Package 'NMA'

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Type Package

Title Network Meta-Analysis Based on Multivariate Meta-Analysis Models

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Description Network meta-analysis tools based on contrast-based approach using the multivariate meta-analysis and meta-regression models (Noma et al. (2023) <Forthcoming>). Standard analysis tools for network meta-analysis and meta-regression (e.g., synthesis analysis, ranking analysis, and creating league table) are available by simple commands. For inconsistency analyses, the local and global inconsistency tests based on the Higgins' design-by-treatment interaction model can be applied. Also, the side-splitting and the Jackson's random inconsistency model are available. Standard graphical tools for network meta-analysis (e.g., network plot, ranked forest plot, and transitivity analysis) can also be utilized. For the synthesis analyses, the Noma-Hamura's improved REML (restricted maximum likelihood)-based methods (Noma et al. (2023) <doi:10.1002/jrsm.1652> <doi:10.1002/jrsm.1651>) are adopted as the default methods.

URL https://www.ism.ac.jp/~noma/file/software/NMA.r

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NMA-package   *The 'NMA' package.*

Description

Network meta-analysis tools based on contrast-based approach using the multivariate meta-analysis and meta-regression models (Noma et al., 2023c). Standard analysis tools for network meta-analysis and meta-regression (e.g., synthesis analysis, ranking analysis, and creating league table) are available by simple commands. For inconsistency analyses, the local and global inconsistency tests based on the Higgins' design-by-treatment interaction model can be applied. Also, the side-splitting and the Jackson's random inconsistency model are available. Standard graphical tools for network meta-analysis (e.g., network plot, ranked forest plot, and transitivity analysis) can also be utilized. For the synthesis analyses, the Noma-Hamura's improved REML (restricted maximum likelihood)-based methods (Noma et al., 2023ab) are adopted as the default methods.

References

Higgins, J. P., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., and White, I. R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* **3**, 98-110.

Nikolakopoulou, A., White, I. R., and Salanti, G. (2021). Network meta-analysis. In: Schmid CH, Stijnen T, White IR, eds. *Handbook of Meta-Analysis*. CRC Press; pp. 187-217.

Noma, H. (2023a). Sidesplitting using network meta-regression. Jxiv, 493. doi:10.51094/jxiv.493.

Noma, H. (2023b). Within-study covariance estimators for network meta-analysis with contrast-based approach. Jxiv, 490. doi:10.51094/jxiv.490.

Noma, H., Hamura, Y., Gosho, M., and Furukawa, T. A. (2023a). Kenward-Roger-type corrections for inference methods of network meta-analysis and meta-regression. *Research Synthesis Methods* **14**, 731-741.

Noma, H., Hamura, Y., Sugasawa, S., and Furukawa, T. A. (2023b). Improved methods to construct prediction intervals for network meta-analysis. *Research Synthesis Methods* **14**, 794-806.

Noma, H., Maruo, K., Tanaka, S. and Furukawa, T. A. (2023c). NMA: R package for network meta-analysis based on the multivariate meta-analysis and meta-regression models. Forthcoming.

Noma, H., Tanaka, S., Matsui, S., Cipriani, A., and Furukawa, T. A. (2017). Quantifying indirect evidence in network meta-analysis. *Statistics in Medicine* **36**, 917-927.

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* **3**, 80-97.

White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods* **3**, 111-125.

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antidiabetic	*Phung et al. (2010)'s network meta-analysis data*

Description

A network meta-analysis dataset for treatments of type-2 diabetes from Chaimani and Salanti (2015).

- `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

```
data(antidiabetic)
```

Format

An arm-based dataset with 20 studies

References

Chaimani, A. and Salanti, G. (2015). Visualizing assumptions and results in network meta-analysis: the network graphs package. *Stata Journal.* **15**: 905-920.

Phung, O. J., Scholle, J. M., Talwar, M. and Coleman, C. I. (2010). Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA.* **303**: 1410-1418.

---

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

Description

A network meta-analysis data from Elliott and Mayer (2007) that compared 5 antihypertensive drug classes and placebo for occurrence of diabetes.

- 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

Elliott, W. J., and Meyer, P. M. (2007). Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet.* **369**: 201-207.

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

Higgins, J. P., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., and White, I. R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* **3**, 98-110.

Jackson, D., Boddington, P., and White, I. R. (2016). The design-by-treatment interaction model: a unifying framework for modelling loop inconsistency in network meta-analysis. *Research Synthesis Methods* **7**, 329-332.

