Running multiple analyses at once using the SelfControlledCaseSeries package

Martijn J. Schuemie

2023-12-11

Contents

1 Introduction

In this vignette we focus on running several different analyses on several exposure-outcome pairs This can be useful when we want to explore the sensitivity to analyses choices, include controls, or run an experiment similar to the OMOP experiment to empirically identify the optimal analysis choices for a particular research question.

This vignette assumes you are already familiar with the `SelfControlledCaseSeries` package and are able to perform single studies. We will walk through all the steps needed to perform an exemplar set of analyses, and we have selected the well-studied topic of the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on gastrointestinal (GI) bleeding-related hospitalization. For simplicity, we focus on one NSAID: diclofenac. We will execute various variations of an analysis for the primary exposure pair and a large set of negative control exposures.

2 General approach

The general approach to running a set of analyses is that you specify all the function arguments of the functions you would normally call, and create sets of these function arguments. The final outcome models as well as intermediate data objects will all be saved to disk for later extraction.

An analysis will be executed by calling these functions in sequence:

1. `getDbSccsData()`
2. `createStudyPopulation()`
3. `createSccsIntervalData()`
4. `fitSccsModel()`

When you provide several analyses to the `SelfControlledCaseSeries` package, it will determine whether any of the analyses and exposure-outcome pairs have anything in common, and will take advantage of this fact. For example, if we specify several exposure-outcome pairs with the same outcome, the data for the outcome will be extracted only once.

The function arguments you need to define have been divided into four groups:

1. **Exposures-outcome sets**: arguments that are specific to a hypothesis of interest, in the case of the self-controlled case series this is a combination of one or more exposures and an outcome.
2. **Analyses**: arguments that are not directly specific to a hypothesis of interest, such as the washout window, whether to adjust for age and seasonality, etc.
3. Arguments that are the output of a previous function in the `SelfControlledCaseSeries` package, such as the `SccsIntervalData` argument of the `createSccsIntervalData` function. These cannot be specified by the user.
4. Arguments that are specific to an environment, such as the connection details for connecting to the server, and the name of the schema holding the CDM data.

3 Preparation for the example

We need to tell R how to connect to the server where the data are. `SelfControlledCaseSeries` 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:

```
connectionDetails <- createConnectionDetails(
  dbms = "postgresql",
  server = "localhost/ohdsi",
  user = "joe",
  password = "supersecret"
)

outputFolder <- "s:/temp/sccsVignette2"

cdmDatabaseSchema <- "my_cdm_data"
cohortDatabaseSchema <- "my_cohorts"
options(sqlRenderTempEmulationSchema = NULL)
cdmVersion <- "5"
```

The last three lines define the `cdmDatabaseSchema` and `cohortDatabaseSchema` 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 store the (outcome) cohorts, 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"`.

We also need to prepare our exposures and outcomes of interest. The drug_era table in the OMOP Common Data Model already contains pre-specified cohorts of users at the ingredient level, so we will use that for the exposures. For the outcome we can use the OHDSI `PhenotypeLibrary` to retrieve a community-approved definition of GI bleeding:

```
giBleed <- 77
cohortDefinitionSet <- PhenotypeLibrary::getPlCohortDefinitionSet(giBleed)
```

We can use the `CohortGenerator` package to instantiate this cohort:

```
connection <- DatabaseConnector::connect(connectionDetails)
cohortTableNames <- CohortGenerator::getCohortTableNames(cohortTable)
CohortGenerator::createCohortTables(connection = connection,
                                    cohortDatabaseSchema = cohortDatabaseSchema,
                                    cohortTableNames = cohortTableNames)
counts <- CohortGenerator::generateCohortSet(connection = connection,
                                             cdmDatabaseSchema = cdmDatabaseSchema,
                                             cohortDatabaseSchema = cohortDatabaseSchema,
                                             cohortTableNames = cohortTableNames,
                                             cohortDefinitionSet = cohortDefinitionSet)
DatabaseConnector::disconnect(connection)
```

4 Specifying exposures-outcome sets

The first group of arguments define the exposures and outcome. Here we demonstrate how to create an exposures-outcome set:

```
diclofenac <- 1124300
negativeControls <- c(
  705178, 705944, 710650, 714785, 719174, 719311, 735340, 742185,
  780369, 781182, 924724, 990760, 1110942, 1111706, 1136601,
  1317967, 1501309, 1505346, 1551673, 1560278, 1584910, 19010309,
  40163731
)
giBleed <- 77

exposuresOutcomeList <- list()
exposuresOutcomeList[[1]] <- createExposuresOutcome(
  outcomeId = giBleed,
  exposures = list(createExposure(exposureId = diclofenac))
)
for (exposureId in c(negativeControls)) {
  exposuresOutcome <- createExposuresOutcome(
    outcomeId = giBleed,
    exposures = list(createExposure(exposureId = exposureId, trueEffectSize = 1))
  )
  exposuresOutcomeList[[length(exposuresOutcomeList) + 1]] <- exposuresOutcome
}
```

We defined the outcome of interest to be the cohort with the ID stored in `giBleed`. The exposures include diclofenac (concept ID 1124300) and a large number of negative control exposures. Note that for the negative controls we specify `trueEffectSize = 1` since we assume negative controls have no causal effect on the outcome.

