Package 'xmeta'

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Type Package

Title A Toolbox for Multivariate Meta-Analysis

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Description A toolbox for meta-analysis. This package includes a collection of functions for (1) implementing robust multivariate meta-analysis of continuous or binary outcomes; and (2) a bivariate Egger's test for detecting publication bias.

Depends R (>= 3.0.0)

License GPL (>= 2)

LazyLoad no

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`xmeta-package` *A Tool Box for Multivariate Meta-Analysis*

Description

The package **xmeta** consists of a collection of functions for making inference and detecting publication bias in multivariate meta-analysis (MMA).

Details

Package:	xmeta
Type:	Package
Version:	1.1
Date:	2017-5-12
License:	GPL>=2

Inference

The aim of the estimation methods is to estimate the coefficients β and the components of the between-study (co)variance matrix Ψ for multivariate random-effects meta-analysis. One major challenge in MMA is the standard inference procedures, such as the maximum likelihood or maximum restricted likelihood inference, require the within-study correlations, which are usually unavailable. Different estimators with and without the knowledge of within study correlation are implemented in the package **xmeta**. The estimation methods available in function `mmeta` are:

- **Restricted maximum likelihood for MMA with continuous outcomes**
- **Composite likelihood method for MMA with continuous outcomes**
- **Method of moment for MMA with continuous outocmes**
- **Improved method for Riley model for MMA with continuous outcomes**
- **Marginal bivariate normal model for MMA with binary outcomes**
- **Marginal beta-binomial model for MMA with binary outcomes**
- **Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy**
- **Trivariate model for multivariate meta-analysis of diagnostic test accuracy**

Publication bias

Detecting and accounting for publication bias are challenging in MMA setting. The multivariate nature is often not fully accounted for by the existing univariate methods. The score test for detecting publication bias in MMA when the within-study correlations are unknown is implemented in the function `mpbt`. The Galaxy method for correcting publication bias in MMA is implemented in the function `galaxy`.

Author(s)

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`ca125` *Recurrent ovarian carcinoma study*

Description

A meta-analysis of 52 studies that were reported between January 1995 and November 2007.

Format

The data frame contains the following columns:

n total number of subjects

PiY disease prevalence

SeY true positive

n1 subjects with disease

SpY true negative

n1 health individuals

Note

The dataset `ca125` is used to conduct multivariate meta-analysis of diagnostic test accuracy.

References

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid C. (2015). A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine (under revision).

Gu P, Pan L, Wu S, Sun L, Huang G. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. European journal of radiology 2009; 71(1):164-174.

See Also

`mmeta`, `summary.mmeta`

Examples

```
data(ca125)
summary(ca125)
```

galaxy *Correcting for publication bias of multivariate meta-analysis*

Description

Correcting for publication bias of multivariate meta-analysis

Usage

```
galaxy(data, rhow, type, method, k, L, estimator, side, maxiter)
```

Arguments

data	dataset
rhow	within-study correlation
method	"galaxy.cl" indicating the Galaxy method for detecting and correcting for publication bias of MMA
type	either "continuous" or "binary" indicating the type of outcomes
k	integer indicating the number of outcomes
L	the coefficient for loss function
side	either "left" or "right", indicating on which side of the funnel plot the missing studies should be imputed
maxiter	maximum number of iterations
estimator	either "R0", "L0" or "Q0"

Details

This function returns the pooled effect size after adjusting for publication bias of multivariate meta-analysis using the Galaxy method.

Value

res returns the pooled effect size, covariance matrix, the estimated number of missing and the side of imputation.

Author(s)

Yong Chen

References

Chen, Y., Hong, C., Chu, H., (2015). Galaxy plot and a multivariate method for correcting publication bias in multivariate meta-analysis (in preparation).

Examples

```
data(prostate)
fit.galaxy=galaxy(data=prostate, type = "continuous",
  method="galaxy.cl", k=2, L=1, estimator="R0", maxiter=150)
summary(fit.galaxy)
```

`mmeta` *Methods for multiviarate random-effects meta-analysis*

Description

Methods for multiviarate random-effects meta-analysis

Usage

```
mmeta(data, rhow, type, k, method)
```

Arguments

`data`	dataset
`rhow`	within-study correlation
`type`	either "continuous" or "binary", indicating the type of outcomes.
`k`	integer indicating the number of outcomes
`method`	either "nn.reml", "nn.cl", "nn.mom", "nn.rs", "bb.cl", "bn.cl", "tb.cl" or "tn.cl", indicating the estimation method.

