Package ‘NMA’

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Title Network Meta-Analysis Package for R
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Description Network meta-analysis tools based on the contrast-based approach using the multivariate meta-analysis and meta-regression models (Noma et al. (2023) <Forthcoming>). The standard REML (restricted maximum likelihood) estimation and the Noma-Hamura's improved REML-based analysis methods (Noma et al. (2023) <doi:10.1002/jrsm.1652> <doi:10.1002/jrsm.1651>) are available. The local and global inconsistency tests based on the Higgins' design-by-treatment interaction model and the side-splitting can be used. Also, standard graphical tools for network meta-analysis (e.g., network plot, ranked forest plot) are available.
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The 'NMA' package.

Description

Network meta-analysis tools based on the contrast-based approach using the multivariate meta-analysis and meta-regression models (Noma et al., 2023c). Standard REML-based frequentist inference methods and the improved Noma-Hamura’s inference and prediction methods (Noma et al., 2023ab) are available. Also, the local and global inconsistency tests based on the Higgins’ design-by-treatment interaction model (Higgins et al., 2012) and the side-splitting method (Dias et al., 2010; Noma et al., 2017; Noma, 2023a) can be used. Standard graphical tools for network meta-analysis (e.g., network plot, ranked forest plot) are also available.

References


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**antidiabetic**  
*A network meta-analysis dataset for treatment of type-2 diabetes from Chaimani and Salanti (2015)*

**Description**
- **id**: Study ID
- **t**: Treatment (Placebo, AGI, DPP-4 inhibitor, Glinine, GLP-1 analog, Sulfonylurea, Thiazolidinedione)
- **y**: Mean of the change in HbA1c
- **sd**: Standard deviation of the change in HbA1c
- **n**: Sample size

**Usage**

```r
data(antidiabetic)
```

**Format**

An arm-based dataset with 20 studies

**References**


diabetes  
*Elliott and Mayer (2007)*'s network meta-analysis data

Description

- **study**: Study ID
- **trt**: Treatment (Diuretic, ACEI (ACE inhibitor), ARB, Beta blocker, CCB (Calcium-channel blocker), Placebo)
- **n**: Sample size
- **d**: Number of events (occurrence of diabetes)

Usage

data(diabetes)

Format

An arm-based dataset with 22 studies

References


global.ict  
*Higgins’ global inconsistency test*

Description

Higgins’ global inconsistency test based on the design-by-treatment interaction model. REML-based Wald test for the all possible design-by-treatment interactions on the network is performed.

Usage

global.ict(x)

Arguments

- **x**: Output object of setup
Value

Results of the global inconsistency test are presented.

- **coding**: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- **reference**: Reference treatment category.
- **number of studies**: Number of studies.
- **designs**: Study designs (combinations of treatments of individual trials) on the network.
- **Coefficients of the design-by-treatment interaction model**: Regression coefficients estimates and their SEs, 95% confidence intervals and P-values.
- **Between-studies_SD**: Between-studies SD estimate.
- **Between-studies_COR**: Between-studies correlation coefficient estimate (=0.50).
- **X2-statistic**: Chi-squared statistic of the global inconsistency test.
- **df**: Degree of freedom.
- **P-value**: P-value of the global inconsistency test.

References


Examples

data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)

global.ict(hf2)

Description

- **study**: Study ID
- **trial**: Trial name
- **trt**: Treatment (AB (Alpha blocker), ACE (ACE inhibitor), ARB, BB (Beta blocker), CCB (Calcium-channel blocker), CT (conventional treatments), Diuretic (DD), Placebo)
- **n**: Sample size
- **d**: Number of events (occurrence of heart failure)
Usage

```r
data(heartfailure)
```

Format

An arm-based dataset with 26 studies

References


---

**local.ict**

*Local inconsistency tests for all closed loops on the network*

Description

Local inconsistency tests for all closed loops on the network are performed. Higgins’ inconsistency test (Generalized Bucher’s test) that assesses the design-by-treatment interactions on the triangle loops are performed and their results are presented.

Usage

```r
local.ict(x)
```

Arguments

- **x**: Output object of `setup`

Value

Results of the local inconsistency tests for all closed loops on the network are presented.

- **coding**: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- **reference**: Reference treatment category.
- **N**: Number of studies.
- **tau**: Between-studies SD estimate.
- **X2-statistic**: Chi-squared statistics of the generalized Bucher’s test.
- **df**: Degree of freedom.
- **P-value**: P-value of the generalized Bucher’s test.
netplot

References


Examples

data(heartfailure)

hf2 <- setup(study=study,trt=trt,d=d,n=n,measure="OR",ref="Placebo",data=heartfailure)

local.ict(hf2)

---

netplot

*Generating a networkplot*

Description

Generate a networkplot. The sizes of the nodes and edges are proportional to the corresponding sample sizes of direct comparisons.