Examples

```
data(heartfailure)

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

global.ict(hf2)
```

---

heartfailure   *Sciarretta et al. (2011)'s network meta-analysis data*

Description

A network meta-analysis data from Sciarretta et al. (2011) that compared 7 antihypertensive drug classes and placebo for occurrence of heart failure.

- 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)
- pubyear: Publication year
- SBP: Mean of baseline systolic blood pressure (mmHg)
- DBP: Mean of diastolic systolic blood pressure (mmHg)

Usage

```
data(heartfailure)
```

Format

An arm-based dataset with 26 studies

References

Sciarretta, S., Palano, F., Tocci, G., Baldini, R., and Volpe, M. (2011). Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Archives of Internal Medicine* **171**: 384-394.

---

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

```
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.

References

Bucher, H. C., Guyatt, G. H., Griffith, L. E., and Walter, S. D. (1997). The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* **50**, 683-691.

Higgins, J. P., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., and White, I. R. (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* **3**, 98-110.

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

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

Usage

```
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

A 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)
method	Estimation and prediction method. NH: Noma-Hamura's improved REML-based methods (default). REML: The ordinary REML method. fixed: Fixed-effect model.

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 (tau^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

Jackson, D., White, I. R., Riley, R. D. (2012). Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Statistics in Medicine* **31**: 3805-3820.

Nikolakopoulou, A., White, I. R., and Salanti, G. (2021). Network meta-analysis. In: Schmid, C. H., Stijnen, T., White, I. R., eds. *Handbook of Meta-Analysis*. CRC Press; pp. 187-217.

Noma, H., Hamura, Y., Gosho, M., and Furukawa, T. A. (2023). Kenward-Roger-type corrections for inference methods of network meta-analysis and meta-regression. *Research Synthesis Methods* **14**, 731-741.

Noma, H., Hamura, Y., Sugasawa, S., and Furukawa, T. A. (2023). Improved methods to construct prediction intervals for network meta-analysis. *Research Synthesis Methods* **14**, 794-806.

White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods* **3**, 111-125.

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)
```

---

nmaforest	*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 by simple command. Details of the forestplot is customized by using the output objects of `obj.forest` function); see also `help(obj.forest)`.

Usage

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

Arguments

x	Output object of `setup`
method	Estimation and prediction method. `NH`: Noma-Hamura's improved REML-based methods (default). `REML`: The ordinary REML method. `fixed`: Fixed-effect model.

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
```

---

nmafunnel   *Comparison-adjusted funnel plot*

Description

A comparison-adjusted funnel plot for the studies involving treatment 1 (reference treatment specified in setup) is generated.

Usage

```
nmafunnel(x, method="NH", legends="topright")
```

Arguments

x	Output object of setup
method	Estimation and prediction method. NH: Noma-Hamura's improved REML-based methods (default). REML: The ordinary REML method.
legends	Location of the legend on the plot (default: topright)

Value

Comparison-adjusted funnel plot for the studies involving treatment 1 (reference treatment specified in setup) is presented.

- coding: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).

- summary: design: design of studies, N: number of the corresponding studies, n: total sample size.

References

Chaimani, A. and Salanti, G. (2012). Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* **3**, 161–176.

Chaimani, A., Higgins, J. P., Mavridis, D., Spyridonos, P., and Salanti, G. (2013). Graphical tools for network meta-analysis in Stata. *PLoS One* **8**, e76654.

Examples

```
data(heartfailure)

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

nmafunnel(hf2,legends="bottomright")
nmafunnel(hf4)
```

---

nmaleague	*Generating a league table*

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. `NH`: Noma-Hamura's improved REML-based methods (default). `REML`: 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 user wants to output the league table as a CSV file (e.g., `out.csv="out_league.csv"`).

Value

A league table is generated.

References

Nikolakopoulou, A., White, I. R., and Salanti, G. (2021). Network meta-analysis. In: Schmid, C. H., Stijnen, T., White, I. R., eds. *Handbook of Meta-Analysis*. CRC Press; pp. 187-217.

Noma, H., Hamura, Y., Gosho, M., and Furukawa, T. A. (2023). Kenward-Roger-type corrections for inference methods of network meta-analysis and meta-regression. *Research Synthesis Methods* **14**, 731-741.

Noma, H., Hamura, Y., Sugasawa, S., and Furukawa, T. A. (2023). Improved methods to construct prediction intervals for network meta-analysis. *Research Synthesis Methods* **14**, 794-806.