Details

Inference on the multivariate random-effects meta-analysis for both continuous and binary outcomes

The function can be used in meta-analyses with continous outcomes and binary outcomes (e.g., mean differences, diagnostic test results in diagnostic accuracy studies, the exposure status of both cases and controls in case-control studies and so on). Different estimators with and without the knowledge of within-study correlations are implemented in this function. The estimation methods include

- **Restricted maximum likelihood for MMA with continuous outcomes**(nn.reml)
- **Composite likelihood method for MMA with continuous outcomes** (nn.cl)
- **Moment of method for MMA with continuous outocmes** (nn.mom)
- **Improved method for Riley model for MMA with continuous outcomes** (nn.rs)
- **Marginal bivariate normal model for MMA with binary outcomes** (bn.cl)
- **Marginal beta-binomial model for MMA with binary outcomes**(bb.cl)
- **Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy** (tb.cl)
- **Trivariate model for multivariate meta-analysis of diagnostic test accuracy**(tn.cl)

Value

An object of class `"mmeta"`. The object is a list containing the following components:

`beta`	estimated coefficients of the model.
`beta.cov`	covariance matrix of the coefficients.

Multivariate random-effects meta analysis

We consider a meta-analysis with m studies where two outcomes in each study are of interest. For the ith study, denote Y_{ij} and s_{ij} the summary measure for the jth outcome of interest and associated standard error respectively, both assumed known, $i = 1, \ldots, m$, and $j = 1, 2$. Each summary measure Y_{ij} is an estimate of the true effect size θ_{ij}. To account for heterogeneity in effect size across studies, we assume θ_{ij} to be independently drawn from a common distribution with overall effect size β_j and between study variance $\tau_j^2, j = 1, 2$. Under normal distribution assumption for Y_{ij} and θ_{ij}, the general bivariate random-effects meta-analysis can be written as

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \Delta_i\right), \quad \Delta_i = \begin{pmatrix} s_{i1}^2 & s_{i1}s_{i2}\rho_{\mathbf{W}i} \\ s_{i1}s_{i2}\rho_{\mathbf{W}i} & s_{i2}^2 \end{pmatrix},$$

$$\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \Omega\right), \quad \Omega = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho_{\mathbf{B}} \\ \tau_1\tau_2\rho_{\mathbf{B}} & \tau_2^2 \end{pmatrix},$$

where Δ_i and Ω are the respective within-study and between-study covariance matrices, and $\rho_{\mathbf{W}i}$ and $\rho_{\mathbf{B}}$ are the respective within-study and between-study correlations.

Restricted maximum likelihood for MMA

When the within-study correlations are known, inference on the overall effect sizes β_1 and β_2 or their comparative measures (e.g., $\beta_1 - \beta_2$) can be based on the marginal distribution of (Y_{i1}, Y_{i2})

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \mathbf{V_i}\right), \mathbf{V_i} = \mathbf{\Delta_i} + \mathbf{\Omega} = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & s_{i1}s_{i2}\rho_{wi} + \tau_1\tau_2\rho_{\mathbf{B}} \\ s_{i1}s_{i2}\rho_{wi} + \tau_1\tau_2\rho_{\mathbf{B}} & s_{i2}^2 + \tau_2^2 \end{pmatrix}.$$

For simplicity of notation, denote $\mathbf{Y_i} = (\mathbf{Y_{i1}}, \mathbf{Y_{i2}})^{\mathbf{T}}$, $\beta = (\beta_1, \beta_2)^T$, $\eta_1 = (\beta_1, \tau_1^2)^T$ and $\eta_2 = (\beta_2, \tau_2^2)^T$. The restricted likelihood of $(\eta_1, \eta_2, \rho_{\mathbf{B}})$ can be written as

$$\log L(\eta_1, \eta_2, \rho_{\mathbf{B}}) = -\frac{1}{2}\left[\log\left(\left|\sum_{i=1}^{m} \mathbf{V_i}^{-\mathbf{1}}\right|\right) + \sum_{i=1}^{m}\left\{\log|\mathbf{V_i}| + (\mathbf{Y_i} - \beta)^{\mathbf{T}}\mathbf{V_i}^{-\mathbf{1}}(\mathbf{Y_i} - \beta)\right\}\right].$$

The parameters $(\eta_1, \eta_2, \rho_{\mathbf{B}})$ can be estimated by the restricted maximum likelihood (REML) approach as described in Van Houwelingen et al. (2002). The REML method for MMA is specified via `method` argument (`method="nn.reml"`).