Usage

```r
netplot(x,text=TRUE,col="black",bg="blue",base.lwd=1,base.cex=1)
```

Arguments

- `x`: Output object of `setup`
- `text`: A logical value that specify whether the treatment labels are added
- `col`: Outer circumferential color of the nodes (default: black)
- `bg`: Color of the node (default: blue)
- `base.lwd`: A parameter adjusting edge widths (default: 1)
- `base.cex`: A parameter adjusting node sizes (default: 1)

Value

The networkplot is generated.
Examples

data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)

netplot(hf2) # default color and sizes
netplot(hf2, base.lwd=1.5, base.cex=1.5) # change the sizes
netplot(hf2, col="red", bg="red") # change the color
netplot(hf2, text=FALSE) # without texts

nma

Network meta-analysis based on contrast-based approach using the multivariate meta-analysis model

Description

Network meta-analysis based on contrast-based approach using the multivariate random-effects meta-analysis model. The synthesis results and prediction intervals based on the consistency assumption are provided. The ordinary REML method and its improved higher order asymptotic methods (Noma-Hamura methods) are available.

Usage

nma(x, eform=FALSE, method="NH")

Arguments

x Output object of setup
eform A logical value that specify whether the outcome should be transformed by exponential function (default: FALSE)

Value

Results of the network meta-analysis using the multivariate meta-analysis model.

• coding: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
• reference: Reference treatment category.
• number of studies: The number of synthesized studies.
• method: The estimation and prediction methods.
• Coef. (vs. treat1): Estimates, their SEs, Wald-type 95% confidence intervals, and P-values for the grand mean parameter vector.
• tau (Between-studies SD) estimate: Between-studies SD (tau) estimate.
• tau2 (Between-studies_variance) estimate: Between-studies variance (τ^2) estimate.
• Multivariate H2-statistic: Jackson's multivariate H2-statistic.
• Multivariate I2-statistic: Jackson's multivariate I2-statistic.
• Test for Heterogeneity: Multivariate Q-statistic and P-value of the test for heterogeneity.
• 95%PI: 95% prediction intervals.

References


Examples

data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)
hf3 <- setup(study=study, trt=trt, d=d, n=n, measure="RR", ref="Placebo", data=heartfailure)
hf4 <- setup(study=study, trt=trt, d=d, n=n, measure="RD", ref="Placebo", data=heartfailure)
nma(hf2, eform=TRUE)
nma(hf3, eform=TRUE)
nma(hf4)

Generating a ranked forest plot for the synthesis results of network meta-analysis

Description

A ranked forest plot for the synthesis results of network meta-analysis is generated based on the forestplot package. Details of the forestplot is customized by using the output objects of obj.forest function); these objects can be directly applied to forestplot function in forestplot package.
Usage

nmaforest(x, method="NH", col.plot="black", digits=3, ascending=TRUE)

Arguments

x Output object of setup
col.plot Color of the confidence interval plot (default: black)
digits Number of decimal places
ascending Type of order. Default is ascending order, but it can be changed to descending order changing to FALSE.

Value

A ranked forest plot for the synthesis results of network meta-analysis is generated.

Examples

data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)
nmaforest(hf2) # Default setting
nmaforest(hf2, col.plot="blue") # Change the color
nmaforest(hf2, ascending=FALSE) # Change to the descending order

of2 <- obj.forest(hf2)

Description

A league table is generated for all possible pairs of the treatments. The league table can be outputted as a CSV file through setting out.csv="filename".

Usage

nmaleague(x, method="NH", eform=FALSE, digits=3, PI=FALSE, out.csv=NULL)
Arguments

- **x**: Output object of `setup`
- **method**: Estimation and prediction method. 
  - N: Noma-Hamura’s improved REML-based methods (default).
  - NH: The ordinary REML method.

- **eform**: A logical value that specify whether the outcome should be transformed by exponential function (default: FALSE)

- **digits**: Number of decimal places

- **PI**: A logical value that specify whether the inference or prediction results are provided

- **out.csv**: A character object that specify a filename if the league table is outputted as a CSV file (e.g., `out.csv="out_league.csv"`).

Value

The league table is generated.