A convenient way to save `exposuresOutcomeList` to file is by using the `saveExposuresOutcomeList` function, and we can load it again using the `loadExposuresOutcomeList` function.

5 Specifying analyses

The second group of arguments are not specific to a hypothesis of interest, and comprise the majority of arguments. For each function that will be called during the execution of the analyses, a companion function is available that has (almost) the same arguments. For example, for the `fitSccsModel()` function there is the `createFitSccsModelArgs()` function. These companion functions can be used to create the arguments to be used during execution:

```
getDbSccsDataArgs <- createGetDbSccsDataArgs(
  useCustomCovariates = FALSE,
  deleteCovariatesSmallCount = 100,
  exposureIds = c(),
  maxCasesPerOutcome = 100000
)

createStudyPopulationArgs <- createCreateStudyPopulationArgs(
  naivePeriod = 180,
  firstOutcomeOnly = FALSE
)

covarExposureOfInt <- createEraCovariateSettings(
  label = "Exposure of interest",
  includeEraIds = "exposureId",
  start = 1,
  end = 0,
  endAnchor = "era end",
  profileLikelihood = TRUE,
  exposureOfInterest = TRUE
)

createSccsIntervalDataArgs1 <- createCreateSccsIntervalDataArgs(
  eraCovariateSettings = covarExposureOfInt
)

fitSccsModelArgs <- createFitSccsModelArgs()
```

Any argument that is not explicitly specified by the user will assume the default value specified in the function. Note that for several arguments for concept or cohort definition IDs we can use the `exposureIdRef` (default = `"exposureId"`) in the `Exposure` objects that we used in `createExposuresOutcome()`. In this case, we defined the argument `includeEraIds` to get the value of the `exposureId` variable, meaning it will take the value of the diclofenac concept ID, or any of the negative control IDs. Also note that we set `exposureOfInterest = TRUE`, which will cause the estimate for this covariate to be included in the result summary later on.

We can now combine the arguments for the various functions into a single analysis:

```
sccsAnalysis1 <- createSccsAnalysis(
  analysisId = 1,
  description = "Simplest model",
  getDbSccsDataArgs = getDbSccsDataArgs,
  createStudyPopulationArgs = createStudyPopulationArgs,
  createIntervalDataArgs = createSccsIntervalDataArgs1,
  fitSccsModelArgs = fitSccsModelArgs
)
```

Note that we have assigned an analysis ID (1) to this set of arguments. We can use this later to link the results back to this specific set of choices. We also include a short description of the analysis.

We can easily create more analyses, for example by including adjustments for age and seasonality, or for including other drugs in the model:

```
ppis <- c(911735, 929887, 923645, 904453, 948078, 19039926)

covarPreExp <- createEraCovariateSettings(
```

```
  label = "Pre-exposure",
  includeEraIds = "exposureId",
  start = -30,
  end = -1,
  endAnchor = "era start"
)

covarProphylactics <- createEraCovariateSettings(
  label = "Prophylactics",
  includeEraIds = ppis,
  start = 1,
  end = 0,
  endAnchor = "era end"
)

createSccsIntervalDataArgs2 <- createCreateSccsIntervalDataArgs(
  eraCovariateSettings = list(
    covarExposureOfInt,
    covarPreExp,
    covarProphylactics
  )
)

sccsAnalysis2 <- createSccsAnalysis(
  analysisId = 2,
  description = "Including prophylactics and pre-exposure",
  getDbSccsDataArgs = getDbSccsDataArgs,
  createStudyPopulationArgs = createStudyPopulationArgs,
  createIntervalDataArgs = createSccsIntervalDataArgs2,
  fitSccsModelArgs = fitSccsModelArgs
)

seasonalitySettings <- createSeasonalityCovariateSettings(seasonKnots = 5)

calendarTimeSettings <- createCalendarTimeCovariateSettings(calendarTimeKnots = 5)

createSccsIntervalDataArgs3 <- createCreateSccsIntervalDataArgs(
  eraCovariateSettings = list(
    covarExposureOfInt,
    covarPreExp,
    covarProphylactics
  ),
  seasonalityCovariateSettings = seasonalitySettings,
  calendarTimeCovariateSettings = calendarTimeSettings
)

sccsAnalysis3 <- createSccsAnalysis(
  analysisId = 3,
  description = "Including prophylactics, season, calendar time, and pre-exposure",
  getDbSccsDataArgs = getDbSccsDataArgs,
  createStudyPopulationArgs = createStudyPopulationArgs,
  createIntervalDataArgs = createSccsIntervalDataArgs3,
  fitSccsModelArgs = fitSccsModelArgs
```

```
)

covarAllDrugs <- createEraCovariateSettings(
  label = "Other exposures",
  excludeEraIds = "exposureId",
  stratifyById = TRUE,
  start = 1,
  end = 0,
  endAnchor = "era end",
  allowRegularization = TRUE
)

createSccsIntervalDataArgs4 <- createCreateSccsIntervalDataArgs(
  eraCovariateSettings = list(
    covarExposureOfInt,
    covarPreExp,
    covarAllDrugs
  ),
  seasonalityCovariateSettings = seasonalitySettings,
  calendarTimeCovariateSettings = calendarTimeSettings
)

sccsAnalysis4 <- createSccsAnalysis(
  analysisId = 4,
  description = "Including all other drugs",
  getDbSccsDataArgs = getDbSccsDataArgs,
  createStudyPopulationArgs = createStudyPopulationArgs,
  createIntervalDataArgs = createSccsIntervalDataArgs4,
  fitSccsModelArgs = fitSccsModelArgs
)

createSccsIntervalDataArgs5 <- createCreateSccsIntervalDataArgs(
  eraCovariateSettings = list(
    covarExposureOfInt,
    covarPreExp,
    covarProphylactics
  ),
  eventDependentObservation = TRUE
)

sccsAnalysis5 <- createSccsAnalysis(
  analysisId = 5,
  description = "Adjusting for event-dependent obs. end",
  getDbSccsDataArgs = getDbSccsDataArgs,
  createStudyPopulationArgs = createStudyPopulationArgs,
  createIntervalDataArgs = createSccsIntervalDataArgs5,
  fitSccsModelArgs = fitSccsModelArgs
)
```

