Package 'dosresmeta'

July 2, 2014

Type Package

Title Performing multivariate dose-response meta-analysis

Version 1.3.0

Date 2014-01-17

Author Alessio Crippa

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

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.

License GPL-2

Depends mvmeta, aod, Matrix

NeedsCompilation no

Repository CRAN

Date/Publication 2014-01-17 11:49:41

R topics documented:

`dosresmeta-package` *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 obtaind a pooled dose-response association.

Details

Package:	dosresmeta
Type:	Package
Version:	1.3
Date:	2013-12-27
License:	GPL-2

Author(s)

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

References

Greenland, S., Longnecker, M. P. (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology, 135(11), 1301-1309.

Orsini, N., Bellocco, R., Greenland, S. (2006). Generalized least squares for trend estimation of summarized dose-response data. Stata Journal, 6(1), 40.

Hamling, J., Lee, P., Weitkunat, R., Ambuhl, M. (2008). Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Statistics in medicine, 27(7), 954-970.

Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. American journal of epidemiology, 175(1), 66-73.

Gasparrini, A., Armstrong, B., Kenward, M. G. (2012). Multivariate meta-analysis for non-linear and other multi-parameter associations. Statistics in Medicine, 31(29), 3821-3839.

Liu, Q., Cook, N. R., Bergstrom, A., Hsieh, C. C. (2009). A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose-response data. Computational Statistics & Data Analysis, 53(12), 4157-4167.

See Also

dosresmeta, mvmeta

`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 errornatural for the logarithm of adjusted "relative risks".

Author(s)

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

References

Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. American journal of epidemiology, 175(1), 66-73.

`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 errornatural for the logarithm of adjusted "relative risks".

Author(s)

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

References

Liu, Q., Cook, N. R., Bergstrom, A., Hsieh, C. C. (2009). A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose-response data. Computational Statistics & Data Analysis, 53(12), 4157-4167.

---

cc_ex *Case-control data on alcohol and breast cancer risk*

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

Rohan, T. E., McMichael, A. J. (1988). Alcohol consumption and risk op breast cancer. International journal of cancer, 41(5), 695-699.

Greenland, S., Longnecker, M. P. (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology, 135(11), 1301-1309.

`coef.dosresmeta` *Extract Coefficients and (Co)Variance Matrix from dosresmeta Objects*

Description

Extract Coefficients and (Co)Variance Matrix from dosresmeta Objects

Usage

```
## 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

```
## 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 avarage covariances (Easton D.). The study-specific estimates are combined according to principles of multivariate random-effects meta-analysis.

Usage

```
dosresmeta(formula, id, type, v, cases, n, data, intercept = F, center = T,
  se, lb, ub, covariance = "gl", method = "reml", fcov, ucov,
  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 (or 1, 2, and 3), respectively.

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.
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 coviariance among set of reported log relative risks, "gl" for the method proposed by Greenland and Longnecker, "h" for the method proposed by Hamling (default), "fl" for absolute floated risks presented by Easton D., or "user" if provided by the user.
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 avarage 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 defaul equal to .05.
...	other useful agurments 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 desing 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 efficienly estimated taking into account the covariance among relative risks. For a theorical 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 sigle study.

Note

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

Author(s)

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

References

Greenland, S., Longnecker, M. P. (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology, 135(11), 1301-1309.

Orsini, N., Bellocco, R., Greenland, S. (2006). Generalized least squares for trend estimation of summarized dose-response data. Stata Journal, 6(1), 40.

Liu, Q., Cook, N. R., Bergstrom, A., Hsieh, C. C. (2009). A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose-response data. Computational Statistics & Data Analysis, 53(12), 4157-4167.

Gasparrini, A., Armstrong, B., Kenward, M. G. (2012). Multivariate meta-analysis for non-linear and other multi-parameter associations. Statistics in Medicine, 31(29), 3821-3839.

See Also

dosresmeta, grl, hamling

Examples

```
## 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)

## Non-linear (quadratic) trend
quadr <- dosresmeta(formula = logrr ~ dose + I(dose^2), type = type, id = id,
                    se = se, cases = cases, n = n, data = alcohol_cvd)
## Summarize the results
summary(quadr)

## Graphical results
with(predict(quadr), {
 plot(dose, pred, log = "y", type = "l",
      xlim = c(0, 45), ylim = c(.4, 2))
 lines(dose,  ci.lb, lty = 2)
 lines(dose, ci.ub, lty = 2)
 rug(dose, quiet = TRUE)
})
```

`grl` *Approximating effective-counts as proposed by Greenland & Longnecker*

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

```
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 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 defaul 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 `order = TRUE` (default).

Value

The results are returned structured in a data frame.

Author(s)

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

References

Greenland, S., Longnecker, M. P. (1992). Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology, 135(11), 1301-1309.

Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. American journal of epidemiology, 175(1), 66-73.

See Also

hamling, dosresmeta

Examples

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

`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 defaul 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 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

Hamling, J., Lee, P., Weitkunat, R., Ambuhl, M. (2008). Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Statistics in medicine, 27(7), 954-970.

Orsini, N., Li, R., Wolk, A., Khudyakov, P., Spiegelman, D. (2012). Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. American journal of epidemiology, 175(1), 66-73.

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 dosreseta.
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.
expo	logical switch indicating if the prediction should be on the exponential scale.
se.incl	logical switch indicating if standard errors need to be included.
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 correspongind 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

```
## 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(.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(.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

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

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

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

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

Arguments

object	an object of class dosresmeta produced by dosresmeta.
x	an object of class dosresmeta or summary.dosresmeta produced by dosresmeta or summary.dosresmeta, respectively.
ci.level	the confidence level used for defining the confidence intervals for the estimates of the (fixed-effects) coefficients.
digits	an integer specifying the number of digits to which printed results must be rounded.
...	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. If multiple studies are included in the meta-analysis, it returns also the usual fit statistics (log-likelihood, AIC, BIC).

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)
```

```
## Defult print
model
## Specify digits
print(model, digit = 2)
## summary with 90th confidence intervals
summary(model, ci.level = .8)
```

Index