Overview of the CohortMethod package

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CohortMethod is part of the OHDSI Methods Library

Estimation methods

Cohort Method

New-user cohort studies using large-scale regression for propensity and outcome models

Self-Controlled Case Series

Self-Controlled Case Series analysis using few or many predictors, includes splines for age and seasonality.

Self-Controlled Cohort

A self-controlled cohort design, where time preceding exposure is used as control.

IC Temporal Pattern Disc.

A self-controlled design, but using temporal patterns around other exposures and outcomes to correct for time-varying confounding.

Case-control

Case-control studies, matching controls on age, gender, provider, and visit date. Allows nesting of the study in another cohort.

Prediction methods

Patient Level Prediction

Build and evaluate predictive models for user-specified outcomes, using a wide array of machine learning algorithms.

Feature Extraction

Automatically extract large sets of features for user-specified cohorts using data in the CDM.

Method characterization

Empirical Calibration

Use negative control exposure-outcome pairs to profile and calibrate a particular analysis design.

Method Evaluation

Use real data and established reference sets as well as simulations injected in real data to evaluate the performance of methods.

Supporting packages

Database Connector

Connect directly to a wide range of database platforms, including SQL Server, Oracle, and PostgreSQL.

Sql Render

Generate SQL on the fly for the various SQL dialects.

Cyclops

Highly efficient implementation of regularized logistic, Poisson and Cox regression.

Ohdsi R Tools

Support tools that didn't fit other categories, including tools for maintaining R libraries.

Under construction

Technologies

CohortMethod uses

- *DatabaseConnector* and *SqlRender* to interact with the CDM data
  - SQL Server
  - Oracle
  - PostgreSQL
  - Amazon RedShift
  - Microsoft APS
- *ff* to work with large data objects
- *Cyclops* for large scale regularized regression

Graham study steps

1. Getting the necessary data from the database
2. Defining the study population
3. Creating a propensity model
4. Matching
5. Fitting the outcome model

+ generating various diagnostics

Generic study steps

1. Getting the necessary data from the database
2. Defining the study population
3. [Creating a propensity model]
4. [Trimming / Matching / Stratification]
5. Fitting the outcome model

+ generating various diagnostics

Replication of Garbe et al. using the OHDSI framework

Eur J Clin Pharmacol (2013) 69:549–557
DOI 10.1007/s00228-012-1334-2

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

High-dimensional versus conventional propensity scores in a comparative effectiveness study of coxibs and reduced upper gastrointestinal complications

E. Garbe · S. Kloss · M. Suling · I. Pigeot · S. Schneeweiss

Received: 28 February 2012 / Accepted: 6 June 2012 / Published online: 5 July 2012

What is the design used by Garbe et al?

Input parameter	Design choice
Target cohort (T)	Celecoxib new users
Comparator cohort (C)	Traditional non-steroid antiflammatory drugs (NSAID) new users
Outcome cohort (O)	Upper gastrointestinal complications (UGIC)
Time-at-risk	cohort start → cohort end
Model specification	1:1 propensity score-matched multivariable conditional Poisson regression

Step 1: Getting the necessary data from the database

Step 1: Getting the necessary data from the database

- Target, comparator, and outcome cohorts
  - From the *cohort* table in the CDM (ATLAS)
  - From a table with the same structure as the *cohort* table
  - From the *drug_era* and/or *condition_era* tables
  - CohortMethod can
    - limit to first exposure
    - remove subjects in both cohorts
    - enforce washout period
- Covariates
  - Automatically constructed default set
  - Custom defined covariates (see *FeatureExtraction* package)
  - Need to exclude drugs of interest (done automatically when using *drug_era*)

getDbCohortMethodData

Arguments for connecting to the database:

- **connectionDetails**: How to connect to the database
- **cdmDatabaseSchema**: The database schema of the CDM
- **oracleTempSchema**: Only used on Oracle
- **cdmVersion**: currently 4 or 5 are supported

getDbCohortMethodData

Arguments for finding the exposures:

- **exposureDatabaseSchema**: Database schema of exposures
- **exposureTable**: Table of exposures
- **targetId**: Cohort definition ID or drug concept ID
- **comparatorId**: Cohort definition ID or drug concept ID
- **firstExposureOnly**: restrict to first exposure per person
- **removeDuplicateSubjects**: remove subjects in both cohorts
- **washoutPeriod**: enforce minimum amount of observation prior to index
- **studyStartDate, studyEndDate**: Also truncates follow-up time

getDbCohortMethodData

Arguments for finding the outcomes:

- **outcomesDatabaseSchema**: Database schema of outcomes
- **outcomesTable**: Table of outcomes
- **outcomeIds:** Cohort definition IDs or condition concept IDs

getDbCohortMethodData

Arguments for creating the covariates:

- **covariateSettings**: Created using the covariateSettings function
- **excludeDrugsFromCovariates**: Automatically exclude drugs of interest from the covariates (only works if targetId and comparatorId are concept IDs)

getDbCohortMethodData

Result:

An object of type *cohortMethodData*

Need to save and load using *saveCohortMethodData* and *loadCohortMethodData*

Diagnostics

Run *summary()* on cohortMethodData object

- Do target, comparator, and outcomes have subjects?
- Are covariates constructed?

```
CohortMethodData object summary

Treatment concept ID: 1
Comparator concept ID: 2
Outcome concept ID(s): 3

Treated persons: 17058
Comparator persons: 13566

Outcome counts:
  Event count Person count
3        6535         4279

Covariates:
Number of covariates: 17
Number of non-zero covariate values: 70605
```

Now try it yourself!

