# Single studies using the CohortMethod package

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# 1 Introduction

This vignette describes how you can use the CohortMethod package to perform a single new-user cohort study. We will walk through all the steps needed to perform an exemplar study, and we have selected the well-studied topic of the effect of coxibs versus non-selective non-steroidal anti-inflammatory drugs (NSAIDs) on gastrointestinal (GI) bleeding-related hospitalization. For simplicity, we focus on one coxib – celecoxib – and one non-selective NSAID – diclofenac.

# 2 Installation instructions

Before installing the CohortMethod package make sure you have Java available. Java can be downloaded from www.java.com. For Windows users, RTools is also necessary. RTools can be downloaded from CRAN.

The CohortMethod package is currently maintained in a Github repository, and has dependencies on other packages in Github. All of these packages can be downloaded and installed from within R using the devtools package:

```
install.packages("devtools")
library(devtools)
install_github("ohdsi/OhdsiRTools")
install_github("ohdsi/SqlRender")
install_github("ohdsi/DatabaseConnector")
install_github("ohdsi/Cyclops")
install_github("ohdsi/PatientLevelPrediction")
install_github("ohdsi/CohortMethod")
```

Once installed, you can type library (Cohort Method) to load the package.

#### 3 Data extraction

The first step in running the CohortMethod is extracting all necessary data from the database server holding the data in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) format.

#### 3.1 Configuring the connection to the server

We need to tell R how to connect to the server where the data are. CohortMethod uses the DatabaseConnector package, which provides the createConnectionDetails function. Type ?createConnectionDetails for the specific settings required for the various database management systems (DBMS). For example, one might connect to a PostgreSQL database using this code:

The last three lines define the cdmDatabaseSchema and resultSchema variables, as well as the CDM version. We'll use these later to tell R where the data in CDM format live, where we want to write intermediate and result tables, and what version CDM is used. Note that for Microsoft SQL Server, databaseschemas need to specify both the database and the schema, so for example cdmDatabaseSchema <- "my\_cdm\_data.dbo".

# 3.2 Preparing the exposures and outcome(s)

We need to define the exposures and outcomes for our study. One could use an external cohort definition tools, but in this example we do this by writing SQL statements against the OMOP CDM that populate

a table of events in which we are interested. The resulting table should have the same structure as the cohort table in the CDM. For CDM v5+, this means it should have the fields cohort\_definition\_id, cohort\_start\_date, cohort\_end\_date,and subject\_id. For CDM v4, the cohort\_definition\_id field must be called cohort\_concept\_id.

For our example study, we have created a file called coxib VsNonselVsGiBleed.sql with the following contents:

```
/************
File coxibVsNonselVsGiBleed.sql
************
IF OBJECT_ID('@resultsDatabaseSchema.coxibVsNonselVsGiBleed', 'U') IS NOT NULL
 DROP TABLE @resultsDatabaseSchema.coxibVsNonselVsGiBleed;
CREATE TABLE @resultsDatabaseSchema.coxibVsNonselVsGiBleed (
 cohort_definition_id INT,
 cohort_start_date DATE,
   cohort_end_date DATE,
   subject_id BIGINT
   );
INSERT INTO @resultsDatabaseSchema.coxibVsNonselVsGiBleed (
   cohort_definition_id,
    cohort start date,
   cohort_end_date,
   subject_id
SELECT 1, -- Exposure
   drug_era_start_date,
   drug_era_end_date,
   person_id
FROM @cdmDatabaseSchema.drug_era
WHERE drug_concept_id = 1118084; -- celecoxib
INSERT INTO @resultsDatabaseSchema.coxibVsNonselVsGiBleed (
    cohort definition id,
   cohort_start_date,
   cohort_end_date,
   subject_id
SELECT 2, -- Comparator
   drug_era_start_date,
   drug_era_end_date,
   person_id
FROM @cdmDatabaseSchema.drug_era
WHERE drug_concept_id = 1124300; --diclofenac
INSERT INTO @resultsDatabaseSchema.coxibVsNonselVsGiBleed (
    cohort_definition_id,
   cohort_start_date,
   cohort_end_date,
   subject_id
SELECT 3, -- Outcome
```

Note on CDM V4 visit\_concept\_id should be place\_of\_service\_concept\_id, and cohort\_definition\_id should be cohort\_concept\_id.