White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods* **3**, 111-125.

Examples

```
data(smoking)

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
```

---

nmaQ   *Multivariate Q-statistic and its factorization*

Description

Multivariate Q-statistic and its factorized versions (within and between designs) are presented. P-values of the corresponding Q-tests are also presented.

Usage

```
nmaQ(x)
```

Arguments

x   Output object of `setup`

Value

Multivariate Q-statistic and its factorized ones (within and between designs) are presented.

- `coding`: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- `number of studies`: The number of synthesized studies.

- `Within designs (individual designs)`: Q-statistics for individual designs and their P-values.
- `Q-statistics`: Multivariate Q-statistics and its factorized ones (within and between designs), and their P-values.

References

Jackson, D., White, I. R., and Riley, R. D. (2012). Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Statistics in Medicine* **31**: 3805-3820.

Krahn, U., Binder, H., and Konig, J. (2013). A graphical tool for locating inconsistency in network meta-analysis. *BMC Medical Research Methodology* **13**, 35.

Examples

```
data(heartfailure)

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

nmaQ(hf2)
```

---

nmarank   *Calculating 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. `NH`: Noma-Hamura's improved REML-based methods (default). `REML`: The ordinary REML method. `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

Salanti, G., Ades, A. E. and Ioannidis, J. P. (2011). Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *Journal of Clinical Epidemiology* **64**, 163–171.

Examples

```
data(heartfailure)

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

nmarank(hf2)
nmarank(hf2, ascending=FALSE)
```

---

nmareg   *Network meta-regression based on contrast-based approach*

Description

Network meta-regression based on contrast-based approach using the multivariate meta-regression model. Effect modifications by study-level covariates (specified in the setup function) can be assessed. In many network meta-analysis, some treatment contrasts involve only 1 or 2 (or 0) direct comparisons, and the regression coefficients of the corresponding outcomes cannot be validly estimated (non-identifiable). Thus, the nmareg function can specify a subset of outcome variables to be modelled by the regression model (to be assessed the effect modifications) by treats. Currently, the parameter estimation is performed by the ordinary REML method.

Usage

```
nmareg(x, z, treats)
```

Arguments

x	Output object of setup
z	Covariate name vector
treats	A vector that specifies treatments to be assessed effect modifications that correspond to the elements of outcome vectors y in x (please specify the treatment numbers of coding; multiple outcomes can be specified jointly, as a vector).

Value

Results of the network meta-regression analysis are presented.

- `coding`: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).

- `Covariates`: Covariate that specified in `setup`.

- `Outcome evaluated the effect modifications`: Treatment contrasts that the effect modifications are evaluated.

- `Coefficients`: Estimates, their SEs, Wald-type 95% confidence intervals, and P-values for the regression parameters (`cons`: intercept, `beta`: regression coefficient for the explanatory variable).

- `Between-studies_SD`: Between-studies SD (tau) estimate.

- `Between-studies_COR`: Between-studies correlation coefficient (should be 0.50).

References

Nikolakopoulou, A., White, I. R., Salanti, G. (2021). Network meta-analysis. In: Schmid, C. H., Stijnen, T., White, I. R., eds. *Handbook of Meta-Analysis*. CRC Press; pp. 187-217.

Noma, H., Hamura, Y., Gosho, M., and Furukawa, T. A. (2023). Kenward-Roger-type corrections for inference methods of network meta-analysis and meta-regression. *Research Synthesis Methods* **14**, 731-741.

White, I. R., Barrett, J. K., Jackson, D., and Higgins, J. P. (2012). Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods* **3**, 111-125.

Examples

```
data(heartfailure)

hf2 <- setup(study=study,trt=trt,d=d,n=n,z=c(SBP,DBP,pubyear),measure="OR",
ref="Placebo",data=heartfailure)

nmareg(hf2,z=SBP,treats=3)
nmareg(hf2,z=c(SBP,DBP),treats=c(3,4,6))
```

---

nmaweight   *Evaluating study weights and contribution matrix*

Description

Contribution weight matrices to assess how individual studies influence the synthesized results are presented. Jackson et al. (2017) and Noma et al. (2017) showed the contribution rates are estimated by the factorized information, and the contribution weight matrices are calculated through the factorized information.

Usage

```
nmaweight(x)
```

Arguments

x	Output object of `setup`

Value

Contribution weight matrices for the consistency model are presented. Also, a heatmap for the contribution matrix of overall evidence is presented.

