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Title Performing Multivariate Dose-Response Meta-Analysis

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Description It estimates a dose-response relation from either a single or multiple summarized data. The trend estimation takes into account the correlation among sets of log relative risks and use it to efficiently estimate the dose-response relation. To obtain a pooled functional relation, the study-specific trends are combined according to principles of multivariate random-effects meta-analysis.

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Performing Multivariate Dose-Response Meta-Analysis

Description

The package dosresmeta consists of a collection of functions to estimate a dose-response relation from either a single or multiple summarized dose-response data. The method was first formalized by Greenland and Longnecker (1992); the authors described how to approximate the covariances of reported log relative risks and how use them to efficiently estimate an exposure-disease relation. The study specific estimates are combined through multivariate random-effect meta-analytical model, to obtain a pooled dose-response association.

Details

Package: dosresmeta
Type: Package
Version: 1.3.2
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License: GPL-2

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

References


**alcohol_crc**

*Eight published studies on the relation between alcohol intake and colon-rectal cancer.*

**Description**

The dataset reports the summarized dose-response results from eight prospective studies on the relation between alcohol intake and colon-rectal risk (Orsini 2012).

**Format**

A data frame with 48 observations on the following 7 variables:

- **id**: label for author’s names (id variable).
- **type**: code for study design.
- **dose**: assigned dose level.
- **cases**: number of cases for each exposure level.
- **peryears**: amount of person-time for each exposure level.
- **logrr**: natural logarithm of adjusted "relative risks".
- **se**: standard error of the natural logarithm of adjusted "relative risks".

**Author(s)**

Alessio Crippa, <<alessio.crippa@ki.se>>

**References**


**alcohol_cvd**

*Six published studies on the relation between alcohol intake and vascular disease risk.*

**Description**

The dataset reports the summarized dose-response results from six observational studies on the relation between alcohol intake and vascular disease risk (Qin Liu 2009). Four are case-control studies, two prospective (cumulative-incidence data).
Format

A data frame with 25 observations on the following 8 variables:

- id: id of the studies included in the analysis.
- author: names of the first author of the study.
- type: code for study design.
- dose: assigned dose level.
- case: number of cases for each exposure level.
- n: total number of subjects for each exposure level.
- logrr: natural logarithm of adjusted "relative risks".
- se: standard error for the logarithm of adjusted "relative risks".

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

References


Description

The dataset reports the summarized dose-response results from a case-control study on alcohol and breast cancer, first presented by Rohan and McMichael.

Format

A data frame with 4 observations on the following 10 variables:

- gday: label for exposure levels.
- dose: assigned dose level.
- case: number of cases for each exposure level.
- control: number of controls for each exposure level.
- n: total number of subjects for each exposure level.
- crudeor: unadjusted odds ratios for each exposure level.
- adjrr: adjusted odds ratios for each exposure level.
- lb: lower bound for the confidence limit of the adjusted odds ratios.
- ub: upper bound for the confidence limit of the adjusted odds ratios.
- logrr: natural logarithm of adjusted odds ratios.
Author(s)
Alessio Crippa, <alessio.crippa@ki.se>

References

coef.dosresmeta

Extract Coefficients and (Co)Variance Matrix from dosresmeta Objects

Description
Extract Coefficients and (Co)Variance Matrix from dosresmeta Objects

Usage

```r
## S3 method for class 'dosresmeta'
coef(object, format = c("vector", "matrix"), ...)

## S3 method for class 'dosresmeta'
vcov(object, ...)
```

Arguments

- `object`: an object of class "dosresmeta"
- `format`: format of the returned object
- `...`: further arguments passed to or from other methods.

Value

For `coef`, a vector (default) or matrix with the estimated (fixed-effects) coefficients.
For `vcov`, the (co)variance matrix of the estimated (fixed-effects) coefficients.

Author(s)
Alessio Crippa, <alessio.crippa@ki.se>

See Also
dosresmeta, coef, vcov
Examples

```r
## Load data and run the model
data("alcohol_cvd")
model <- dosresmeta(formula = logrr ~ dose + I(dose^2), type = type, id = id,
                    se = se, cases = cases, n = n, data = alcohol_cvd)

## Fixed-effect coefficients
coef(model)

## Fixed-effect (co)variance matrix
vcov(model)
```

**dosresmeta**  
*Performing multivariate dose-response meta-analysis*

**Description**

Estimates a dose-response relation from either a single or multiple summarized data, taking into account the correlation among set of log relative risks. The covariances are approximated according to two different methods, proposed respectively by Greeland S., Longnecker M., and Hamling J.; alternatively the user can provide directly the covariance matrices or the average covariances (Easton D.). The study-specific estimates are combined according to principles of multivariate random-effects meta-analysis.