This is parameterized SQL which can be used by the SqlRender package. We use parameterized SQL so we do not have to pre-specify the names of the CDM and result schemas. That way, if we want to run the SQL on a different schema, we only need to change the parameter values; we do not have to change the SQL code. By also making use of translation functionality in SqlRender, we can make sure the SQL code can be run in many different environments.

In this code, we first read the SQL from the file into memory. In the next line, we replace the two parameter names with the actual values. We then translate the SQL into the dialect appropriate for the DBMS we already specified in the connectionDetails. Next, we connect to the server, and submit the rendered and translated SQL.

If all went well, we now have a table with the events of interest. We can see how many events per type:

# 3.3 Extracting the data from the server

Now we can tell CohortMethod to define the cohorts based on our events, and extract all necessary data for our analysis:

```
# Get all NSAID Concept IDs for exclusion:
sql <- paste("SELECT concept id",</pre>
             "FROM @cdmDatabaseSchema.concept_ancestor",
             "INNER JOIN @cdmDatabaseSchema.concept",
             "ON descendant_concept_id = concept_id",
             "WHERE ancestor_concept_id = 21603933")
sql <- SqlRender::renderSql(sql, cdmDatabaseSchema = cdmDatabaseSchema)$sql</pre>
sql <- SqlRender::translateSql(sql, targetDialect = connectionDetails$dbms)$sql</pre>
nsaids <- querySql(connection, sql)</pre>
nsaids <- nsaids$CONCEPT_ID</pre>
# Define which types of covariates must be constructed:
covarSettings <- createCovariateSettings(useCovariateDemographics = TRUE,</pre>
                                          useCovariateConditionOccurrence = TRUE,
                                          useCovariateConditionOccurrence365d = TRUE,
                                          useCovariateConditionOccurrence30d = TRUE,
                                          useCovariateConditionOccurrenceInpt180d = TRUE,
                                          useCovariateConditionEra = TRUE,
                                          useCovariateConditionEraEver = TRUE,
                                          useCovariateConditionEraOverlap = TRUE,
                                          useCovariateConditionGroup = TRUE,
                                          useCovariateDrugExposure = TRUE,
                                          useCovariateDrugExposure365d = TRUE,
                                          useCovariateDrugExposure30d = TRUE,
                                          useCovariateDrugEra = TRUE,
                                          useCovariateDrugEra365d = TRUE,
                                          useCovariateDrugEra30d = TRUE,
                                          useCovariateDrugEraEver = TRUE,
                                          useCovariateDrugEraOverlap = TRUE,
                                          useCovariateDrugGroup = TRUE,
                                          useCovariateProcedureOccurrence = TRUE,
                                          useCovariateProcedureOccurrence365d = TRUE,
                                          useCovariateProcedureOccurrence30d = TRUE,
                                          useCovariateProcedureGroup = TRUE,
                                          useCovariateObservation = TRUE,
                                          useCovariateObservation365d = TRUE,
                                          useCovariateObservation30d = TRUE,
                                          useCovariateObservationCount365d = TRUE,
                                          useCovariateMeasurement365d = TRUE,
                                          useCovariateMeasurement30d = TRUE,
                                          useCovariateMeasurementCount365d = TRUE,
                                          useCovariateMeasurementBelow = TRUE,
                                          useCovariateMeasurementAbove = TRUE,
                                          useCovariateConceptCounts = TRUE,
                                          useCovariateRiskScores = TRUE,
                                          useCovariateRiskScoresCharlson = TRUE,
                                          useCovariateRiskScoresDCSI = TRUE,
                                          useCovariateRiskScoresCHADS2 = TRUE,
                                          useCovariateInteractionYear = FALSE,
```

```
useCovariateInteractionMonth = FALSE,
                                          excludedCovariateConceptIds = nsaids,
                                          deleteCovariatesSmallCount = 100)
#Load data:
cohortMethodData <- getDbCohortMethodData(connectionDetails = connectionDetails,</pre>
                                           cdmDatabaseSchema = cdmDatabaseSchema,
                                           oracleTempSchema = resultsDatabaseSchema,
                                           targetId = 1,
                                           comparatorId = 2,
                                           outcomeIds = 3,
                                           studyStartDate = "",
                                           studyEndDate = "",
                                           exposureDatabaseSchema = resultsDatabaseSchema,
                                           exposureTable = "coxibVsNonselVsGiBleed",
                                           outcomeDatabaseSchema = resultsDatabaseSchema,
                                           outcomeTable = "coxibVsNonselVsGiBleed",
                                           cdmVersion = cdmVersion,
                                           excludeDrugsFromCovariates = FALSE,
                                           firstExposureOnly = TRUE,
                                           removeDuplicateSubjects = TRUE,
                                           washoutPeriod = 180,
                                           covariateSettings = covariateSettings)
cohortMethodData
```

```
#> CohortMethodData object
#>
#> Treatment concept ID: 1
#> Comparator concept ID: 2
#> Outcome concept ID(s): 3
```

