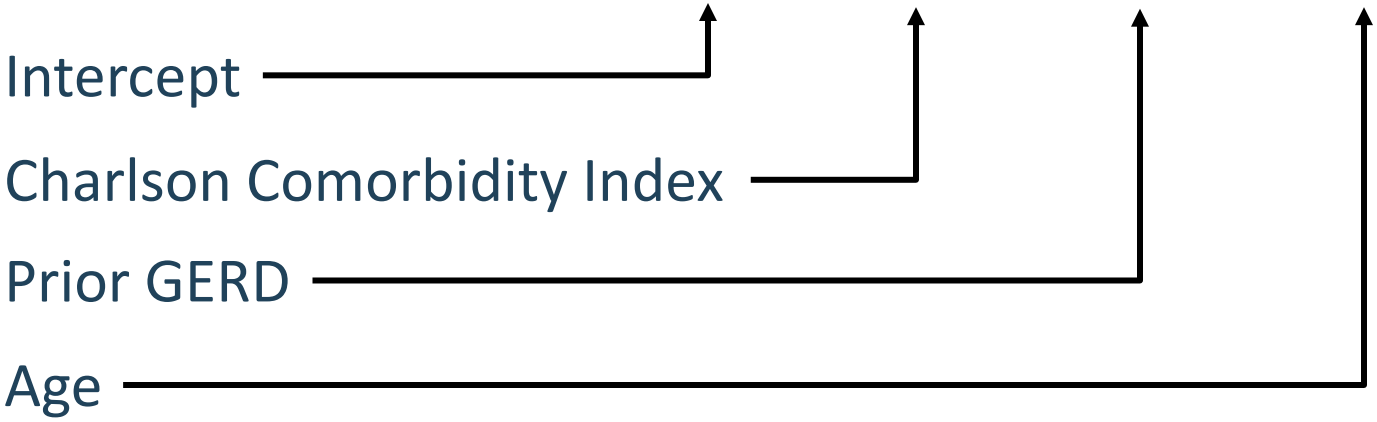
On the CohortMethod GitHub front page:



Propensity score (PS)

The propensity score is the probability of receiving the treatment, conditional on a set of baseline characteristics

$$P(\,treatment \mid X) = f(\,\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots\,)$$



Which variables go into the PS model?

- Traditional: hard thinking by expert
- High-Dimensional PS: rank many variables (e.g. all drugs, conditions) by correlation with exposure (and maybe outcome), pick top n
- Our approach: put everything (demographics, all drugs, all drug classes, all conditions, all disease classes, all procedures, all observations, all severity indexes) in a regularized regression

Regularized regression

- Advantages:
  - Stable, even with many (> 10,000) variables in the model
  - LaPlace prior causes most betas to shrink to 0: easy to interpret final model
  - Let the data decide what is predictive (and what is not)

- Feasible even at large scale:
  - OHDSI Cyclops package can run with millions of persons, hundreds of thousands of covariates

Using the PS

- **Trimming**

  if P(treatment) is around 50%, treatment assignment 'must be random'