- Go to http://hix.jnj.com/atlas/#/estimation/5
- Click on *Export* and then *R Code*
- Run the *library* commands
- Specify the connection details…

Now try it yourself!

- Specify the connection details…
- Run commands up to and including *saveCohortMethodData* command
- Run *summary* on cohortMethodData object
- Did everything go ok?

This is what you should get

CohortMethodData object summary

Treatment concept ID: 1
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Treated persons: 17058
Comparator persons: 13566

Outcome counts:

	Event count	Person count
3	6535	4279

Covariates:
Number of covariates: 17
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Step 2: Defining the study population

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- Select one of the outcomes of interest
- Enforce additional filtering criteria
- Define risk window

createStudyPopulation

Misc arguments:

- **cohortMethodData**: As created using getDbCohortMethodData
- **outcomeId**: The ID of the outcome of interest
- **firstExposureOnly, removeDuplicateSubjects, washoutPeriod**: Same as in getDbCohortMethodData
- **removeSubjectsWithPriorOutcome**: Remove subjects who have the outcome prior to the index date?
- **priorOutcomeLookback**: How many days should we look back

createStudyPopulation

Arguments for risk window:

- **riskWindowStart**: Start day relative to index
- **addExposureDaysToStart**: Set to TRUE if riskWindowStart should be relative to exposure end date instead
- **riskWindowEnd**: End day relative to index
- **addExposureDaysToEnd**: Set to TRUE if riskWindowEnd should be relative to exposure end date instead
- **minDaysAtRisk**: Remove subjects with less than this number of days at risk

Risk window = time e
riskWind
addExpo
riskWind
addExpo

Risk windov
riskWindow
addExposur
riskWindow
addExposureDaysToEnd = FALSE

Risk window = time exposed + 30 days
riskWindowStart =
addExposureDaysToStart =
riskWindowEnd =
addExposureDaysToEnd =

Risk window = 30 days following index

riskWindowStart	= 0
addExposureDaysToStart	= FALSE
riskWindowEnd	= 30
addExposureDaysToEnd	= FALSE

createStudyPopulation

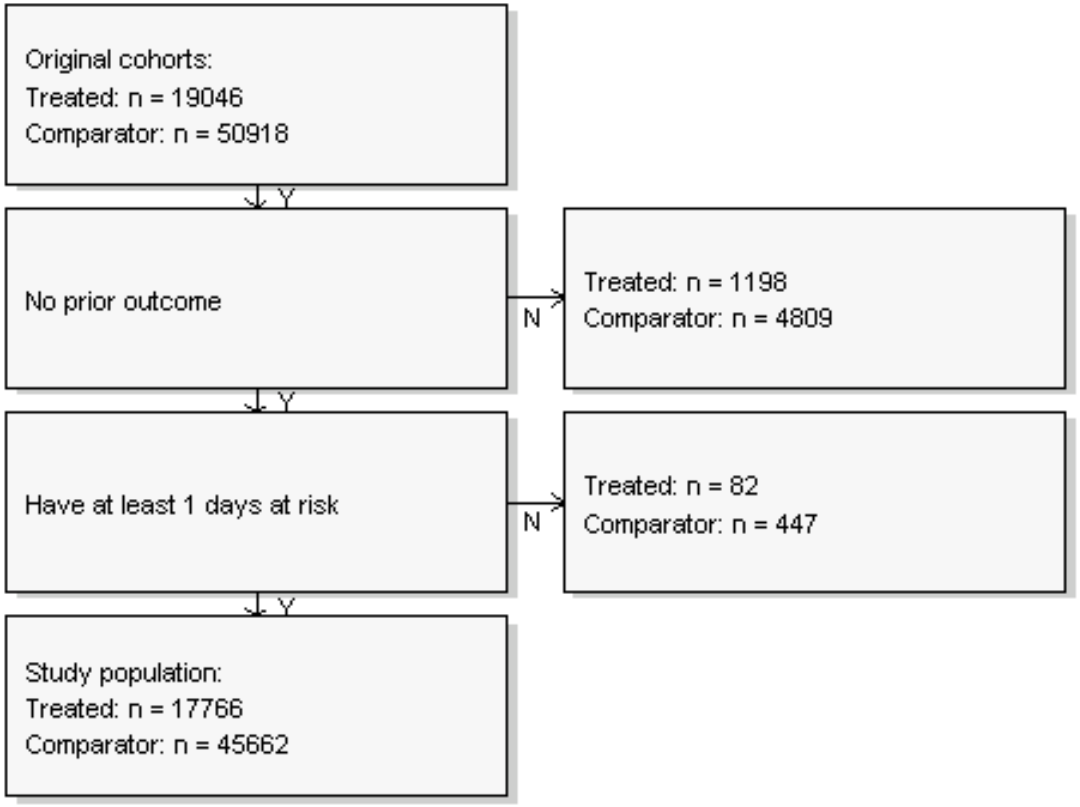
Result:

A data frame specifying the study population

Diagnostics

run *getAttritionTable* or *drawAttritionDiagram*

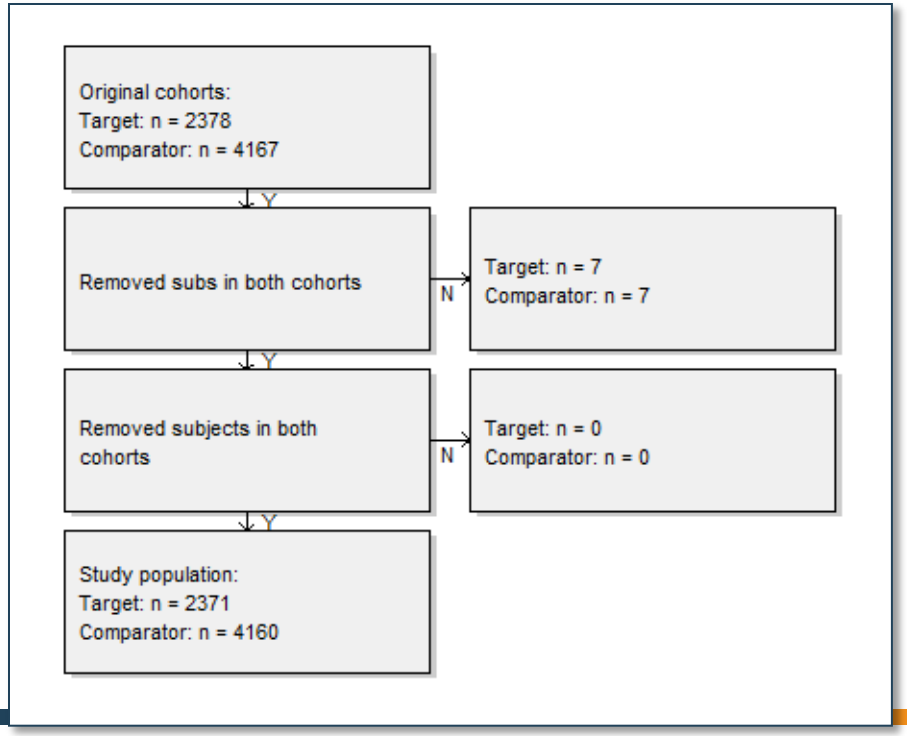
- Are the number of dropouts what you'd expect?



Now try it yourself!

- Run code in section *Defining the study population*
- Check the attrition diagram

This is what you should get:



Step 3: Creating a propensity model

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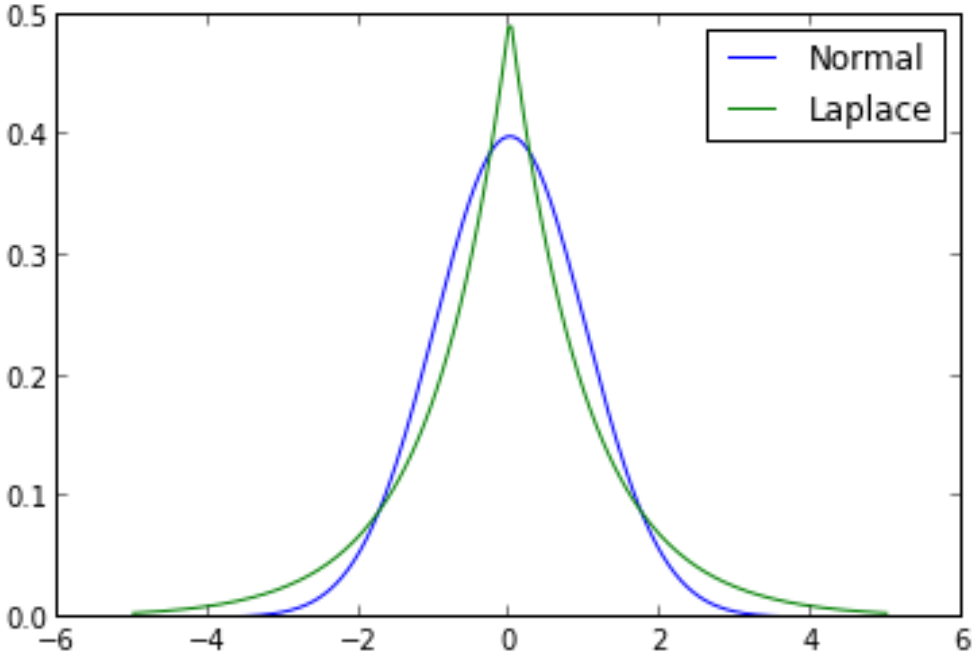
Using regularized logistic regression

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

With prior for every β:



Hyper-parameter

What is the right width of the prior distribution?

Too wide:

- convergence problems
- overfitting

Too narrow:

- ‘underfitting’: missing important predictors

Default: select hyper-parameter through 10-fold cross-validation. This aims to optimize the out-of-sample likelihood

createPs

Important arguments:

- **cohortMethodData**: As created using getDbCohortMethodData
- **population**: The study population
- **prior**: object as created using *createPrior*
  - **priorType**: “laplace” or “none”
  - **variance**: variance of the prior (when not using cross-validation)
  - **useCrossValidation**: TRUE or FALSE
  - **exclude**: exclude these covariate IDs from regularization
- **control**: object as created using *createControl*
  - **tolerance**: numerical tolerance
  - **folds**: number of cross-validation folds
  - **cvRepetitions:** number of cross-validation repetitions
  - **threads**: number of CPU threads to use

createPs

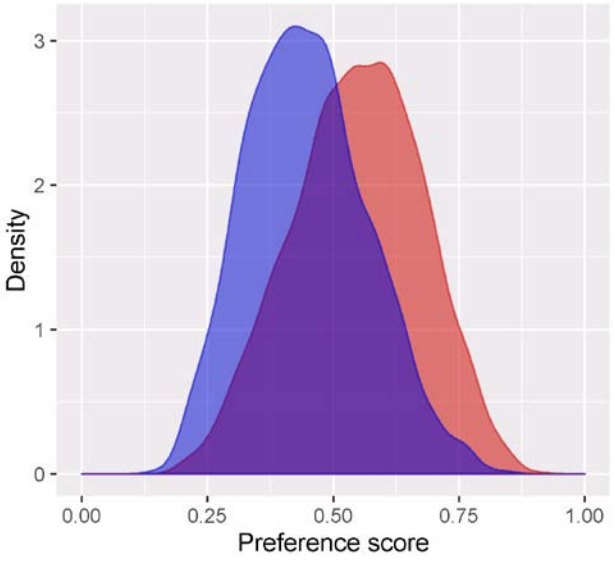
Returns:

The study population data frame with an extra column for the propensity score

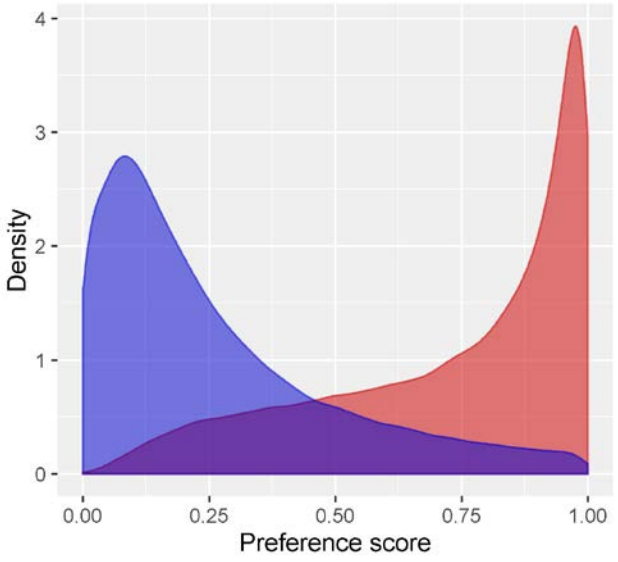
Diagnostics

- Did *createPs* complain about perfect prediction?
- Run *computePsAuc*: 0.5 < AUC < 1?
- Run *getPsModel*: Strongest predictors are not the drugs of interest?
- Run *plotPs*: overlap between cohorts?

Good:



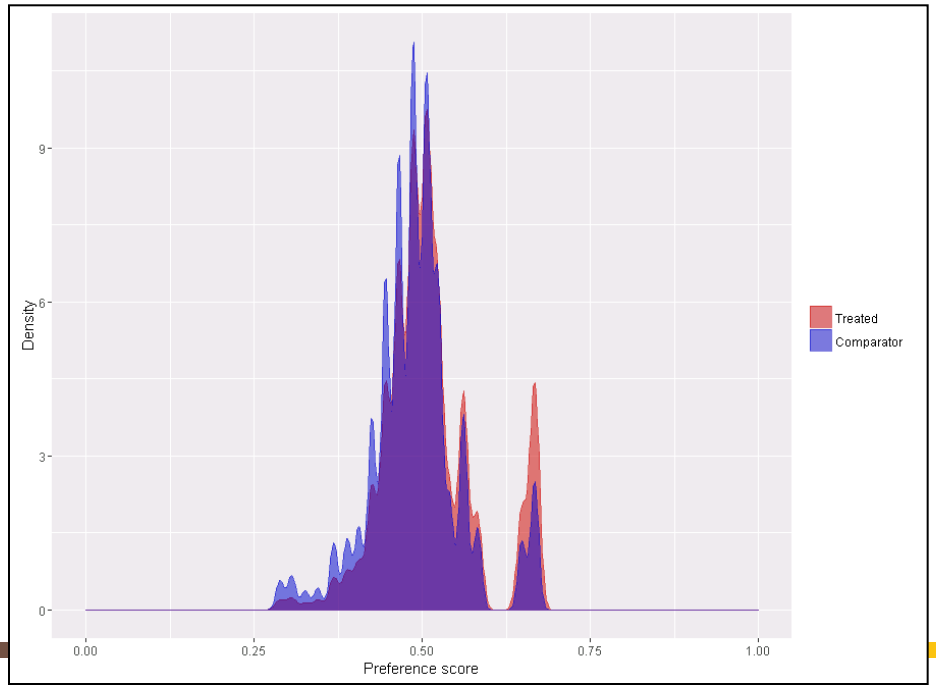
Bad:



Now try it yourself!