There are many parameters, but they are all documented in the CohortMethod manual. The createCovariateSettings function is described in the FeatureExtraction package. In short, we are pointing the function to the table created earlier and indicating which concept IDs in that table identify the target, comparator and outcome. We instruct that many different covariates should be constructed, including covariates for all conditions, drug exposures, and procedures that were found on or before the index date.

Important: The target and comparator drug must not be included in the covariates, including any descendant concepts. If the targetId and comparatorId arguments represent real concept IDs, you can set the excludeDrugsFromCovariates argument to TRUE and automatically the drugs and their descendants will be excluded from the covariates. However, if the targetId and comparatorId arguments do not represent concept IDs, such as in the example above, you will need to manually add the drugs and descendants to the excludedCovariateConceptIds of thecovariateSettings argument.

All data about the cohorts, outcomes, and covariates are extracted from the server and stored in the cohortMethodData object. This object uses the package ff to store information in a way that ensures R does not run out of memory, even when the data are large.

We can use the generic summary() function to view some more information of the data we extracted:

```
summary(cohortMethodData)
```

#> CohortMethodData object summary

```
#>
#> Treatment concept ID: 1
#> Comparator concept ID: 2
#> Outcome concept ID(s): 3
#> Treated persons: 34412
#> Comparator persons: 180669
#>
#> Outcome counts:
#>
     Event count Person count
#> 3
           15655
                        10424
#>
#> Covariates:
#> Number of covariates: 23458
#> Number of non-zero covariate values: 100012246
```

#### 3.3.1 Saving the data to file

Creating the cohortMethodData file can take considerable computing time, and it is probably a good idea to save it for future sessions. Because cohortMethodData uses ff, we cannot use R's regular save function. Instead, we'll have to use the savecohortMethodData() function:

```
savecohortMethodData(cohortMethodData, "coxibVsNonselVsGiBleed")
```

We can use the loadCohortMethodData() function to load the data in a future session.

#### 3.3.2 Defining new users

Typically, a new user is defined as first time use of a drug (either target or comparator), and typically a washout period (a minimum number of days prior first use) is used to make sure it is truly first use. When using the CohortMethod package, you can enforce the necessary requirements for new use in three ways:

- 1. When creating the cohorts in the database, for example when using a cohort definition tool.
- 2. When loading the cohorts using the getDbCohortMethodData function, you can use the firstExposureOnly, removeDuplicateSubjects, and washoutPeriod arguments. (As shown in the example above).
- 3. When defining the study population using the createStudyPopulation function (see below) using the firstExposureOnly, removeDuplicateSubjects, and washoutPeriod arguments.