These analyses can be combined in a list:

```
sccsAnalysisList <- list(
  sccsAnalysis1,
  sccsAnalysis2,
```

```
  sccsAnalysis3,
  sccsAnalysis4,
  sccsAnalysis5
)
```

A convenient way to save `sccsAnalysisList` to file is by using the `saveSccsAnalysisList` function, and we can load it again using the `loadSccsAnalysisList` function.

6 Executing multiple analyses

We can now run the analyses against the hypotheses of interest using the `runSccsAnalyses()` function. This function will run all specified analyses against all hypotheses of interest, meaning that the total number of outcome models is `length(sccsAnalysisList) * length(exposuresOutcomeList)`. (If we want, we can skip some of these combinations using the `analysesToExclude` argument.)

```
multiThreadingSettings <- createDefaultSccsMultiThreadingSettings(
  parallel::detectCores() - 1
)

referenceTable <- runSccsAnalyses(
  connectionDetails = connectionDetails,
  cdmDatabaseSchema = cdmDatabaseSchema,
  exposureDatabaseSchema = cdmDatabaseSchema,
  exposureTable = "drug_era",
  outcomeDatabaseSchema = cohortDatabaseSchema,
  outcomeTable = cohortTable,
  cdmVersion = cdmVersion,
  outputFolder = outputFolder,
  combineDataFetchAcrossOutcomes = TRUE,
  exposuresOutcomeList = exposuresOutcomeList,
  sccsAnalysisList = sccsAnalysisList,
  sccsMultiThreadingSettings = multiThreadingSettings
)
```

In the code above, we first specify how many parallel threads `SelfControlledCaseSeries` can use. Many of the computations can be computed in parallel, and providing more than one CPU core can greatly speed up the computation. Here we specify `SelfControlledCaseSeries` can use all but one of the CPU cores detected in the system (using the `parallel::detectCores()` function).

We call `runSccsAnalyses`, providing the arguments for connecting to the database, which schemas and tables to use, as well as the analyses and hypotheses of interest. The `outputFolder` specifies where the outcome models and intermediate files will be written.

6.1 Restarting

If for some reason the execution was interrupted, you can restart by re-issuing the `runSccsAnalyses()` command. Any intermediate and final products that have already been completed and written to disk will be skipped.

7 Retrieving the results

The result of the `runSccsAnalyses()` is a data frame with one row per exposures-outcome-analysis combination, so one row per fitted SCCS model. It provides the file names of the intermediate and end-result files

that were constructed. For example, we can retrieve the fitted model for the combination of our drug of interest, outcome, and first analysis:

```
sccsModelFile <- referenceTable$sccsModelFile[result$exposureId == diclofenac &
  referenceTable$outcomeId == giBleed &
  referenceTable$analysisId == 1]
sccsModel <- readRDS(file.path(outputFolder, sccsModelFile))
sccsModel
```

```
## SccsModel object
##
## Outcome ID: 77
##
## Outcome count:
##    outcomeSubjects outcomeEvents outcomeObsPeriods observedDays
## 77            9390         13725              9392     25940825
##
## Estimates:
## # A tibble: 1 x 7
##   Name                     ID Estimate LB95CI UB95CI LogRr SeLogRr
##   <chr>                 <dbl>    <dbl>  <dbl>  <dbl> <dbl>   <dbl>
## 1 Exposure of interest  1000     1.11   1.02   1.20 0.101  0.0403
```

Note that some of the file names will appear several times in the table. In our example all analysis share the same `sccsData` object.