**Usage**

```r
dosresmeta(formula, id, type, v, cases, n, data, intercept = FALSE, center = TRUE,
            se, lb, ub, covariance = "gl", method = "reml", fcox, ucox,
            alpha = 0.05, ...)
```

**Arguments**

- `formula`: an object of class "formula" offering a symbolic description of the dose-response functional relation. Terms in the formula need to be provided in the data below.
- `id`: an optional vector to specify the id variable for the studies included in the analysis.
- `type`: a vector (or a string) to specify the study-specific design. The values for case-control, incidence-rate, and cumulative incidence data are `cc`, `ir`, and `ci`.
- `v`: a vector to specify the variances of the reported log relative risks. Alternatively the user can provide the standard error in the `se` argument, or the confidence interval for the reported relative risks in the `lb` and `ub` arguments.
- `cases`: a vector to specify the number of cases for each exposure level.
- `n`: a vector to specify the total number of subjects for each exposure level. For incidence-rate data `n` indicates the amount of person-time for each exposure level.
**dosresmeta**

- **data**: a data frame (or object coercible by `as.data.frame` to a data frame) containing the variables in the previous arguments.

- **intercept**: a logical value to specify if an intercept term needs to be included in the model. See details.

- **center**: a logical value to specify if the exposures level need to be center at the referent ones. See details.

- **se**: an optional vector to specify the standard error of the reported log relative risks; needed if `v` is not provided.

- **lb**: an optional vector to specify the lower bound of the confidence interval for the reported relative risks; needed if `v` and `se` are not provided.

- **ub**: an optional vector to specify the upper bound of the confidence interval for the reported relative risks; needed if `v` and `se` are not provided.

- **covariance**: method to approximate the covariance among set of reported log relative risks, "g1" for the method proposed by Greenland and Longnecker, "h" for the method proposed by Hamling (default), "f1" for absolute floated risks presented by Easton D., "user" if provided by the user, or "independent" for assuming independence.

- **method**: method used to estimate the pooled dose-response relation: "fixed" for fixed-effects models, "ml" or "reml" for random-effects models fitted through (restricted) maximum likelihood, and "mm" for random-effects models fitted through method of moments. The default method is "reml". See `mvmeta`.

- **fcov**: an optional vector to specify the average covariances for the set of reported log relative risks. It is required if `covariance = "fl"`.

- **ucov**: an optional list of matrices to specify the covariance matrices for the set of reported log relative risks. It is required if `covariance = "user"`.

- **alpha**: a scalar to specify the alpha nominal value used in the published data, by default equal to .05.

- **...**: other useful arguments related to `mvmeta` model.

**Details**

The function estimates the dose response-relation specified in the `formula` for each study included in the analysis. Typically the model does not have an intercept (intercept = FALSE by default) term since the log relative risk for the exposure level (usually zero) is zero (RR = 1). For that reason, the values in the design matrix need to be centered at the referent values, as described by Qin Liu et al, 2009. This is automatically done by the function when `center = TRUE` (default value). The study-specific trends are efficiently estimated taking into account the covariance among relative risks. For a theoretical description see Orsini et al, 2006. The study specific trends are then combined according to the principles of multivariate random-effects meta-analysis, and relies on `mvmeta` package.

**Value**

The `dosresmeta` function typically returns a list of object of class `dosresmeta` which resembles a `mvmetaObject`, with differences in case of trend estimation for a single study.
Note

The function requires the packages mvmeta and aod to be installed and loaded.

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

References


See Also
dosresmeta, grl, hamling

Examples

```r
## FIRST EXAMPLE: Single case-control study
## Linear trend estimation
## Inspect data
data("cc_ex")

## Fitting the model
mod1 <- dosresmeta(formula = logrr ~ dose, type = "cc", cases = case, 
n = n, lb = lb, ub = ub, data = cc_ex)
summary(mod1)
## Results
predict(mod1, delta = 1)

## SECOND EXAMPLE: Multiple studies
## Linear and quadratic trend using random-effects meta-analysis
## Inspect data
data("alcohol_cvd")

## Linear trend
lin <- dosresmeta(formula = logrr ~ dose, type = type, id = id, 
se = se, cases = cases, n = n, data = alcohol_cvd)
## Summarize the results
summary(lin)
predict(lin, delta = 1)
```
### Description

The function `grl` reconstructs the set of pseudo-numbers (or "effective" numbers) of cases and non-cases consistent with the input data (log relative risks) for either a single or multiple summarized data. The method was proposed in 1992 by Greenland and Longnecker.