- Run code in section *Propensity scores* up to *head(propensityModel)*
  - Modify the number of threads!
- Inspect the PS distribution plot
- Inspect the PS model

This is what I should get:



Step 4:
Matching / Stratification / Trimming

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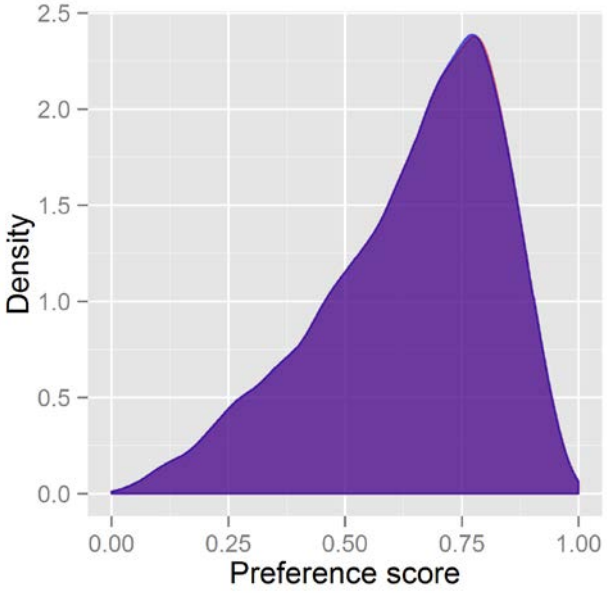
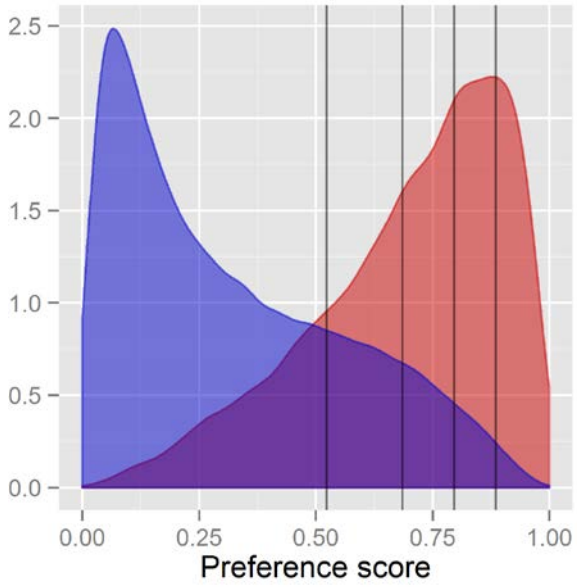
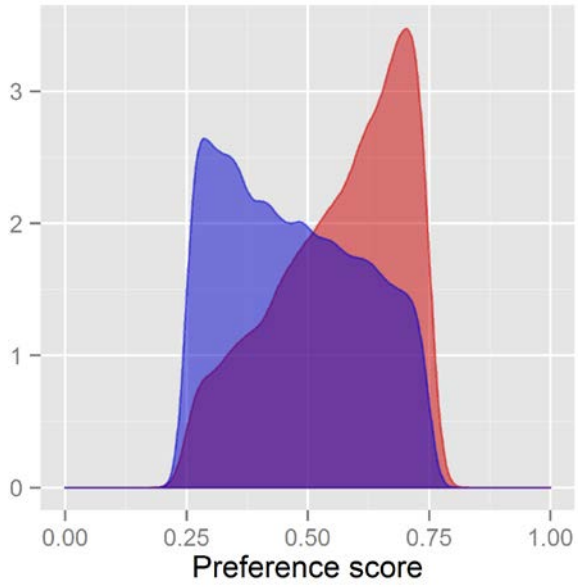






Matching
For every treated subject, select n comparators using greedy matching

Stratification
Stratify into equally-sized strata based on PS

Trimming
Remove subjects with high and low PS

matchOnPs & matchOnPsAndCovariates

Arguments for both functions:

- **population**: population object with propensity scores
- **caliper**: maximum allowed difference in PS
- **caliperScale**: “standardized” or “propensity score”
- **maxRatio**: maximum number of comparators per target

Arguments for matchOnPsAndCovariates:

- **cohortMethodData**: As created using getDbCohortMethodData
- **covariateIds**: must match on these covariates

stratifyByPs & stratifyByPsAndCovariates

Arguments for both functions:

- **population**: population object with propensity scores
- **numberOfStrata**: number of strata

Arguments for stratifyByPsAndCovariates :

- **cohortMethodData**: As created using getDbCohortMethodData
- **covariateIds**: must match on these covariates

trimByPs & trimByPsToEquipoise

Argument for both functions:

- **population**

Argument for trimByPs :

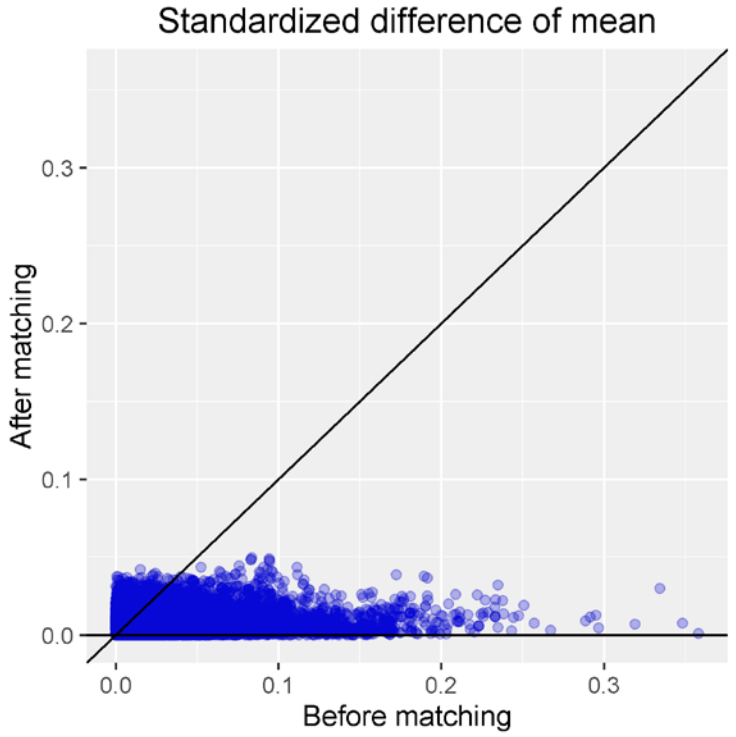
- **trimFraction**: Fraction to be removed from each group