- `coding`: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).
- `Contribution of direct and indirect information`: Contribution rates of direct and indirect evidence for individual treatment pairs.
- `Contribution weights: Direct comparison`: Contribution weight matrix for direct evidence.
- `Contribution weights: Indirect comparison (BoS)`: Contribution weight matrix for indirect evidence (BoS; borrowing of strength of Jackson et al. (2017)).
- `Contribution weights: Overall evidence`: Contribution weight matrix for overall evidence.

References

Jackson, D., White, I. R., Price, M., Copas, J., and Riley, R. D. (2017). Borrowing of strength and study weights in multivariate and network meta-analysis. *Statistical Methods in Medical Research* **26**, 2853-2868.

Noma, H., Tanaka, S., Matsui, S., Cipriani, A., and Furukawa, T. A. (2017). Quantifying indirect evidence in network meta-analysis. *Statistics in Medicine* **36**, 917-927.

Examples

```
data(smoking)

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

nmaweight(smk2)
```

---

obj.forest	*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

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

Arguments

x	Output object of `setup`
method	Estimation and prediction method. NH: Noma-Hamura's improved REML-based methods (default). REML: The ordinary REML method. fixed: Fixed-effect model.
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

```
data(heartfailure)

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

obj.forest(hf2)
```

---

pairwise	*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 `rma` and `regtest` in `metafor` package.

Usage

```
pairwise(x,method="REML")
```

Arguments

x	Output object of `setup`
method	Method of the estimation of pairwise meta-analysis. All possible options of `rma` function in `metafor` package is available(default: REML).

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`: N (number of studies), summary estimates, 95% confidence intervals, and P-values for all possible pairs.

- `Heterogeneity measures`: N (number of studies), tau2 (heterogeneity variance) estimate, I2-statistic, and H2-statistic.

- `Egger test`: N (number of studies), P-value of the Egger test for assessing publication bias.

References

DerSimonian, R., and Laird, N. M. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**, 177-188.

Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629-634.

Higgins, J. P. T., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**, 1539-1558.

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* **36**, Issue 3.

Examples

```
data(heartfailure)

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

pairwise(hf2)
```

---

random.icm	*Jackson's random inconsistency model*

Description

Jackson's random inconsistency model for modelling the design-by-treatment interactions. Model-based testing results for heterogeneity and inconsistency (design-by-treatment interactions) and the I2-statistics are presented.

Usage

```
random.icm(x)
```

Arguments

x   Output object of `setup`

Value

Results of the analysis of Jackson's random inconsistency model and I2-statistics 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.

- `number of designs`: Number of designs.

- `designs`: Study designs (combinations of treatments of individual trials) on the network.

- `Coef. (vs. treat 1)`: Regression coefficients estimates and their SEs, 95% confidence intervals and P-values.

- `Between-studies_SD`: Between-studies SD estimate.

- `Between-designs_SD`: Between-designs SD estimate.

- `Likelihood ratio tests for the variance components`: Results of the likelihood ratio tests for comparing (1) the fixed- and random-effects models without inconsistency effects (heterogeneity), (2) the random-effects models with and without inconsistency effects (inconsistency), and (3) the fixed-effect model without inconsistency effects and the random-effects model with inconsistency effects (heterogeneity + inconsistency).

- `Heterogeneity and inconsistency statistics`: R-statistics and I2-statistics for comparing (1) the fixed- and random-effects models without inconsistency effects (heterogeneity), (2) the random-effects models with and without inconsistency effects (inconsistency), and (3) the fixed-effect model without inconsistency effects and the random-effects model with inconsistency effects (heterogeneity + inconsistency).

References

Jackson, D., White, I. R., and Riley, R. D. (2012). Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Statistics in Medicine* **31**: 3805-3820.

Jackson, D., Barrett, J. K., Rice, S., White, I. R., and Higgins, J. P. T. (2014). A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in Medicine* **33**, 3639-3654.

Law, M., Jackson, D., Turner, R., Rhodes, K., and Viechtbauer, W. (2016). Two new methods to fit models for network meta-analysis with random inconsistency effects. *BMC Medical Research Methodology* **16**, 87.

Nikolakopoulou, A., White, I. R., and Salanti, G. (2021). Network meta-analysis. In: Schmid, C. H., Stijnen, T., White, I. R., eds. *Handbook of Meta-Analysis*. CRC Press; pp. 187-217.