### Usage

```r
grl(logrr, v, cases, n, type, id, data, se, lb, ub, order = TRUE, alpha = 0.05)
```

### Arguments

- `logrr`: a vector to specify the reported log relative risks.
- `v`: a vector to specify the variances of the reported log relative risks. Alternatively the user can provide the standard error in the `se` argument, or the confidence interval for the reported relative risks in the `lb` and `ub` arguments.
- `cases`: a vector to specify the number of cases for each exposure level.
- `n`: a vector to specify the total number of subjects for each exposure level. For incidence-rate data `n` indicates the amount of person-time for each exposure level.
- `type`: a vector (or a string) to specify the study-specific design. The values for case-control, incidence-rate, and cumulative incidence data are `cc`, `ir`, and `ci` (or 1, 2, and 3), respectively.
- `id`: an optional vector to specify the id variable for the studies included in the analysis.
data an optional data frame (or object coercible by \texttt{as.data.frame} to a data frame) containing the variables in the previous arguments.

se an optional vector to specify the standard error of the reported log relative risks; needed if \( v \) is not provided.

lb an optional vector to specify the lower bound of the confidence interval for the reported relative risks; needed if \( v \) and \( se \) are not provided.

ub an optional vector to specify the upper bound of the confidence interval for the reported relative risks; needed if \( v \) and \( se \) are not provided.

order a logical value to specify if the vectors need to be sorted. See details.

alpha a scalar to specify the alpha nominal value used in the published data, by default equal to .05.

Details
The function reconstructs the effective counts corresponding to the multivariable adjusted log relative risks as well as their standard errors. A unique solution is guaranteed by keeping the margins of the table of pseudo-counts equal to the margins of the crude or unadjusted data (Greenland and Longnecker 1992). The function requires the data to be sorted by id and in such a way that the referent values correspond to the first record for each study. This is automatically done by the function when \( \text{order} = \text{TRUE} \) (default).

Value
The results are returned structured in a data frame.

Author(s)
Alessio Crippa, \texttt{alessio.crippa@ki.se}

References


See Also
\texttt{hamling}, \texttt{dosresmeta}

Examples
\begin{verbatim}
data("alcohol_cvd")
grl(logrr = logrr, se = se, cases = cases, n = n, type = type, id = id, data = alcohol_cvd)
\end{verbatim}
hamling

Approximating effective-counts as proposed by Hamling

Description

The function `hamling` reconstructs the set of pseudo-numbers (or "effective" numbers) of cases and non-cases consistent with the input data (log relative risks) for either a single or multiple summarized data. The method was proposed in 2008 by Hamling.

Usage

`hamling(logrr, v, cases, n, type, id, data, se, lb, ub, order = TRUE, alpha = 0.05)`

Arguments

logrr  
a vector to specify the reported log relative risks.

v  
a vector to specify the variances of the reported log relative risks. Alternatively the user can provide the standard error in the `se` argument, or the confidence interval for the reported relative risks in the `lb` and `ub` arguments.

cases  
a vector to specify the number of cases for each exposure level.

n  
a vector to specify the total number of subject for each exposure level. For incidence-rate data `n` indicates the amount of person-time for each exposure level.

type  
a vector (or a string) to specify the study-specific design. The values for case-control, incidence-rate, and cumulative incidence data are `cc`, `ir`, and `ci` (or `1`, `2`, and `3`), respectively.

id  
an optional vector to specify the id variable for the studies included in the analysis.

data  
an optional data frame (or object coercible by `as.data.frame` to a data frame) containing the variables in the previous arguments.

se  
an optional vector to specify the standard error of the reported log relative risks; needed if `v` is not provided.

lb  
an optional vector to specify the lower bound of the confidence interval for the reported relative risks; needed if `v` and `se` are not provided.

ub  
an optional vector to specify the upper bound of the confidence interval for the reported relative risks; needed if `v` and `se` are not provided.

order  
a logical value to specify if the vectors need to be sorted. See details.

alpha  
a scalar to specify the alpha nominal value used in the published data, by default equal to .05.
predict.dosresmeta

Details

The function reconstructs the effective counts corresponding to the multivariable adjusted log relative risks as well as their standard errors. A unique solution is guaranteed by keeping the ratio non-cases to cases and the fraction of unexposed subjects equal to the unadjusted data (Hamling). The function requires the data to be sorted by id and in such a way that the referent values correspond to the first record for each study. This is automatically done by the function when order = TRUE (default).

Value

The results are returned structured in a data frame.

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

References


Examples

data("alcohol_cvd")
hamling(logrr = logrr, se = se, cases = cases, n = n, type = type, id = id, data = alcohol_cvd)

predict.dosresmeta Predicted Values from dosresmeta Models

Description

This method function computes predictions from fitted dose-response models represented in objects of class "dosresmeta", optionally for a new set of exposure levels. Predictions are optionally accompanied by confidence intervals and/or standard errors for the predictions.