The standard inference procedures, such as the maximum likelihood or maximum restricted likelihood inference, require the within-study correlations, which are usually unavailable. In case within-study correlations are unknown, then one can leave the ρ_w argument unspecified, and specify a method that does not require the within-study correlations via `method` argument.

Composite likelihood method for MMA with continuous outcomes

Chen et al. (2014) proposed a pseudolikelihood method for MMA with unknown within-study correlation. The pseudolikelihood method does not require within-study correlations, and is not prone to singular covariance matrix problem. In addition, it can properly estimate the covariance between pooled estimates for different outcomes, which enables valid inference on functions of pooled estimates, and can be applied to meta-analysis where some studies have outcomes MCAR. This composite likelihood method for MMA is specified via `method` argument (`method="nn.cl"`).

Moment of method for MMA with continuous outocmes

Chen et al. (2015) proposed a simple non-iterative method that can be used for the analysis of multivariate meta-analysis datasets that has no convergence problems and does not require the use of within-study correlations. The strategy is to use standard univariate methods for the marginal effects but also provides valid joint inference for multiple parameters. This method method can directly handle missing outcomes under missing completely at random assumption. This moment of method for MMA is specified via `method` argument (`method="nn.mom"`)

Improved method for Riley model for MMA with continuous outcomes

Riley et al.(2008) proposed a working model and an overall synthesis correlation parameter to account for the marginal correlation between outcomes, where the only data needed are those required for a separate univariate random-effects meta-analysis. As within-study correlations are not required, the Riley method is applicable to a wide variety of evidence synthesis situations. However, the standard variance estimator of the Riley method is not entirely correct under many important settings. As a consequence, the coverage of a function of pooled estimates may not reach the nominal level even when the number of studies in the multivariate meta-analysis is large. Hong et al. (2015) improved the Riley method by proposing a robust variance estimator, which is asymptotically correct even when the model is misspecified (i.e., when the likelihood function is incorrect). The improved method for Riley model MMA is specified via `method` argument (`method="nn.rs"`)

Marginal bivariate normal model for MMA with binary outcomes

Diagnostic systematic review is a vital step in the evaluation of diagnostic technologies. In many applications, it invovles pooling paris of sensitivity and specificity of a dichotomized diagnostic test from multiple studies. Chen et al. (2014) proposed a composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. The idea of marginal bivariate normal model for MMA with binary outcomes is to construct a composite likelihood (CL) funciton by using an independent working assumption between sensitivity and specificity. There are three immediate advantages of using this CL method. First, the non-convergence or non positive definite covariance matrix problem is resolved since there is no correlation parameter involved in the CL. Secondly, because the two-dimensional integration involved in the standard likelihood is substituted by one-dimensional integrals, the approximation errors are substantially reduced. Thirdly, the inference based on the CL only relies on the marginal normality of logit sensitivity and specificity. Hence the proposed method can be more robust than the standard likelihood inference to mis-specifications of the joint distribution assumption. This method is specified via `method` argument (`method="bn.cl"`)

Marginal beta-binomial model for MMA with binary outcomes

When conducting a meta-analysis of studies with bivariate binary outcomes, challenges arise when the within-study correlation and between-study heterogeneity should be taken into account. Chen et al. (2015) proposed a marginal beta-binomial model for the meta-analysis of studies with binary outcomes. This model is based on the composite likelihood approach, and has several attractive features compared to the existing models such as bivariate generalized linear mixed model (Chu and Cole, 2006) and Sarmanov beta-binomial model (Chen et al., 2012). The advantages of the proposed marginal model include modeling the probabilities in the original scale, not requiring any transformation of probabilities or any link function, having closed-form expression of likelihood function, and no constraints on the correlation parameter. More importantly, since the marginal beta-binomial model is only based on the marginal distributions, it does not suffer from potential misspecification of the joint distribution of bivariate study-specific probabilities. Such misspecification is difficult to detect and can lead to biased inference using currents methods. This method is specified via `method` argument (`method="bb.cl"`)

Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy

Meta-analysis of diagnostic test accuracy often involves mixture of case-control and cohort studies. The existing bivariate random effects models, which jointly model bivariate accuracy indices (e.g., sensitivity and specificity), do not differentiate cohort studies from case-control studies, and thus do not utilize the prevalence information contained in the cohort studies. The trivariate generalized linear mixed models are only applicable to cohort studies, and more importantly, they assume the common correlation structure across studies, and the trivariate normality on disease prevalence, test sensitivity and specificity after transformation by some pre-specified link functions. In practice, very few studies provide justifications of these assumptions, and sometimes these assumptions are violated. Chen et al. (2015) evaluated the performance of the commonly used random effects model under violations of these assumptions and propose a simple and robust method to fully utilize the information contained in case-control and cohort studies. The proposed method avoids making the aforementioned assumptions and can provide valid joint inferences for any functions of overall summary measures of diagnostic accuracy. This method is specified via `method` argument (`method="tb.cl"`)