The advantage of option 1 is that the input cohorts are already fully defined outside of the CohortMethod package, and for example external cohort characterization tools can be used on the same cohorts used in this package. The advantage of options 2 and 3 is that it saves you the trouble of limiting to first use yourself, for example allowing you to directly use the drug\_era table in the CDM. Option 2 is more efficient than 3, since only data for first use will be fetched, while option 3 is less efficient but allows you to compare the original cohorts to the study population.

# 4 Defining the study population

Typically, the exposure cohorts and outcome cohorts will be defined independently of each other. When we want to produce an effect size estimate, we need to further restrict these cohorts and put them together, for

example by removing exposed subjects that had the outcome prior to exposure, and only keeping outcomes that fall within a defined risk window. For this we can use the createStudyPopulation function:

Note that we've set firstExposureOnly and removeDuplicateSubjects to FALSE, and washoutPeriod to zero because we already filtered on these arguments when using the getDbCohortMethodData function. We specify the outcome ID we will use, and that people with outcomes prior to the risk window start date will be removed. The risk window is defined as starting at the index date (riskWindowStart = 0 and addExposureDaysToStart = FALSE), and the risk windows ends 30 days after exposure ends (riskWindowEnd = 30 and addExposureDaysToEnd = TRUE). Note that the risk windows are truncated at the end of observation or the study end date. We also remove subjects who have no time at risk. To see how many people are left in the study population we can always use the getAttritionTable function:

```
getAttritionTable(studyPop)
```

```
description
#>
#> 1
                                                               Original cohorts
#> 2 First exp. only & removed subs in both cohorts & 180 days of obs. prior
#> 3
                                                               No prior outcome
#> 4
                                                              Have time at risk
#>
     treatedPersons comparatorPersons treatedExposures comparatorExposures
#> 1
              73768
                                279333
                                                                       420205
                                                  129173
#> 2
              34412
                                180669
                                                   34412
                                                                        180669
#> 3
              33235
                                176404
                                                   33235
                                                                        176404
                                176404
#> 4
              33235
                                                   33235
                                                                        176404
```

One additional filtering step that is often used is matching or trimming on propensity scores, as will be discussed next.

# 5 Propensity scores

The CohortMethod can use propensity scores to adjust for potential confounders. Instead of the traditional approach of using a handful of predefined covariates, CohortMethod typically uses thousands to millions of covariates that are automatically constructed based on conditions, procedures and drugs in the records of the subjects.

#### 5.1 Fitting a propensity model

We can fit a propensity model using the covariates constructed by the getDbcohortMethodData() function:

```
ps <- createPs(cohortMethodData = cohortMethodData, population = studyPop)
```

The createPs() function uses the Cyclops package to fit a large-scale regularized logistic regression.

To fit the propensity model, Cyclops needs to know the hyperparameter value which specifies the variance of the prior. By default Cyclops will use cross-validation to estimate the optimal hyperparameter. However, be aware that this can take a really long time. You can use the prior and control parameters of the createPs() to specify Cyclops behavior, including using multiple CPUs to speed-up the cross-validation.

# 5.2 Propensity score diagnostics

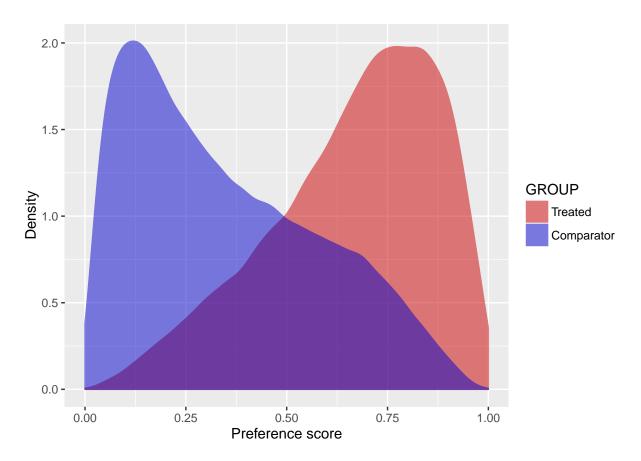
We can compute the area under the receiver-operator curve (AUC) for the propensity score model:

```
computePsAuc(ps)
```