Usage

## S3 method for class 'dosresmeta'
predict(object, newdata, xref, se.incl = FALSE, expo = TRUE, ci.incl = TRUE, ci.level = 0.95, order = TRUE, delta, ...)
Arguments

- **object**: an object of class `dosresmeta`.
- **newdata**: an optional data frame or matrix in which to look for variables values with which to predict from dose-response models.
- **xref**: an optional scalar to indicate which levels should serve as referent for the predicted relative risks. See details.
- **se.incl**: logical switch indicating if standard errors need to be included.
- **expo**: logical switch indicating if the prediction should be on the exponential scale.
- **ci.incl**: logical switch indicating if confidence intervals need to be included.
- **ci.level**: a numerical value between 0 and 1, specifying the confidence level for the computation of confidence intervals.
- **order**: logical to indicate if the predictions need to be sorted by exposure levels.
- **delta**: an optional scalar to specify to predict the linear trend related to that increase.
- **...**: further arguments passed to or from other methods.

Details

The method function `predict` produces predicted values from `dosresmeta` objects. When more than one study is included in the analysis, estimated predictions are only based on the fixed part of the model.

If `newdata` is omitted, the predictions are based on the data used for the fit. If `xref` is provided, it must be equal to one of the modeled values. If not provided, the minimum modeled referent value will be used as referent for the predicted relative risks.

If `newdata` is specified, it should include all the variables used to model the dose-response relation. Again, if specified, `xref` must be equal to one of the value in the newdata. If omitted, the minimum value for the newdara will be used as referent.

Only for the linear trend it is possible to specify the predicted increase of risk corresponding to an increase equal to `delta` argument.

By default (`order = TRUE`), the predictions are sorted by exposure levels to facilitate understanding and possible graphical presentation of the results.

Value

The results are returned structured in a data frame.

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

See Also

dosresmeta, predict
Examples

```r
## Load data and run the model
data("alcohol_cvd")
model <- dosresmeta(formula = logrr ~ dose + I(dose^2), type = type, id = id,
                     se = se, cases = cases, n = n, data = alcohol_cvd)

## Predicted modeled data
predict(model, order = FALSE)

## Plot predicted dose-response relation
with(predict(model), {
  plot(dose, pred, log = "y", type = "l",
       xlim = c(0, 45), ylim = c(0.4, 2))
  lines(dose, ci.lb, lty = 2)
  lines(dose, ci.ub, lty = 2)
  rug(dose, quiet = TRUE)
})

## Prediction for new values
newdata <- data.frame(dose = seq(0, 50, 1))
predict(model, newdata)

## Smoother plot
with(predict(model, newdata), {
  plot(dose, pred, log = "y", type = "l",
       ylim = c(0.4, 2))
  lines(dose, ci.lb, lty = 2)
  lines(dose, ci.ub, lty = 2)
  rug(alcohol_cvd$dose, quiet = TRUE)
})

## Tabular results
newdata <- data.frame(dose = seq(0, 50, 5))
round(predict(model, newdata), 2)
```

---

**print.dosresmeta**

**summarizing dosresmeta Models**

**Description**

Print and summary method functions for dose-response models represented in objects of class "dosresmeta".

**Usage**

```r
## S3 method for class 'dosresmeta'
print(x, digits = 4, ...)

## S3 method for class 'dosresmeta'
```

print.dosresmeta

summary(object, ci.level = 0.95, ...)

## S3 method for class 'summary.dosresmeta'
print(x, digits = 4, ...)

Arguments

x an object of class dosresmeta or summary.dosresmeta produced by dosresmeta or summary.dosresmeta, respectively.
digits an integer specifying the number of digits to which printed results must be rounded.
object an object of class dosresmeta produced by dosresmeta.
ci.level the confidence level used for defining the confidence intervals for the estimates of the (fixed-effects) coefficients.
... further arguments passed to or from other methods.

Details

the print method for class dosresmeta only returns basic information of the fitted model, namely the call, estimated (fixed-effects) coefficients, and dimensions).

The summary method function computes additional statistics and tests, and produces a list object of class summary.dosresmeta. The print method function for this class, depending on the number of studies included in the analysis, shows additional information, such as tables reporting the estimates for the fixed and random-effects parts of the model, Chi-square test for model significance, Cochran Q test for heterogeneity and I-square.

Value

The summary method function for dosresmeta objects produces a list of class "summary.dosresmeta" which resembles a list object of class summary.mvmeta.

As usual, the print method functions for classes "dosresmeta" and "summary.dosresmeta" do not return any value.

Author(s)

Alessio Crippa, <alessio.crippa@ki.se>

See Also

dosresmeta, summary

Examples

## Load data and run the model
data("alcohol_cvd")
model <- dosresmeta(formula = logrr ~ dose + I(dose^2), type = type, id = id, 
se = se, cases = cases, n = n, data = alcohol_cvd)
## Default print

## S3 method for class 'summary.dosresmeta'
print(x, digits = 4, ...)
model
  ## Specify digits
  print(model, digit = 2)
  ## summary with 90th confidence intervals
  summary(model, ci.level = .8)
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