Trivariate model for multivariate meta-analysis of diagnostic test accuracy

The standard methods for evaluating diagnostic accuracy only focus on sensitivity and specificity and ignore the information on disease prevalence contained in cohort studies. Consequently, such methods cannot provide estimates of measures related to disease prevalence, such as population averaged or overall positive and negative predictive values, which reflect the clinical utility of a diagnostic test. Chen et al. (2014) proposed a hybrid approach that jointly models the disease prevalence along with the diagnostic test sensitivity and specificity in cohort studies, and the sensitivity and specificity in case-control studies. In order to overcome the potential computational difficulties in the standard full likelihood inference of the proposed hybrid model, an alternative inference procedure was proposed based on the composite likelihood. Such composite likelihood based inference does not suffer computational problems and maintains high relative efficiency. In addition, it is more robust to model mis-specifications compared to the standard full likelihood inference. This method is specified via `method` argument (`method="tn.cl"`)

Author(s)

Yong Chen, Yulun Liu

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Hong, C., Riley, R. D. and Chen, Y. (2015). An improved method for multivariate random-effects meta-analysis (in preparation).

Chen, Y., Liu, Y., Ning, J., Nie, L., Zhu, H. and Chu, H. (2014). A composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. Statistical methods in medical research (in press).

Chen, Y., Cai, Y., Hong, C. and Jackson, D. (2015). Inference for correlated effect sizes using multiple univariate meta-analyses, Statistics in Medicine (provisional acceptance).

Chen, Y., Liu, Y., Ning, J., Cormier J. and Chu H. (2014). A hybrid model for combining case-control and cohort studies in systematic reviews of diagnostic tests, Journal of the Royal Statistical Society: Series C (Applied Statistics) 64.3 (2015): 469-489.

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid C. (2015). A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine (under revision).

Examples

```
data(prostate)
fit.nn=mmeta(data=prostate, type="continuous", k=2, method="nn.cl")
summary(fit.nn)

rhow=runif(dim(prostate)[1], -0.2, 0.8)
fit.reml=mmeta(data=prostate, rhow=rhow, type="continuous", k=2, method="nn.reml")
print(fit.reml)

data(nat2)
fit.bb=mmeta(data=nat2, type="binary", k=2, method="bb.cl")
summary(fit.bb)

data(ca125)
fit.tb=mmeta(data=ca125, type="binary", k=2, method="tb.cl")
summary(fit.tb)
```

`mpbt` *Testing and correcting for publication bias of multivariate meta-analysis*

Description

Testing and correcting for publication bias of multivariate meta-analysis

Usage

```
mpbt(data, method, type, k)
```

Arguments

data	dataset
method	"nn.cl" indicating the score test for detecting publication bias of MMA
type	either "continuous" or "binary" indicating the type of outcomes
k	integer indicating the number of outcomes

Details

This function returns the test statistics for testing publication bias of multivariate meta-analysis using regression method.

Value

`mpbt.TS` returns the test statistic and p value of the score test.

A score test for detecting publication bias in multivariate meta-analysis

Publication bias occurs when the publication of research results depends not only on the quality of the research but also on the direction, magnitude or statistical significance of the results. The consequence is that published studies may not represent all valid studies undertaken, and this bias may threaten the validity of systematic reviews and meta-analyses - on which comparative effectiveness research and evidence-based medicine increasingly relies. Multivariate meta-analysis has recently received increasing attention for its potential ability in reducing bias and improving statistical efficiency by borrowing information across outcomes. However, detecting and accounting for publication bias are more challenging in multivariate meta-analysis setting because some studies may be completely unpublished whereas other studies may selectively report part of multiple outcomes. Hong et al. (2015) propose a pseudolikelihood-based score test for detecting publication bias in multivariate random-effects meta-analysis. This is the first test for detecting publication bias in multivariate meta-analysis setting.

Author(s)

Chuan Hong

References

Hong, C., Chu, H. and Chen Y. (2015). A score test for detecting publication bias in multivariate random-effects meta-analysis (in preparation).