We can always retrieve the file reference table again using the `getFileReference()` function:

```
referenceTable <- getFileReference(outputFolder)
```

We can get a summary of the results using `getResultsSummary()`:

```
resultsSum <- getResultsSummary(outputFolder)
head(resultsSum)
```

```
## # A tibble: 6 x 30
##   exposuresOutcomeSetId outcomeId analysisId covariateAnalysisId covariateId covariateName          c
##                   <dbl>     <dbl>      <int>               <dbl>       <dbl> <chr>                 <
## 1                     1        77          1                   1        1000 Exposure of interest 11
## 2                     2        77          1                   1        1000 Exposure of interest  7
## 3                     3        77          1                   1        1000 Exposure of interest  7
## 4                     4        77          1                   1        1000 Exposure of interest  7
## 5                     5        77          1                   1        1000 Exposure of interest  7
## 6                     6        77          1                   1        1000 Exposure of interest  7
## # i 23 more variables: outcomeSubjects <dbl>, outcomeEvents <dbl>, outcomeObservationPeriods <dbl>,
## #   observedDays <dbl>, covariateSubjects <dbl>, covariateDays <dbl>, covariateEras <dbl>,
## #   covariateOutcomes <dbl>, rr <dbl>, ci95Lb <dbl>, ci95Ub <dbl>, p <dbl>, logRr <dbl>, seLogRr <dbl
## #   llr <dbl>, trueEffectSize <int>, calibratedRr <dbl>, calibratedCi95Lb <dbl>, calibratedCi95Ub <dl
## #   calibratedP <dbl>, calibratedLogRr <dbl>, calibratedSeLogRr <dbl>, ease <dbl>
```

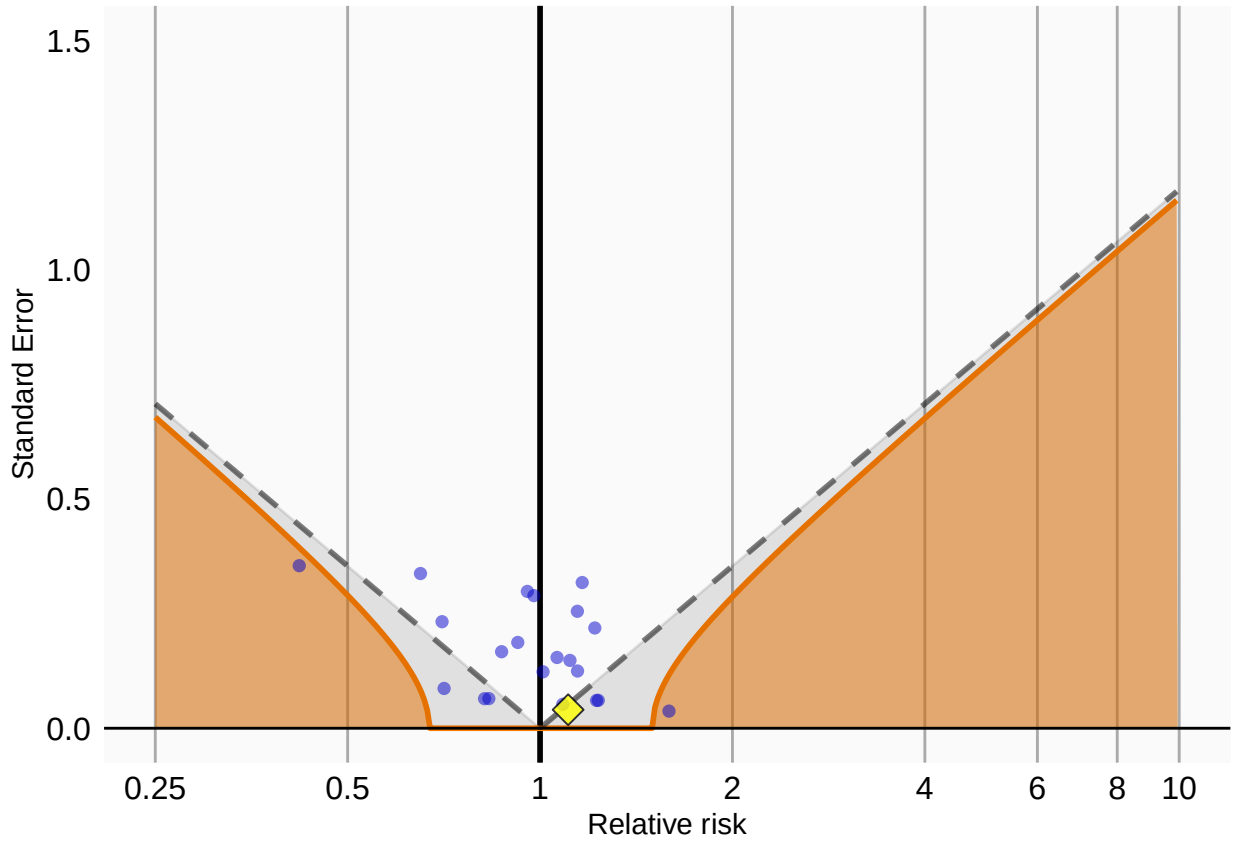
This tells us, per exposure-outcome-analysis combination (so possible multiple rows per SCCS model) the estimated relative risk and 95% confidence interval, as well as the number of subjects (cases) and the number of events observed for those subjects. The only covariates included in this summary are those we marked with `exposureOfInterest = TRUE` when calling `createEraCovariateSettings()` earlier.