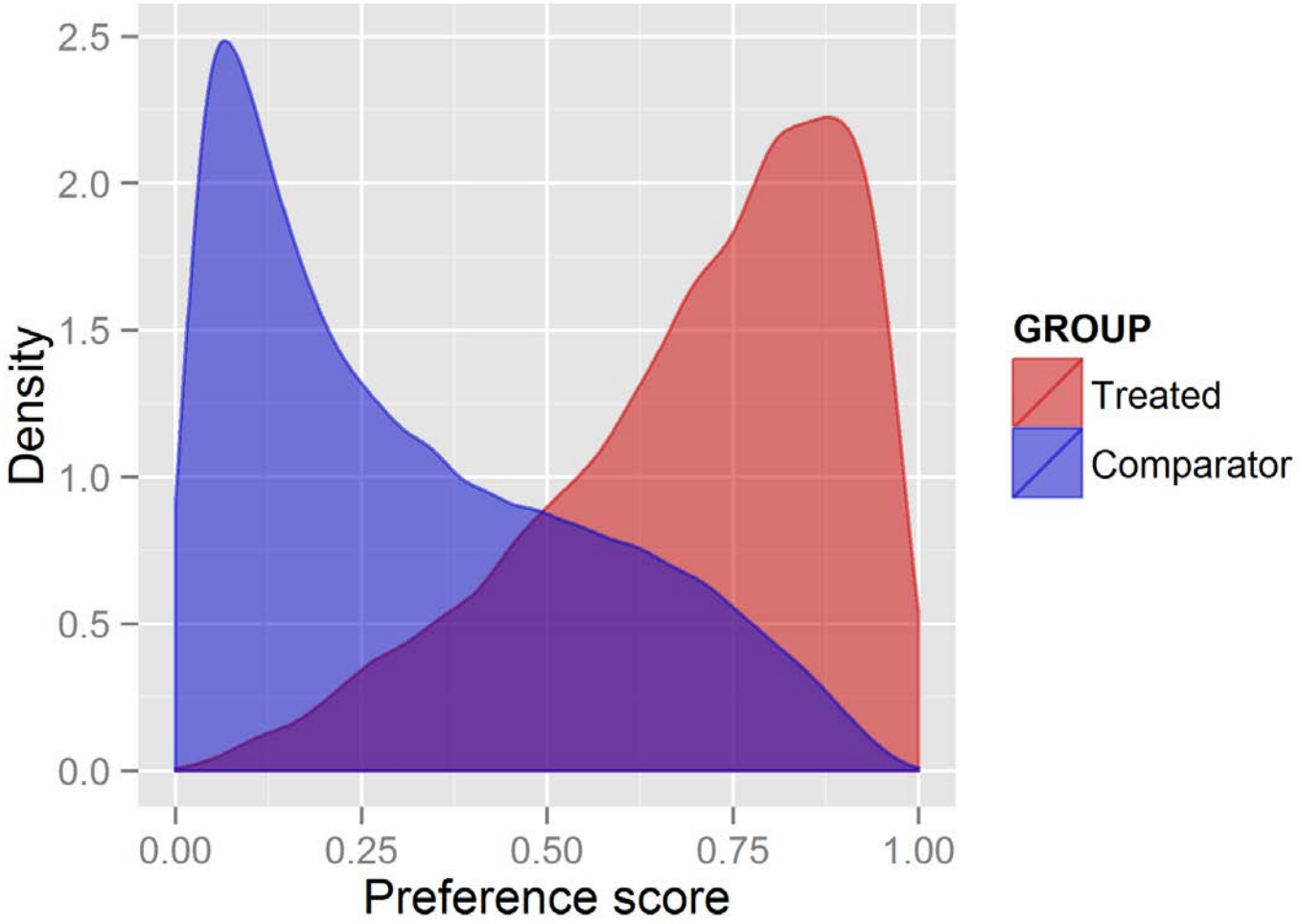
- **Stratification or matching**

  only compare subjects to subjects with a similar PS

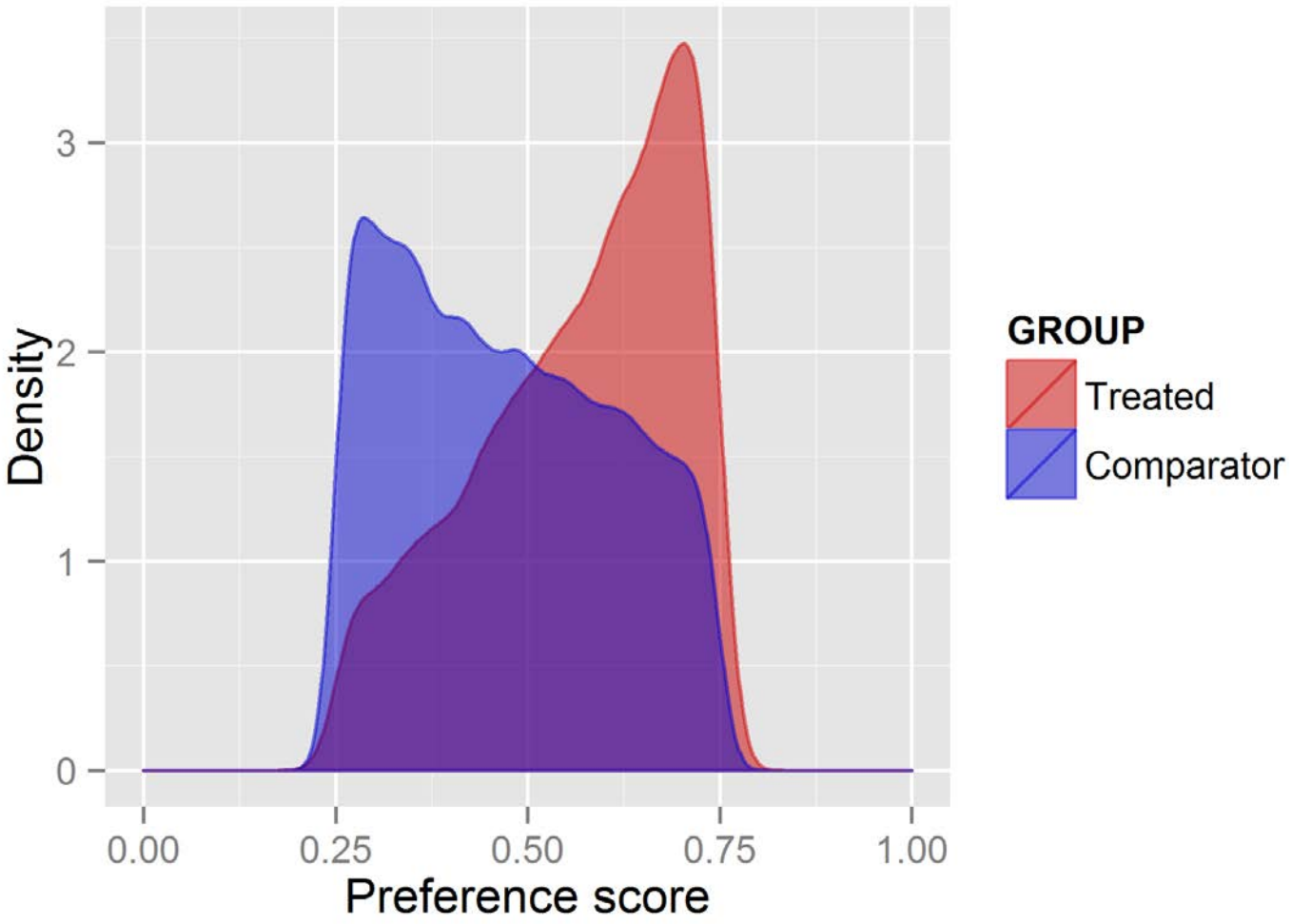