Examples

```
data(prostate)
fit.mpbt=mpbt(data=prostate, method = "nn.cl", type = "continuous", k=2)
summary(fit.mpbt)
```

nat2 *A meta-analysis of the association between N-acetyltransterase 2 acetylation status and colorectal cancer*

Description

A meta-analysis of 20 published case-control studies from January 1985 to October 2001

Format

The data frame contains the following columns:

y1 acetylator status (exposed) in control group

n1 total number of subjects in control group

y2 acetylator status (exposed) in case group

n2 total number of subjects in case group

Note

The dataset nat2 is used to conduct marginal bivariate normal model for MMA with binary outcomes

References

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Ye Z, Parry JM. Meta-analysis of 20 case-control studies on the n-acetyltransferase 2 acetylation status and colorectal cancer risk. Medical Science Review 2002; 8(8):CR558-CR565.

See Also

mmeta, summary.mmeta

Examples

```
data(nat2)
summary(nat2)
```

`prostate` *Comparison between overall survival and disease-free survival for prostate cancer*

Description

Results from five randomized clinical trials published between 1988 and 2011

Format

The data frame contains the following columns:

- **y1** log-hazard ratio estimates comparing combined therapy using Goserelin acetate with radiotherapy with respect to overall survival
- **s1** within-study standard error for outcome 1
- **y2** log-hazard ratio estimates comparing combined therapy using Goserelin acetate with radiotherapy with respect to disease-free survival
- **s2** within-study stamdard error for outcome 2

Note

The dataset `prostate` is used to conduct bivariate random-effects meta-analysis when the within-study correlations are unknown.

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Sasse A, Sasse E, Carvalho A, Macedo L. Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review. BMC cancer 2012; 12(1):54. 30.

See Also

`mmeta`, `summary.mmeta`

Examples

```
data(prostate)
summary(prostate)
```

summary.galaxy *Summarize the objects* galaxy

Description

Summary a model of class galaxy fitted by galaxy.

Usage

```
      ## S3 method for class 'galaxy'
summary(object,...)
```

Arguments

object	an object inheriting from class galaxy.
...	additional arguments; currently none is used.

Value

A list with the following components: adjusted parameter estimates, variances of estimated parameters

References

Chen, Y., Hong, C., Chu, H., (2015). Galaxy plot and a multivariate method for correcting publication bias in multivariate meta-analysis (in preparation).

See Also

galaxy

Examples

```
data(prostate)
fit.galaxy=galaxy(data=prostate, type = "continuous",
 method="galaxy.cl", k=2, L=1, estimator="R0", maxiter=150)
summary(fit.galaxy)
```

summary.mmeta *Summarize the objects* mmeta

Description

Summary a model of class mmeta fitted by mmeta.

Usage

```
      ## S3 method for class 'mmeta'
summary(object,...)
```

Arguments

object	an object inheriting from class mmeta.
...	additional arguments; currently none is used.

Value

A list with the following components: coefficients, covariance matrix.

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Hong, C., Riley, R. D. and Chen, Y. (2015). An improved method for multivariate random-effects meta-analysis (in preparation).

Chen, Y., Liu, Y., Ning, J., Nie, L., Zhu, H. and Chu, H. (2014). A composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. Statistical methods in medical research (in press).

Chen, Y., Cai, Y., Hong, C. and Jackson, D. (2015). Inference for correlated effect sizes using multiple univariate meta-analyses, Statistics in Medicine (provisional acceptance).

Chen, Y., Liu, Y., Ning, J., Cormier J. and Chu H. (2014). A hybrid model for combining case-control and cohort studies in systematic reviews of diagnostic tests, Journal of the Royal Statistical Society: Series C (Applied Statistics) 64.3 (2015): 469-489.

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid C. (2015). A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine (under revision).

See Also

mmeta

Examples

```
data(prostate)
fit.nn=mmeta(data=prostate, type="continuous", k=2, method="nn.cl")
summary(fit.nn)
```

`summary.mpbt` *Summarize the objects* `mpbt`

Description

Summary a model of class `mpbt` fitted by `mpbt`.

Usage

```
      ## S3 method for class 'mpbt'
summary(object,...)
```

Arguments

`object`	an object inheriting from class `mpbt`.
`...`	additional arguments; currently none is used.

Value

A list with the following components: test statistics (mpbt) and p-value.

References

Hong, C., Chu, H. and Chen Y. (2015). A score test for detecting publication bias in multivariate random-effects meta-analysis (in preparation).

See Also

`mpbt`

Examples

```
data(prostate)
fit.mpbt=mpbt(data=prostate, method = "nn.cl", type = "continuous", k=2)
summary(fit.mpbt)
```

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