References


Examples

data(smoking)

```r
smk2 <- setup(study=study,trt=trt,d=d,n=n,measure="OR",ref="A",data=smoking)
nmaleague(smk2) # default setting
nmaleague(smk2, eform=TRUE) # transformed to exponential-scale
nmaleague(smk2, eform=TRUE, digits=2) # digits can be changed
nmaleague(smk2, eform=TRUE, PI=TRUE) # prediction intervals
```
Calculating the ranking statistics of network meta-analysis

Description

Ranking statistics of network meta-analysis such as SUCRA, MEANRANK, and probability of ranking are calculated by parametric bootstrap.

Usage

\[
nmarank(x, B=20000, method="NH", ascending=TRUE)\]

Arguments

- **x**: Output object of setup
- **B**: Number of parametric bootstrap resampling (default: 20000)
- **method**: Estimation and prediction method. \text{NH}: Noma-Hamura's improved REML-based methods (default). \text{REML}: The ordinary REML method. \text{fixed}: Fixed-effect model.
- **ascending**: A logical value that specify whether the ranking is defined by ascending or descending order

Value

Results of the ranking statistics of network meta-analysis are provided. Also, ranking probability plots are generated.

- **SUCRA**: SUCRA estimates of individual treatment by parametric bootstrap.
- **MEANRANK**: Mean rank estimates of individual treatment by parametric bootstrap.
- **Probability of ranking**: Probability of ranking (best, 2nd, 3rd,..., worst) estimates of individual treatment by parametric bootstrap.

References


Examples

```r
data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)

nmarank(hf2)
nmarank(hf2, ascending=FALSE)
```
Numerical objects of ranked forest plot for the synthesis results of network meta-analysis

Description

Numerical objects of ranked forest plot for the synthesis results of network meta-analysis are generated. These objects can be used to make a customized forest plot using forestplot function of forestplot package.

Usage

```r
obj.forest(x, method = "NH", digits = 3, ascending = TRUE)
```

Arguments

- **x**: Output object of setup
- **digits**: Number of decimal places
- **ascending**: Type of order. Default is ascending order, but it can be changed to descending order changing to FALSE.

Value

Numerical objects of ranked forest plot is generated. They can be used for forestplot function of forestplot package to make a customized ranked forest plot.

- **labeltext**: A matrix that presents the label text table of the forestplot.
- **coef**: A matrix that presents the point estimates and confidence limits.
- **boxsize**: A vector that indicates the boxsizes.

Examples

```r
data(heartfailure)
hf2 <- setup(study = study, trt = trt, d = d, n = n, measure = "OR", ref = "Placebo", data = heartfailure)
obj.forest(hf2)
```
Pairwise meta-analyses for all treatment pairs with direct comparisons on the network

Description

Pairwise meta-analyses for all treatment pairs with direct comparisons on the network are performed. The synthesis analyses are performed by \textit{rma} and \textit{regtest} in \texttt{metafor} package.

Usage

\begin{verbatim}
pairwise(x, method="REML")
\end{verbatim}

Arguments

\begin{itemize}
\item \textbf{x} \hspace{1cm} Output object of setup
\item \textbf{method} \hspace{1cm} Method of the estimation of pairwise meta-analysis. All possible options of \texttt{rma} function in \texttt{metafor} package is available (default: REML).
\end{itemize}

Value

Results of the meta-analyses for all possible treatment pairs are presented.

- **coding**: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- **measure**: Outcome measure.
- **Summary effect measures**: \texttt{N} (number of studies), summary estimates, 95\% confidence intervals, and P-values for all possible pairs.
- **Heterogeneity measures**: \texttt{N} (number of studies), \texttt{tau2} (heterogeneity variance) estimate, \texttt{I2}-statistic, and \texttt{H2}-statistic.
- **Egger test**: \texttt{N} (number of studies), P-value of the Egger test for assessing publication bias.

References


Examples

data(heartfailure)

hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)

pairwise(hf2)

---

```
rdc(a, digits)
```

**Description**

A function that returns a rounded value as a character.

**Usage**

```
rdc(a, digits)
```

**Arguments**

- **a**: A numerical value to be rounded
- **digits**: Number of decimal places

**Value**

The rounded value is returned as a character.

**Examples**

```
rdc(2.412, 3)
rdc(2.41, 3)
rdc(2.4, 3)
rdc(2, 3)
rdc(-2.41, 3)
rdc(-2.4, 3)
rdc(-2, 3)
rdc(0, 3)
```
setup

Transforming arm-level data to contrast-based summary statistics and making objects for the network meta-analysis

Description

A setup function to generate R objects that can be used for various network meta-analysis functions in this package. Users should prepare arm-level datasets from literatures, and this function can transform them to the contrast-based summary statistics. Both of dichotomous and continuous outcomes can be handled. The type of outcome variable can be specified by the measure. If the measure is specified as OR, RR or RD, the outcome should be dichotomous, and d and n are needed to compute the summary statistics. Besides, if the measure is specified as MD or SMD, the outcome should be continuous, and m, s and n are needed to compute the summary statistics. The output objects of setup function is used for the other computational or graphical tools in this package.