- **Adding to the outcome model**

  correct for the PS in the model used to predict the outcome

PS score distribution



Trimming


Density
3
2
1
0
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0.50
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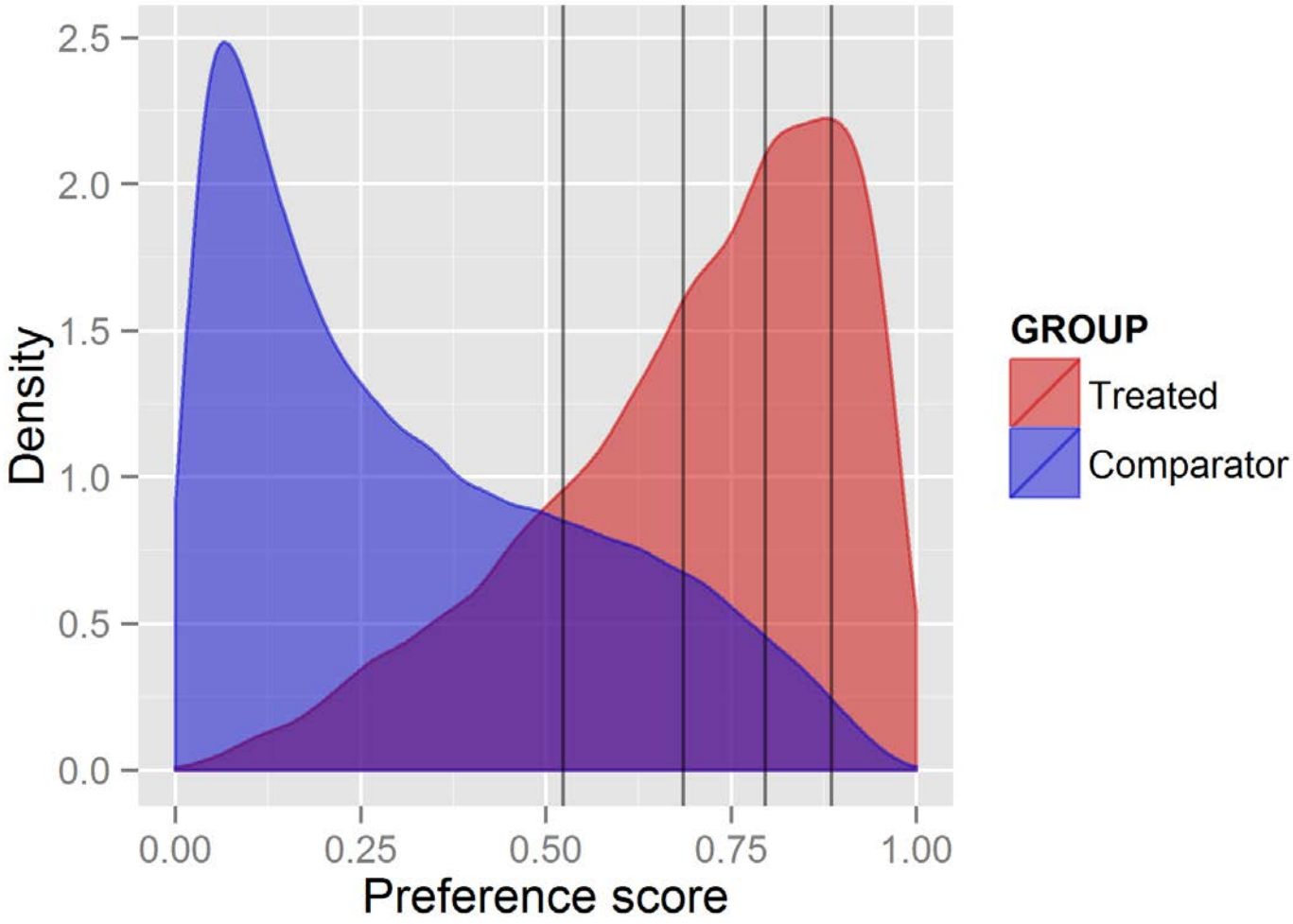
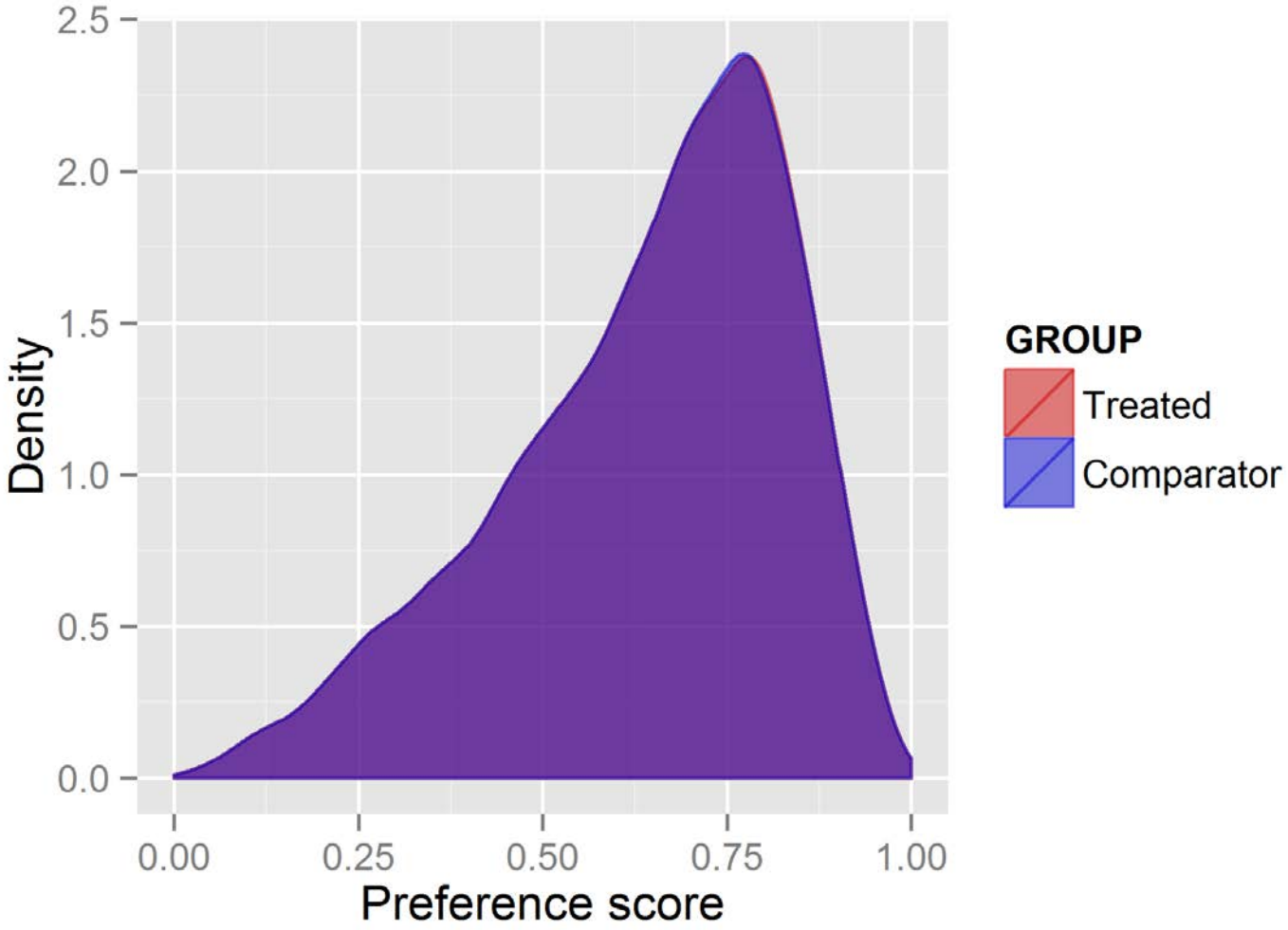
1.00
Preference score
GROUP
Treated
Comparator