7.1 Negative control distribution

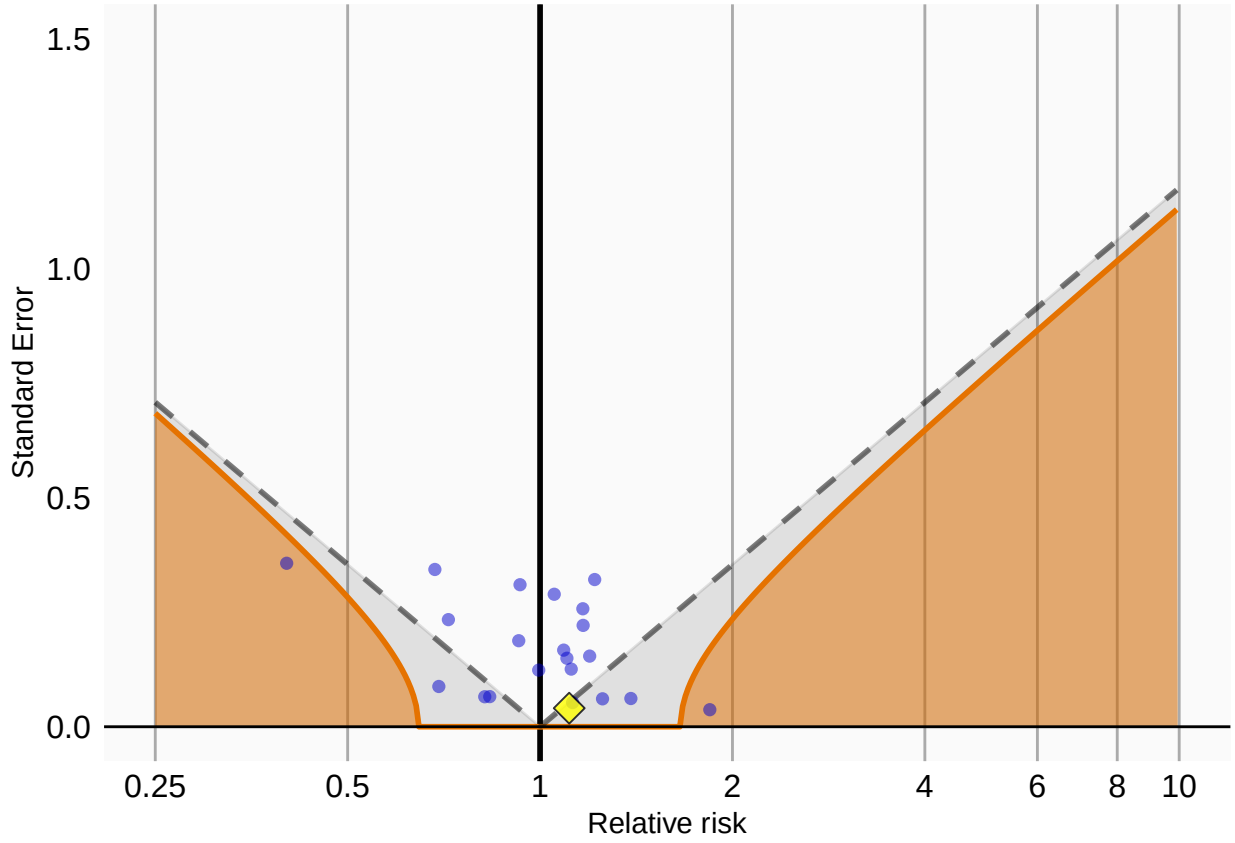
Now that we have produced estimates for all outcomes including our negative controls, we can look at the distrubtion of negative controls. In each plot, the blue dots represent our negative control exposures, and the yellow diamond represents our exposure of interest: diclofenac. An unbiased, well-calibrated analysis should have 95% of the negative controls between the dashed lines (ie. 95% should have p > .05). Note that empirical calibration was already automatically performed, and calibrated confidence intervals and p-values are included separately in the analyses summary.

```
install.packages("EmpiricalCalibration")
library(EmpiricalCalibration)

# Analysis 1: Simplest model
negCons <- resultsSum[resultsSum$analysisId == 1 & resultsSum$eraId != diclofenac, ]
ei <- resultsSum[resultsSum$analysisId == 1 & resultsSum$eraId == diclofenac, ]
null <- fitNull(
  negCons$logRr,
  negCons$seLogRr
)
plotCalibrationEffect(
  logRrNegatives = negCons$logRr,
  seLogRrNegatives = negCons$seLogRr,
  logRrPositives = ei$logRr,
  seLogRrPositives = ei$seLogRr,
  null
)
```