#### #> [1] 0.8345953

We can also plot the propensity score distribution, although we prefer the preference score distribution:





It is also possible to inspect the propensity model itself by showing the covariates that have non-zero coefficients:

```
propensityModel <- getPsModel(ps, cohortMethodData)
head(propensityModel)</pre>
```

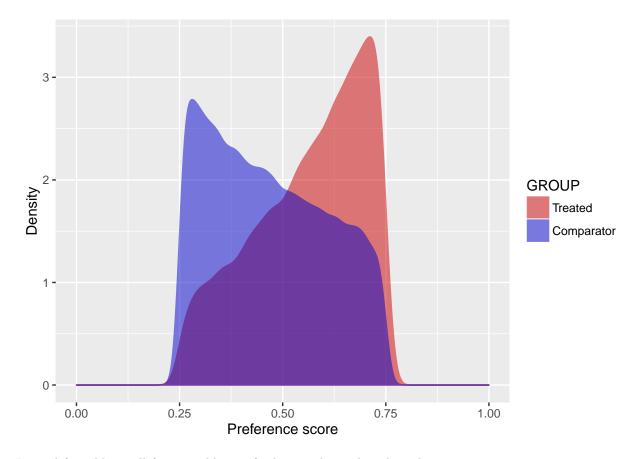
```
#>
        coefficient
                             id
                                                               covariateName
          -2.510859 1150871503
#> 1134
                                ... with cohort index:
                                                         1150871-Misoprostol
#> 2
          -1.218723
                             13
                                                            Age group: 15-19
          -1.174053
#> 1
                             12
                                                            Age group: 10-14
#> 1510
          -1.108988 2721679901 ...dex:
                                         2721679-Case management, per month
#> 33
           1.053843
                           2007
                                                            Index year: 2007
#> 667
           1.031093
                     434007201 ...ereditary factor VIII deficiency disease
```

One advantage of using the regularization when fitting the propensity model is that most coefficients will shrink to zero and fall out of the model. It is a good idea to inspect the remaining variables for anything that should not be there.

## 5.3 Using the propensity score

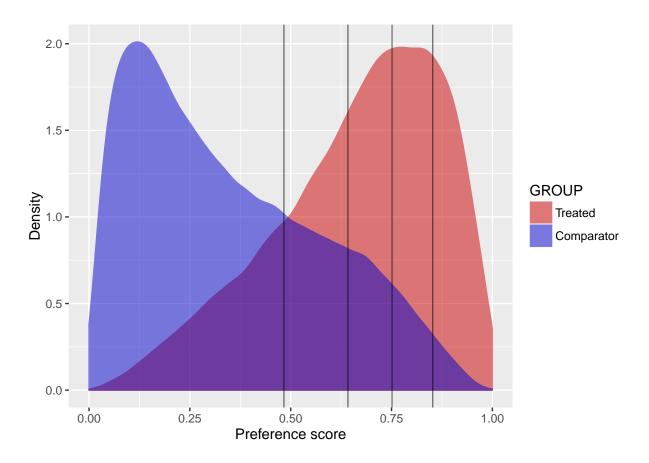
We can use the propensity scores to trim, stratify, or match our population. For example, one could trim to equipoise, meaning only subjects with a preference score between 0.25 and 0.75 are kept:

```
trimmedPop <- trimByPsToEquipoise(ps)
plotPs(trimmedPop, ps, scale = "preference")</pre>
```