Stratifying

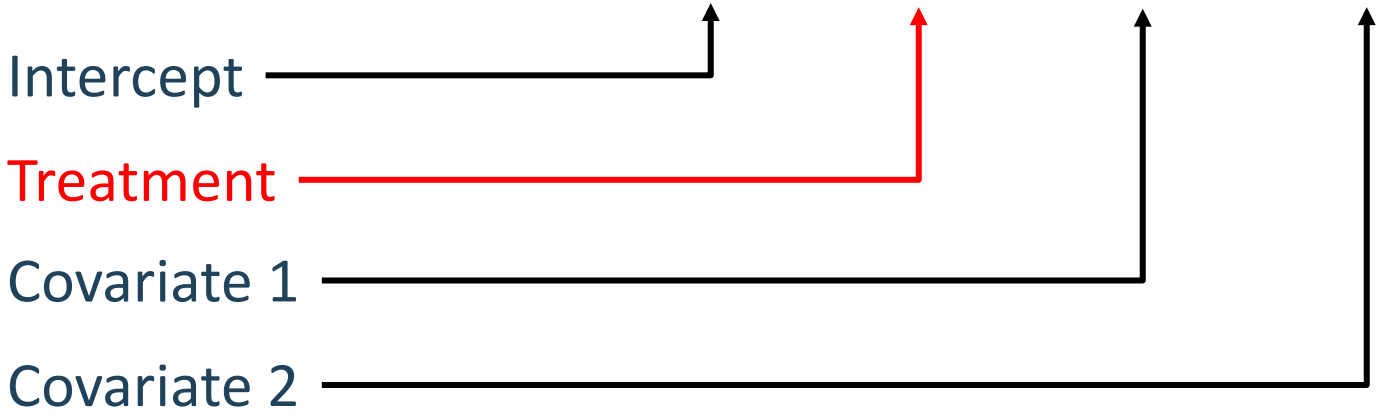


Matching


2.5
2.0
1.5
1.0
0.5
0.0
Density
0.00
0.25
0.50
0.75
1.00
Preference score
GROUP
Treated
Comparator

Outcome modeling

$$P(\,outcome|\,X) = f(\,\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots\,)$$



β_1 is the treatment effect

With prior for every β except the intercept and treatment variable.

Types of outcome models

- Logistic

  Did the outcome occur yes/no?

- Poisson

  How many times did the outcome occur?

- Cox

  What was the time to the first outcome or end of observation?

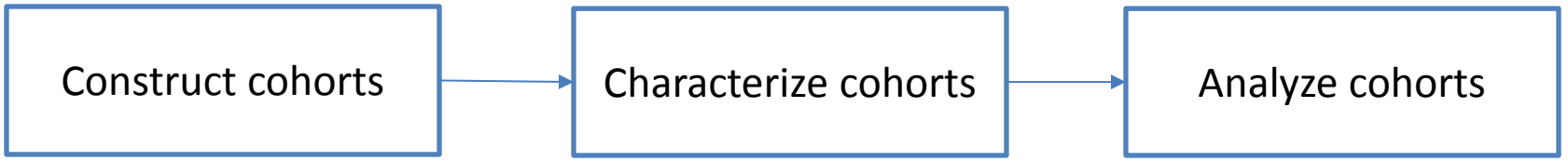
- Conditional or non-conditional (Logistic, Poisson, Cox)