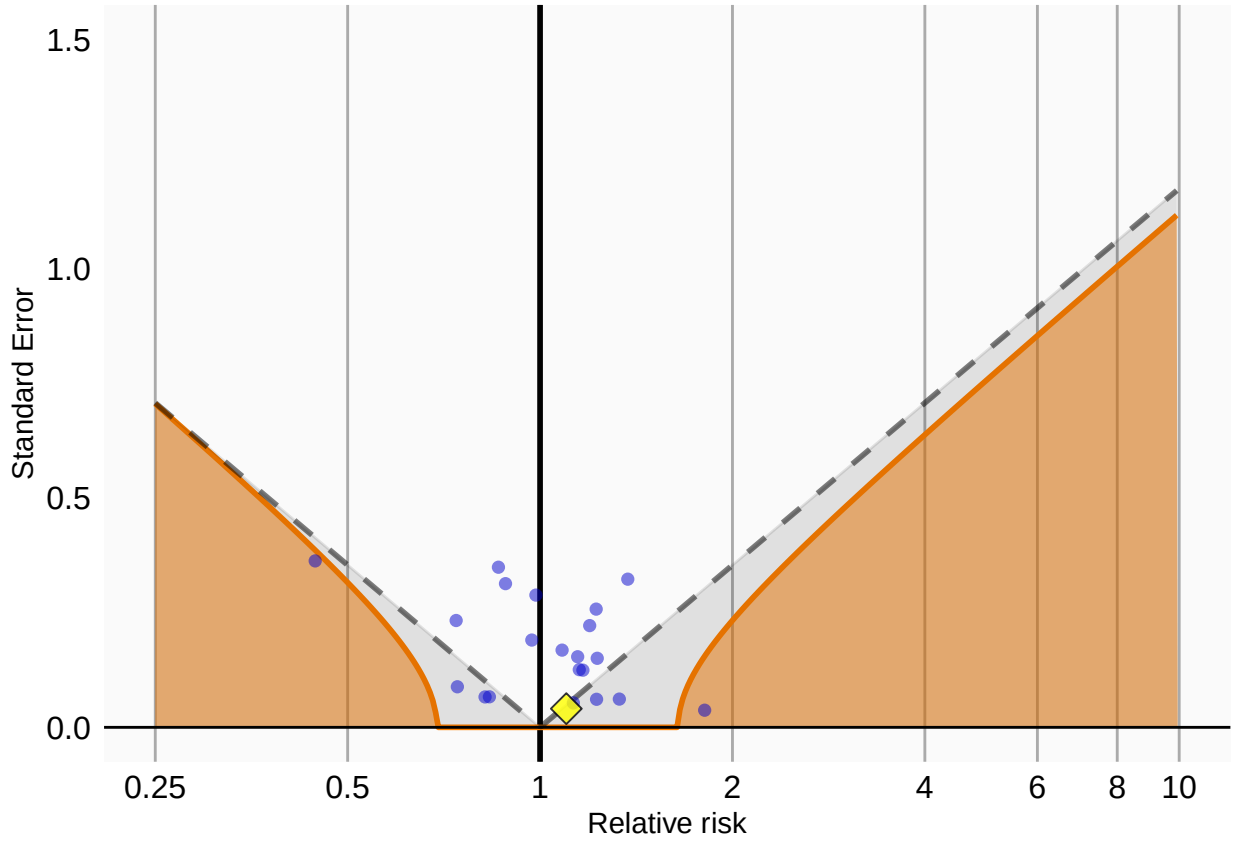


```
# Analysis 2: Including prophylactics and pre-exposure
negCons <- resultsSum[resultsSum$analysisId == 2 & resultsSum$eraId != diclofenac, ]
ei <- resultsSum[resultsSum$analysisId == 2 & resultsSum$eraId == diclofenac, ]
null <- fitNull(
  negCons$logRr,
  negCons$seLogRr
)
plotCalibrationEffect(
  logRrNegatives = negCons$logRr,
  seLogRrNegatives = negCons$seLogRr,
  logRrPositives = ei$logRr,
  seLogRrPositives = ei$seLogRr,
  null
)
```