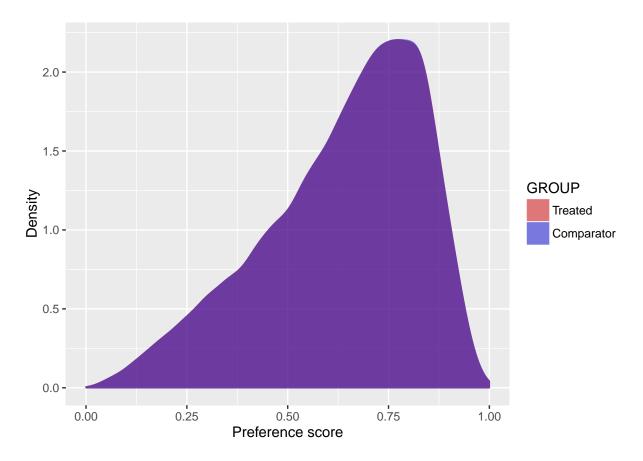
Instead (or additionally), we could stratify the population based on the propensity score:

```
stratifiedPop <- stratifyByPs(ps, numberOfStrata = 5)
plotPs(stratifiedPop, ps, scale = "preference")</pre>
```



We can also match subjects based on propensity scores. In this example, we're using one-to-one matching:

```
matchedPop <- matchOnPs(ps, caliper = 0.25, caliperScale = "standardized", maxRatio = 1)
plotPs(matchedPop, ps)</pre>
```



Note that for both stratification and matching it is possible to specify additional matching criteria such as age and sex using the stratifyByPsAndCovariates() and matchOnPsAndCovariates() functions, respectively.

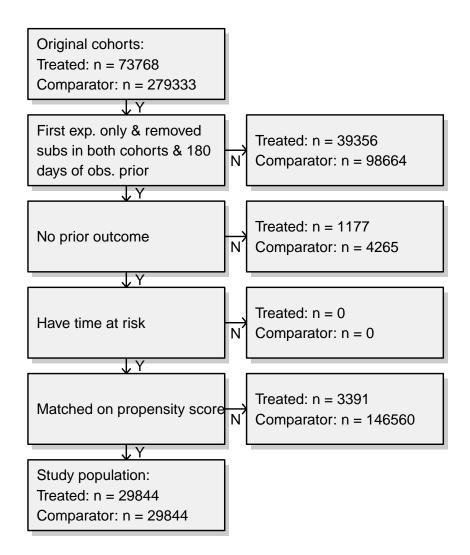
We can see the effect of trimming and/or matching on the population using the getAttritionTable function:

## getAttritionTable(matchedPop)

#>				description
#>	1			Original cohorts
#>	2 First exp. only	% removed subs in	both cohorts & 1	180 days of obs. prior
#>	3			No prior outcome
#>	4			Have time at risk
#>	5		Matche	ed on propensity score
#>	${\tt treatedPersons}$	${\tt comparatorPersons}$	treatedExposures	${\tt comparatorExposures}$
#>	1 73768	279333	129173	420205
#>	2 34412	180669	34412	180669
#>	3 33235	176404	33235	176404
#>	4 33235	176404	33235	176404
#>	5 29844	29844	29844	29844

Or, if we like, we can plot an attrition diagram:

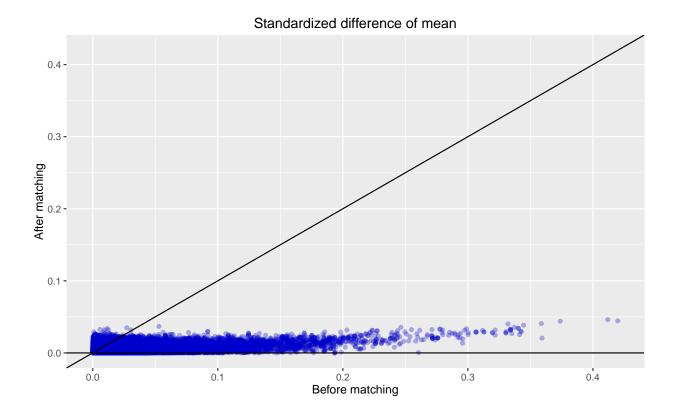
## drawAttritionDiagram(matchedPop)