  stratify by PS strata or matched sets

Recent applications

- Population-level estimation
  - Medical product safety surveillance
    - Does **<target exposure X>** increase the risk of **<outcome Y>**?
    - Does **<target exposure X>** increase the risk of **<outcome Y>** in patients with **<condition W>**?
  - Comparative effectiveness research
    - Are **<target exposure X>** and **<comparator exposure Z>** meaningfully comparable treatments for patients with **<condition W>**?
    - Does **<target exposure X>** increase the risk of **<outcome Y>** more than **<comparator exposure Z>** for patients with **<condition W>**?
  - Health behaviors
    - Among patients with **< exposure X>**, does persistence (target cohort) increase the risk of **<outcome Y>**, relative to non-persistence (comparator cohort)?
    - Among patients with **< exposure X>**, does adherence (target cohort) increase the risk of **<outcome Y>**, relative to non-adherence (comparator cohort)?

Typical workflow



What OHDSI tools?

ATLAS to define concept set expressions
CIRCE to define cohort definition and generate populations for target exposure, comparator exposure, outcome(s), negative controls

CALYPSO to evaluate cohort inclusion criteria
HERACLES to summarize demographics, comorbidities, concomitant medications, etc.

CohortMethod to conduct population-level estimation
PatientLevelPrediction to conduct patient-level prediction

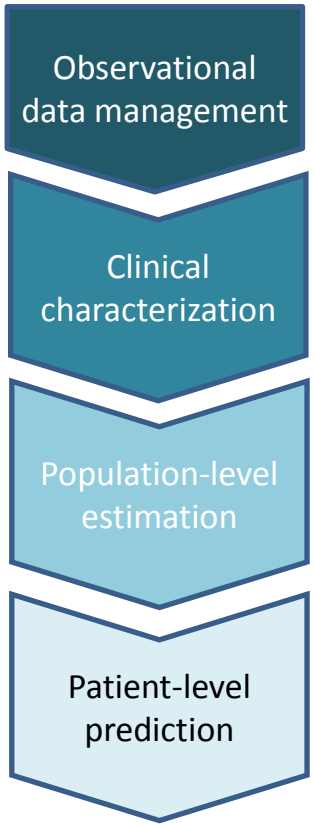
Insights from recent applications (1)

- Choice of comparator matters
  - For safety surveillance, approximating the counterfactual is hard:
    - 'unexposed' cohorts are often not comparable with target drug
    - 'active comparator' are hard to ensure no association with outcome
  - For comparative effectiveness, changing the comparator changes the question…AND changes the composition of the 'matched' target drug cohort
  - This isn't just for drugs! Can apply to compare drug vs. procedure, …
- Selection of index date matters
  - Need to be careful to ensure that only features PRIOR to index are used to predict outcome AFTER index
  - If index date doesn't reflect the same health system experience (e.g. visit, dispensing), residual bias can exist that propensity score matching won't correct

Insights from recent applications (2)

- Time matters
  - When comparing a newly marketed product to an existing treatment, calendar time may be a strong predictor in propensity model
  - Seasonal patterns can impact covariate imbalance
- Sensitivity analyses across different databases and across different design settings is important
  - Replication can increase confidence in findings
  - Inconsistency can point to areas for further post-hoc exploration
- Empirical calibration works as an important diagnostic to detect systematic error
  - Create sample of negative control outcomes (conditions not associated with target or comparator exposures)
  - Apply method to negative controls in same way you've designed for outcome of interest ('Multiple studies' vignette shows you how)
  - Empirical null complements (not replace) other diagnostics, but identifies error that goes beyond residual imbalance in propensity score

OHDSI collaboration opportunities around CohortMethod



- Cohort construction: additional features for inferring 'cohort end date' (to infer time-at-risk)
- Feature construction: build new covariates with logical aggregations
- Feature selection: methods beyond regularized regression
- Comparator selection
- Descriptive profiles and comparisons of cohorts
  - 'Table 1' summary, simplified from covariateBalance
  - Incidence rates before/after matching
  - Time-to-event distribution
- Handling time in cohort analysis: time as PS covariate vs. *time interactions vs. matching on time + PS
- Impact of PS matching in subgroup analyses
- Empirical performance – comparison with active comparator RCTs
- Empirical performance – comparison across OHDSI network for known studies