Argument for trimByPsToEquipoise :

- **bounds**: Bounds on the preference score

Diagnostics

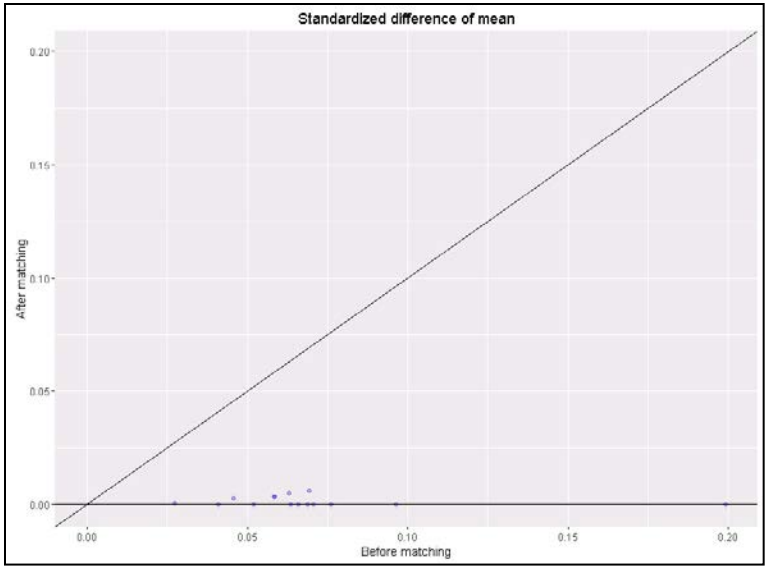
- Run *getAttritionTable* or *drawAttritionDiagram:* did we not lose everyone?
- Run *computeCovariateBalance* and *plotCovariateBalanceScatterPlot*: standardized difference < 0.1 for all covariates?



Now try it yourself!

- Run the rest of the code in section *Propensity scores*
- Inspect the attrition diagram
- Inspect the balance scatter plot

This is what you should get:



Step 5: Fitting the outcome model

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Regression for outcome with at least treatment as predictor

Types:

- **Logistic**: compares risks
- **Poisson**: compares rates
- **Cox**: compares time-to-event

Conditioning:

- **Not conditioned**
- **Conditioned on matches set / strata**

Covariates:

- **None**
- **Same as used in propensity model**

fitOutcomeModel

Arguments:

- **population**: population with or without strata
- **cohortMethodData**: As created using getDbCohortMethodData
- **modelType**: “logistic”, “poisson”, or “cox”
- **stratified**: condition on strata?
- **useCovariates**: add same covariates as used in PS?
- **prior**: object as created using *createPrior*
  - **priorType**: “laplace” or “none”
  - **variance**: variance of the prior (when not using cross-validation)
  - **useCrossValidation**: TRUE or FALSE
  - **exclude**: exclude these covariate IDs from regularization
- **control**: object as created using *createControl*
  - **tolerance**: numerical tolerance
  - **folds**: number of cross-validation folds
  - **cvRepetitions:** number of cross-validation repetitions
  - **threads**: number of CPU threads to use

Diagnostics

- For Cox models run *plotKaplanMeier*: Evidence of non-proportionality?

Now try it yourself!

1. Run code in the section *Outcome Model*
2. Change the model to Cox regression

This is what you should get after step 2:

Model type: cox
Stratified: TRUE
Use covariates: FALSE
Status: OK

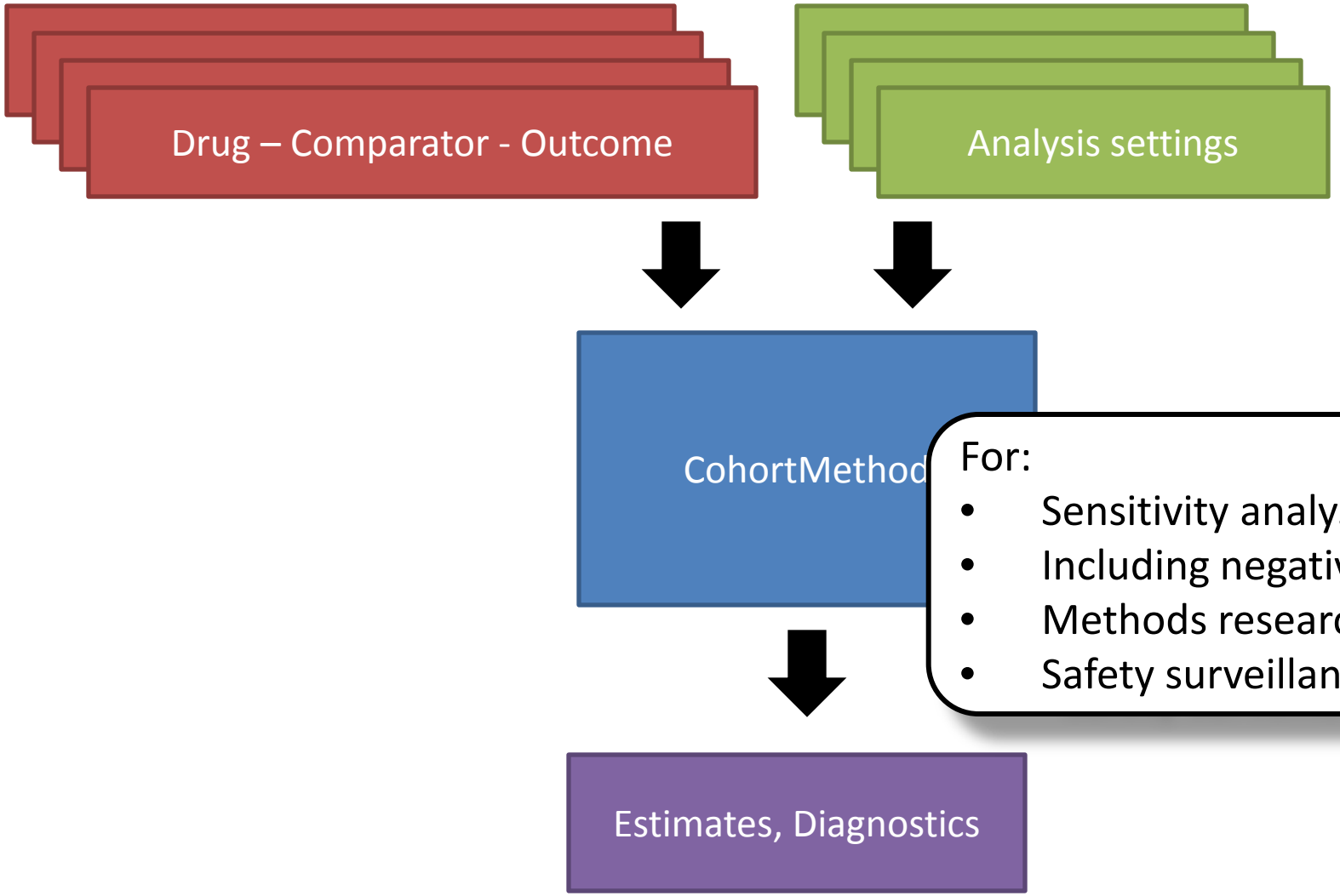
	Estimate	lower .95	upper .95	logRr	seLogRr
treatment	0.62500	0.18883	1.87314	-0.47000	0.5853

Generic study steps

1. Getting the necessary data from the database
2. Defining the study population
3. [Creating a propensity model]
4. [Trimming / Matching / Stratification]
5. Fitting the outcome model