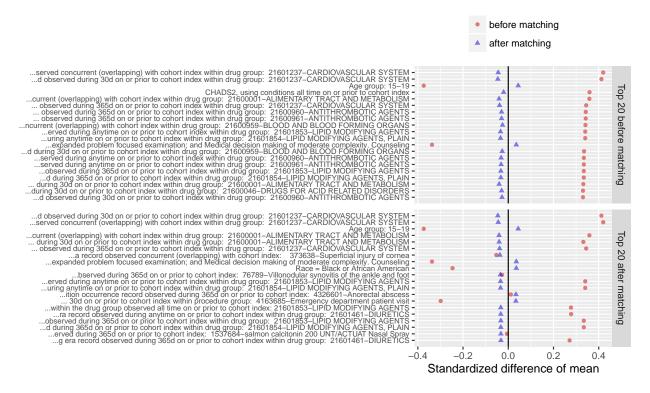
# 5.4 Evaluating covariate balance

To evaluate whether our use of the propensity score is indeed making the two cohorts more comparable, we can compute the covariate balance before and after trimming, matching, and/or stratifying:

```
balance <- computeCovariateBalance(matchedPop, cohortMethodData)
plotCovariateBalanceScatterPlot(balance)</pre>
```



plotCovariateBalanceOfTopVariables(balance)



The 'before matching' population is the population as extracted by the getDbCohortMethodData function, so

before any further filtering steps.

# 5.5 Inserting the population cohort in the database

For various reasons it might be necessary to insert the study population back into the database, for example because we want to use an external cohort characterization tool. We can use the insertDbPopulation function for this purpose:

This function will store the population in a table with the same structure as the cohort table in the CDM, in this case in the same table where we had created our original cohorts.

#### 6 Outcome models

#> Model type: cox

The outcome model is a model describing which variables are associated with the outcome.

# 6.1 Fitting the outcome model

In theory we could fit an outcome model without using the propensity scores. In this example we are fitting an outcome model using a Cox regression:

```
#> Stratified: FALSE
#> Use covariates: FALSE
#> Status: OK
#>
#> Estimate lower .95 upper .95 logRr seLogRr
#> treatment 0.973207 0.825208 1.144220 -0.027158 0.0834
```

But of course we want to make use of the matching done on the propensity score:

```
#> Model type: cox
#> Stratified: TRUE
#> Use covariates: FALSE
#> Status: OK
#>
#> Estimate lower .95 upper .95 logRr seLogRr
#> treatment 0.85417 0.63506 1.14624 -0.15763 0.1506
```

Note that we define the sub-population to be only those in the matchedPop object, which we created earlier by matching on the propensity score. We also now use a stratified Cox model, conditioning on the propensity score match sets.

One final refinement would be to use the same covariates we used to fit the propensity model to also fit the outcome model. This way we are more robust against misspecification of the model, and more likely to remove bias. For this we use the regularized Cox regression in the Cyclops package. (Note that the treatment variable is automatically excluded from regularization.)

```
#> Model type: cox
#> Stratified: TRUE
#> Use covariates: TRUE
#> Status: OK
#> Prior variance: 0.0355817957978861
#>
#> Estimate lower .95 upper .95 logRr seLogRr
#> treatment 0.90446 0.64314 1.26682 -0.10042 0.1729
```

# 6.2 Injecting the outcome model

We can inspect more details of the outcome model:

#### summary(outcomeModel)

```
#> Model type: cox
#> Stratified: TRUE
#> Use covariates: TRUE
#> Status: OK
#> Prior variance: 0.0355817957978861
#>
#>
             Estimate lower .95 upper .95
                                             logRr seLogRr
#> treatment 0.90446
                        0.64314
                                1.26682 -0.10042 0.1729
#> Population counts
#>
         treatedPersons comparatorPersons treatedExposures
                  29844
                                    29844
                                                     29844
#> Count
         comparatorExposures
#>
```

```
#> Count
                       29844
#>
#> Outcome counts
        treatedPersons comparatorPersons treatedExposures
#> Count
                    181
                                      136
         comparator Exposures
#>
#> Count
#>
#> Time at risk
        treatedDays comparatorDays
#>
#> Days
            3965876
                           2547211
exp(coef(outcomeModel))
#> [1] 0.9044606
exp(confint(outcomeModel))
#> [1] 0.6431429 1.2668171
```