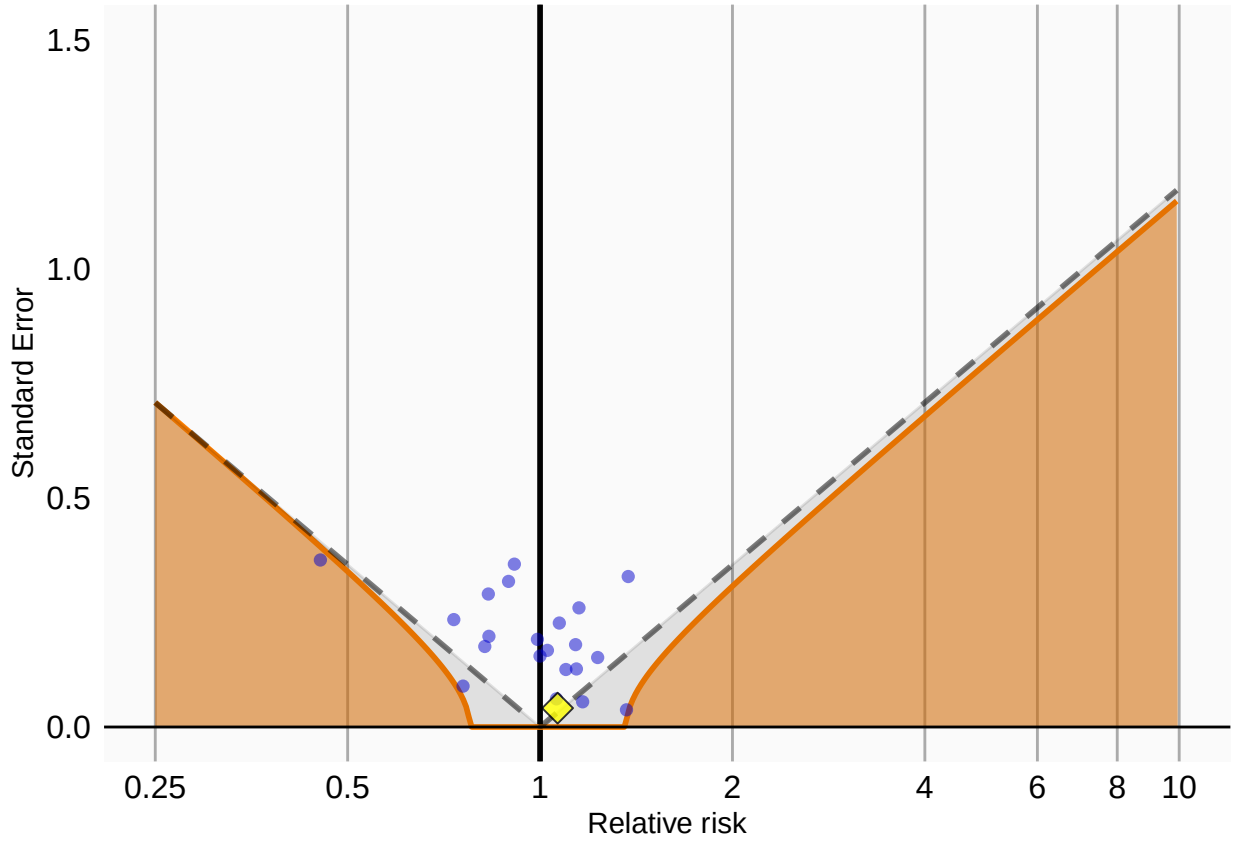



```
# Analysis 3: Including prophylactics, season, calendar time, and pre-exposure
negCons <- resultsSum[resultsSum$analysisId == 3 & resultsSum$eraId != diclofenac, ]
ei <- resultsSum[resultsSum$analysisId == 3 & resultsSum$eraId == diclofenac, ]
null <- fitNull(
  negCons$logRr,
  negCons$seLogRr
)
plotCalibrationEffect(
  logRrNegatives = negCons$logRr,
  seLogRrNegatives = negCons$seLogRr,
  logRrPositives = ei$logRr,
```