Examples

```
data(heartfailure)

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

random.icm(hf2)
```

---

rdc   *Rounding a numerical value*

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 network meta-analysis

---

Description

A setup function to generate R objects that can be used for network meta-analysis. Users should prepare arm-level datasets, and the `setup` function transforms the arm-level data to the contrast-based summary statistics. Both of dichotomous and continuous outcomes can be treated. 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. Also, if the `measure` is specified as `HR`, the outcome should be survival (time-to-event), and `d` and `n` are needed to compute the summary statistics. Note `HR` corresponds to rate-ratio in ordinary sense and this option corresponds to the person-time analysis; hazard ratio accords to rate-ratio if the survival time distribution is exponential distribution. Several covariates can be involved as `z` for network meta-regression analysis (`nmareg`) and transitivity analysis (`transitivity`).

Usage

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

Arguments

study	Study ID
trt	Treatment variable. It can be formed as both of numbered treatment (=1,2,...) and characters (e.g., "Placebo", "ARB", "Beta blocker").
d	Number of events (for dichotomous outcome and survival outcome).
n	Sample size (for dichotomous and continuous outcome) or total person-time at risk (for survival outcome).
m	Mean of the outcome variable (for continuous outcome).
s	Standard deviation of the outcome variable (for continuous outcome).
z	Covariate name vector to be used for network meta-regression analysis or transitivity analysis (optional).
measure	Outcome measure (can be `OR` (odds ratio), `RR` (risk ratio), and `RD` (risk difference) for dichotomous outcome, `MD` (mean difference) and `SMD` (standardized mean difference) for continuous outcome, and `HR` (hazard ratio) for survival outcome.
ref	Reference treatment category that should be involved in `trt`.
data	A data frame that involves the arm-based data.

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.
- covariate: Covariate name(s).
- N: The number of study.
- p: The dimension of the contrast-based statistics.
- 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.
- Z: The data frame that specifies covariates matrix (design matrix).
- y: Contrast-based summary estimates.
- S: Vectored within-study covariance matrix.

References

Noma, H. (2023). Within-study covariance estimators for network meta-analysis with contrast-based approach. Jxiv, 490. doi:10.51094/jxiv.490.

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)

hf5 <- setup(study=study,trt=trt,d=d,n=n,z=c(SBP,DBP,pubyear),measure="OR",
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

Dias, S., Welton, N. J., Caldwell, D. M., and Ades, A. E. (2010). Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* **29**, 932-944.

Noma, H. (2023). Sidesplitting using network meta-regression. Jxiv, 493. doi:10.51094/jxiv.493.

Noma, H., Tanaka, S., Matsui, S., Cipriani, A., and Furukawa, T. A. (2017). Quantifying indirect evidence in network meta-analysis. *Statistics in Medicine* **36**, 917-927.

Examples

```
data(smoking)

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

sidesplit(smk2)
```

---

smoking   *Smoking cessation data*

Description

A network meta-analysis data for smoking cessation from Lu and Ades (2006) and Higgins et al. (2012).

- 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.

Usage

```
data(smoking)
```

Format

An arm-based dataset with 24 studies.

References

Lu, G., Ades, A. E. (2006). Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* **101**:447-459.

Higgins, J. P. T., Jackson, D., Barrett, J. K. et al (2012). Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* **3**:98-110.

---

transitivity   *Checking transitivity*

Description

To check transitivity on the network, summary statistics of a certain covariate among different study designs are presented. Also, a summary plot for these statistics is presented.

Usage

```
transitivity(x, z, gcol="blue", yrange)
```

Arguments

x	Output object of `setup`
z	Covariate name for assessing transitivity (must be involved in `covariate` of the output object of `setup`
gcol	Color of the plot
yrange	Range of y-axis of the plot

Value

Summary statistics of the covariate among different study designs and its summary plot are presented.

- `coding`: A table that presents the correspondence between the numerical code and treatment categories (the reference category is coded as 1).

- `covariate`: Covariate that specified in `setup`.

- `summary`: Summary of the covariate among different study designs. N: number of the corresponding studies, n: total sample size, `wt.mean`: weighted mean, `min`: minimum, `max`: maximum.

References

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* **3**, 80-97.

Examples

```
data(heartfailure)

hf2 <- setup(study=study,trt=trt,d=d,n=n,z=c(SBP,DBP,pubyear),measure="OR",
ref="Placebo",data=heartfailure)

transitivity(hf2, SBP)
transitivity(hf2, DBP)
transitivity(hf2, pubyear)
```

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