+ generating various diagnostics

All-by-all support

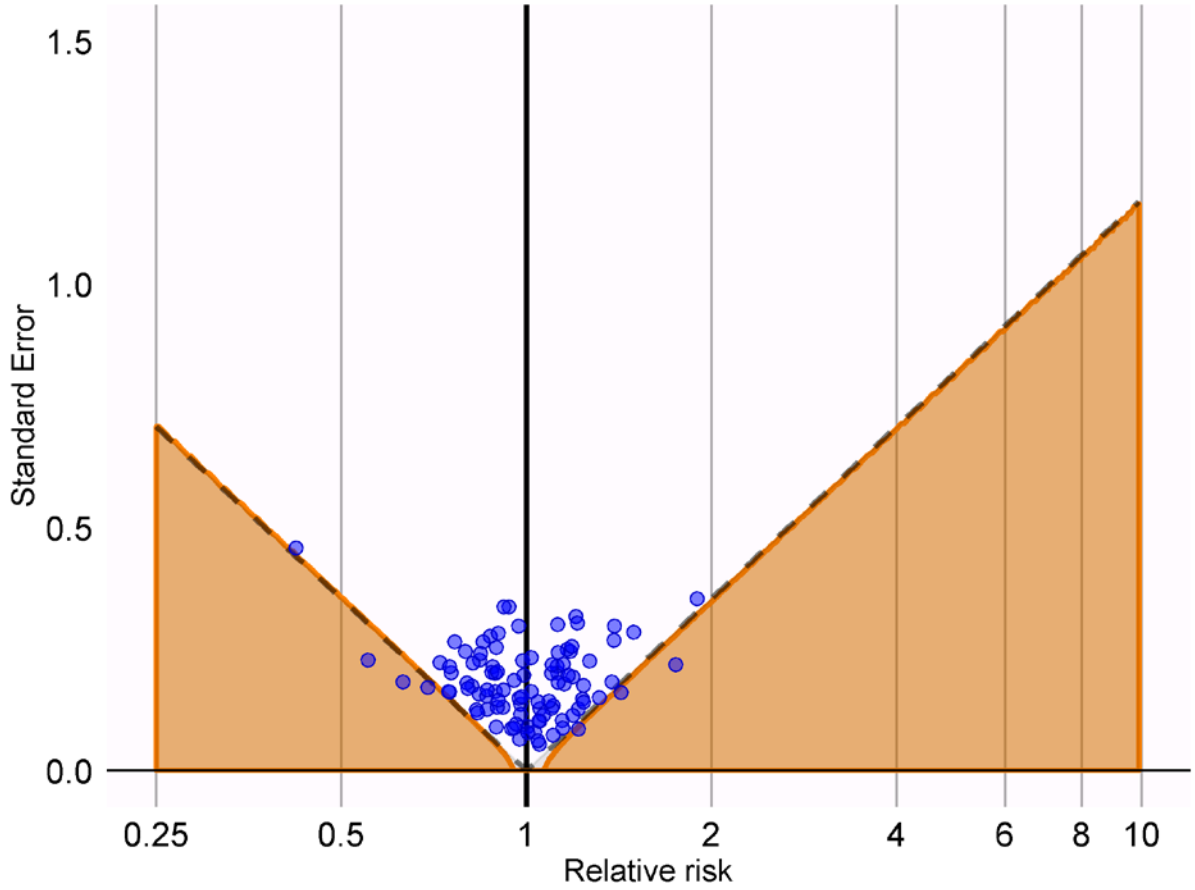


Negative controls as study diagnostics

- Negative control outcomes are outcomes not believed to be caused by either exposure
- Assume true HR = 1
- Observe distribution of estimates

Negative control distribition

Approx. 95% of estimates should have 1 inside 95% confidence interval

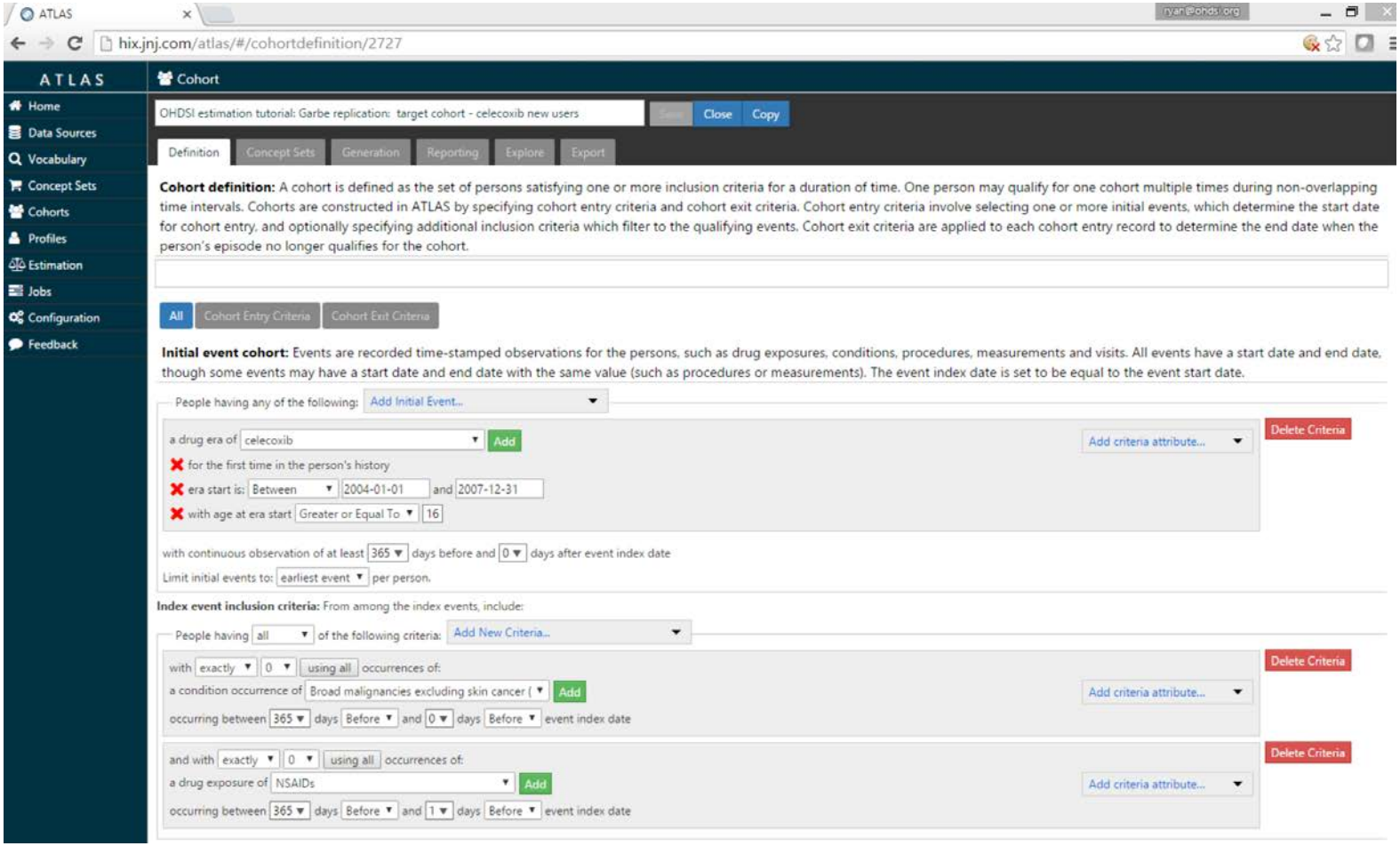


Further things to try

- Change code to use all covariates (instead of handpicked ones)
- Remove people with prior outcomes
- Create a Kaplan-Meier plot

Counterfactual – other track

- Learned how to create the cohorts we used



Counterfactual – other track

- Learned how to create the cohorts we used
- Learned to think about the study design
- Learned how to use Atlas to generate starting R code