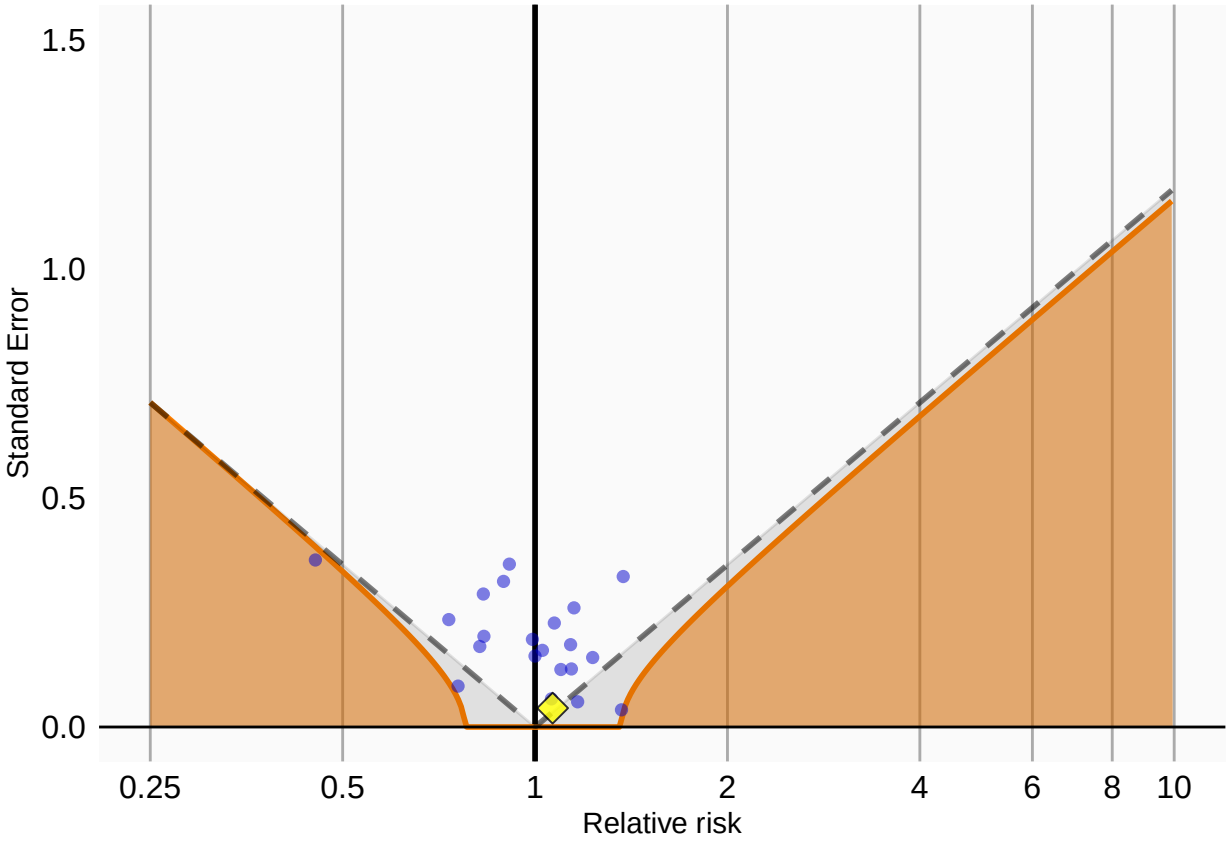
```
  seLogRrPositives = ei$seLogRr,
  null
)
```




```
# Analysis 4: Including all other drugs
negCons <- resultsSum[resultsSum$analysisId == 4 & resultsSum$eraId != diclofenac, ]
ei <- resultsSum[resultsSum$analysisId == 4 & resultsSum$eraId == diclofenac, ]
null <- fitNull(
  negCons$logRr,
  negCons$seLogRr
)
plotCalibrationEffect(
  logRrNegatives = negCons$logRr,
  seLogRrNegatives = negCons$seLogRr,
  logRrPositives = ei$logRr,
  seLogRrPositives = ei$seLogRr,
  null
)
```




```
# Analysis 5: Adjusting for event-dependent obs. end
negCons <- resultsSum[resultsSum$analysisId == 4 & resultsSum$eraId != diclofenac, ]
ei <- resultsSum[resultsSum$analysisId == 4 & resultsSum$eraId == diclofenac, ]
null <- fitNull(
  negCons$logRr,
  negCons$seLogRr
)
plotCalibrationEffect(
  logRrNegatives = negCons$logRr,
  seLogRrNegatives = negCons$seLogRr,
  logRrPositives = ei$logRr,
  seLogRrPositives = ei$seLogRr,
  null
)
```



8 Acknowledgments

Considerable work has been dedicated to provide the `SelfControlledCaseSeries` package.

```
citation("SelfControlledCaseSeries")
```

```
## To cite package 'SelfControlledCaseSeries' in publications use:
##
##   Schuemie M, Ryan P, Shaddox T, Suchard M (2023). _SelfControlledCaseSeries: Self-Controlled
##   Case Series_. R package version 5.1.0, <https://github.com/OHDSI/SelfControlledCaseSeries>.
##
## A BibTeX entry for LaTeX users is
##
##   @Manual{,
##     title = {SelfControlledCaseSeries: Self-Controlled Case Series},
##     author = {Martijn Schuemie and Patrick Ryan and Trevor Shaddox and Marc Suchard},
##     year = {2023},
##     note = {R package version 5.1.0},
##     url = {https://github.com/OHDSI/SelfControlledCaseSeries},
##   }
```

Further, `SelfControlledCaseSeries` makes extensive use of the `Cyclops` package.

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

```
## To cite Cyclops in publications use:
##
```

```
##   Suchard MA, Simpson SE, Zorych I, Ryan P, Madigan D (2013). "Massive parallelization of
##   serial inference algorithms for complex generalized linear models." _ACM Transactions on
##   Modeling and Computer Simulation_, *23*, 10.
##   <https://dl.acm.org/doi/10.1145/2414416.2414791>.
##
## 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 = {https://dl.acm.org/doi/10.1145/2414416.2414791},
##   }
```

This work is supported in part through the National Science Foundation grant IIS 1251151.