We can also see the covariates that ended up in the outcome model:

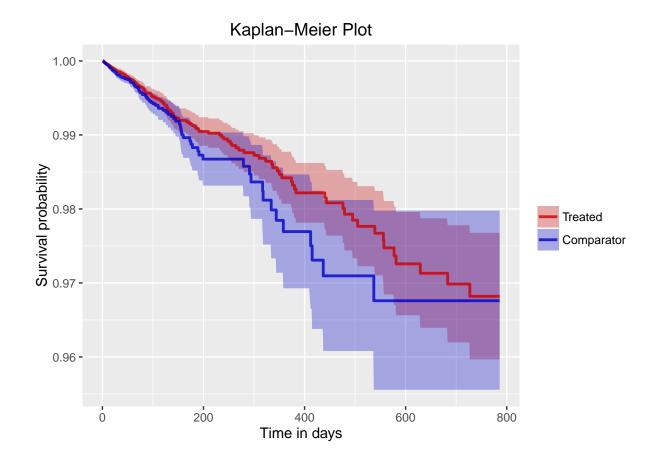
```
fullOutcomeModel <- getOutcomeModel(outcomeModel, cohortMethodData)
head(fullOutcomeModel)</pre>
```

## 6.3 Kaplan-Meier plot

We can create the Kaplan-Meier plot:

```
plotKaplanMeier(matchedPop, includeZero = FALSE)
```

```
#> Warning in plotKaplanMeier(matchedPop, includeZero = FALSE): The population
#> has strata, but the stratification is not visible in the plot
```



# 7 Acknowledgments

Considerable work has been dedicated to provide the CohortMethod package.

```
citation("CohortMethod")
```

```
#>
#> To cite package 'CohortMethod' in publications use:
#>
     Martijn J. Schuemie, Marc A. Suchard and Patrick B. Ryan (2015).
#>
#>
     CohortMethod: New-user cohort method with large scale propensity
#>
     and outcome models. R package version 2.0.0.
#>
#> A BibTeX entry for LaTeX users is
#>
#>
     @Manual{,
#>
       title = {CohortMethod: New-user cohort method with large scale propensity and outcome models},
       author = {Martijn J. Schuemie and Marc A. Suchard and Patrick B. Ryan},
#>
#>
       year = \{2015\},\
       note = {R package version 2.0.0},
#>
#>
#> ATTENTION: This citation information has been auto-generated from
#> the package DESCRIPTION file and may need manual editing, see
```

```
#> 'help("citation")'.
```

Further, CohortMethod makes extensive use of the Cyclops package.

```
citation("Cyclops")
```

```
#> To cite Cyclops in publications use:
#> Suchard MA, Simpson SE, Zorych I, Ryan P and Madigan D (2013).
#> "Massive parallelization of serial inference algorithms for
#> complex generalized linear models." _ACM Transactions on Modeling
#> and Computer Simulation_, *23*, pp. 10. <URL:</pre>
#> http://dl.acm.org/citation.cfm?id=2414791>.
#>
#> A BibTeX entry for LaTeX users is
#>
#>
     @Article{,
#>
       author = {M. A. Suchard and S. E. Simpson and I. Zorych and P. Ryan and D. Madigan},
       title = {Massive parallelization of serial inference algorithms for complex generalized linear m
#>
       journal = {ACM Transactions on Modeling and Computer Simulation},
#>
       volume = \{23\},
#>
       pages = \{10\},
#>
#>
      year = {2013},
       url = {http://dl.acm.org/citation.cfm?id=2414791},
#>
```

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