Usage

setup(study, trt, d, n, m, s, measure, ref, data)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>study</td>
<td>Study ID</td>
</tr>
<tr>
<td>trt</td>
<td>Treatment variable. It can be formed as both of numbered treatment (=1,2,...) and characters (e.g., &quot;Placebo&quot;, &quot;ARB&quot;, &quot;Beta blocker&quot;).</td>
</tr>
<tr>
<td>d</td>
<td>Number of events (for dichotomous outcome).</td>
</tr>
<tr>
<td>n</td>
<td>Sample size (for dichotomous and continuous outcome).</td>
</tr>
<tr>
<td>m</td>
<td>Mean of the outcome variable (for continuous outcome).</td>
</tr>
<tr>
<td>s</td>
<td>Standard deviation of the outcome variable (for continuous outcome).</td>
</tr>
<tr>
<td>measure</td>
<td>Outcome measure (can be OR (odds ratio), RR (risk ratio), and RD (risk difference) for dichotomous outcome, and MD (mean difference) and SMD (standardized mean difference) for continuous outcome.</td>
</tr>
<tr>
<td>ref</td>
<td>Reference treatment category that should be involved in trt.</td>
</tr>
<tr>
<td>data</td>
<td>A data frame that involves the arm-based data.</td>
</tr>
</tbody>
</table>

Value

Contrast-based summary statistics are generated.

- **coding**: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- **reference**: Reference treatment category.
- **measure**: Outcome measure.
- **N**: The number of study.
- **p**: The dimension of the contrast-based statistics.
sidesplit

- **df**: The degree of freedom.
- **study**: The ID variable that specifies studies.
- **trt**: The original vector that specifies treatment categories.
- **treat**: A numerical vector that specifies treatment categories based on the coding table.
- **d**: The original vector that specifies number of events.
- **n**: The original vector that specifies sample sizes.
- **m**: The original vector that specifies means.
- **s**: The original vector that specifies standard deviations.
- **y**: Contrast-based summary estimates.
- **S**: Vectored within-study covariance matrix.

**References**


**Examples**

```r
data(heartfailure)
hf2 <- setup(study=study, trt=trt, d=d, n=n, measure="OR", ref="Placebo", data=heartfailure)
hf3 <- setup(study=study, trt=trt, d=d, n=n, measure="RR", ref="Placebo", data=heartfailure)
hf4 <- setup(study=study, trt=trt, d=d, n=n, measure="RD", ref="Placebo", data=heartfailure)

data(antidiabetic)
ad2 <- setup(study=id, trt=t, m=y, s=sd, n=n, measure="MD", ref="Placebo", data=antidiabetic)
ad3 <- setup(study=id, trt=t, m=y, s=sd, n=n, measure="SMD", ref="Placebo", data=antidiabetic)
```

---

**sidesplit**

*Sidesplitting for quantifying direct and indirect evidence for all possible treatment pairs and the inconsistency test*

**Description**

Noma’s sidesplitting for quantifying direct and indirect evidence for all possible treatment pairs based on network meta-regression and the inconsistency tests are performed. For the bias correction that causes the involvement of multi-arm trials, we adopted the adjustment method of Noma et al. (2017) and Noma (2023).

**Usage**

`sidesplit(x)`
Arguments

x  Output object of setup

Value

Results of the sidesplitting for all possible treatment pairs are presented.

• coding: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
• reference: Reference treatment category.
• Direct evidence: Summary estimates, SEs, 95% confidence intervals, and P-values for the direct evidence.
• Indirect evidence: Summary estimates, SEs, 95% confidence intervals, and P-values for the indirect evidence.
• Difference: Differences of the summary estimates of direct and indirect evidence, and their inconsistency tests.

References


Examples

data(smoking)

smk2 <- setup(study=study,trt=trt,d=d,n=n,measure="OR",ref="A",data=smoking)

sidesplit(smk2)

<table>
<thead>
<tr>
<th>smoking</th>
<th>Smoking cessation data</th>
</tr>
</thead>
</table>

Description

• study: Study ID.
• trt: A character variable that indicates the type of intervention, A: No contact, B: Self help, C: Individual counselling, D: Group counselling.
• n: Number of participants of the intervention.
• d: Number of successes of the intervention.
smoking

Usage

data(smoking)

Format

An arm-based dataset with 24 trials.

References


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