

Package ‘MR.Rerand’

January 9, 2024

Title Re-Randomized Inverse-Variance Weighted Estimator in Two-Sample Mendelian Randomization with Summary-Data and Mediation Analysis in Mendelian Randomization with Summary-Data

Version 0.0.1

Description Conducting rerandomization in two sample GWAS with summary data to estimate the causal effect or in three samples GWAS to estimate the mediation effect.

Encoding UTF-8

Roxygen list(markdown = TRUE)

RoxygenNote 7.2.3

Imports stats,
MASS,
msm

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Suggests knitr,
rmarkdown

VignetteBuilder knitr

R topics documented:

MAGIC	1
pre_screening	3
pre_selection	4
RIVW	5
Index	7

MAGIC	<i>Main function for using MAGIC framework to conduct mediation analysis.</i>
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Description

MAGIC stands for the Mediation Analysis framework through GWAS summary data Integration with the winner’s (and the loser’s) curse and measurement bias Correction. Our framework efficiently integrates information stored in three independent GWAS summary data and mitigates the commonly encountered winner’s curse and measurement error bias (a.k.a. instrument selection and weak instrument bias) in MR.

Usage

```
MAGIC(
  beta.exposure,
  beta.mediator,
  beta.outcome,
  se.exposure,
  se.mediator,
  se.outcome,
  Conf.level = 0.95,
  pval.select = c(5e-05, 5e-05),
  eta = c(0.5, 0.5),
  seed = 0
)
```

Arguments

<code>beta.exposure</code>	SNP effect size's vector of the exposure vairable (GWAS(I))
<code>beta.mediator</code>	SNP effect size's vector of the mediator vairable (GWAS(III))
<code>beta.outcome</code>	SNP effect size's vector of the outcome vairable (GWAS(II))
<code>se.exposure</code>	SNP effect size's standard errors of <code>beta.exposure</code>
<code>se.mediator</code>	SNP effect size's standard errors of <code>beta.mediator</code>
<code>se.outcome</code>	SNP effect size's standard errors of <code>beta.outcome</code>
<code>Conf.level</code>	Confidence level. Default is 0.95.
<code>pval.select</code>	A vector of specified pre-screening threshold in the ordering of (exposure, mediator). Default is (5e-5, 5e-5). (corresponding λ is 4.06)
<code>eta</code>	A vector of rerandomized scale in the ordering of (exposure, mediator). Default is (0.5,0.5).
<code>seed</code>	The value of the random seed. Default is 0.

Value

A list

theta.hat Estimated direct effect from exposure to outcome variable
tauy.hat Estimated direct effect from mediator to outcome variable
taux.hat Estimated indirect effect from exposure to mediator variable
tau.hat Estimated mediation effect
tau_total.hat Estimated total effect
theta.se Standard error of `theta.hat`
tauy.se Standard error of `tauy.hat`
taux.se Standard error of `taux.hat`
tau.se Standard error of `tau.hat`
tau_total.se Standard error of `tau_total.hat`
n.IV.exp Number of IVs used in exposure dataset
n.IV.med Number of IVs used in mediator dataset
Conf.Interval Confidence interval given `Conf.level`
IV.exp The index of IVs selected in \mathcal{S}_x
IV.med The index of IVs selected in \mathcal{S}_m

References

Rita Qiuran Lyu, Chong Wu, Xinwei Ma, Jingshen Wang (2023). Mediation Analysis with Mendelian Randomization and Efficient Multiple GWAS Integration. <https://arxiv.org/abs/2312.10563>.

pre_screening	<i>Supplementary function for RIVW to conduct rerandomization and Rao-Blackwellization in GWAS (I).</i>
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Description

For GWAS (I) $(\hat{\beta}_{X_j}, \sigma_{X_j})$, the formula is $\hat{\beta}_{X_j, \text{RB}} = \hat{\beta}_{X_j} - \frac{\sigma_{X_j}}{\eta} \left(\phi(A_{j,+}) - \phi(A_{j,-}) \right) \left(\frac{\mathbf{1}_{(j \in S_x)}}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} \right)$, $\hat{\sigma}_{X_j, \text{RB}}^2 = \sigma_{X_j}^2 \left(1 - \frac{1}{\eta^2} \frac{A_{j,+} \phi(A_{j,+}) - A_{j,-} \phi(A_{j,-})}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} + \frac{1}{\eta^2} \left(\frac{\phi(A_{j,+}) - \phi(A_{j,-})}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} \right)^2 \right)$, and $\phi(\cdot)$ is the density function of standard normal distribution, $\Phi(\cdot)$ is the cumulative function of standard normal distribution.

Usage

```
pre_screening(
  gamma1.exp,
  se1.exp,
  etamean = 0.5,
  pthr = 5e-05,
  seed = 0,
  smoothing = FALSE
)
```

Arguments

gamma1.exp	SNP effect size's vector of the exposure variable
se1.exp	SNP effect size's standard errors of beta.exposure
etamean	rerandomized scale of exposure variable. Default is 0.5.
pthr	The specified pre-screening threshold. Default is 5e-5. (corresponding λ is 4.06)
seed	The value of the random seed. Default is 0.
smoothing	Whether to use smoothing to decrease variance . Default is FALSE.

Value

A list

filter1 Indexs of selected relevant IVs.

gamma_exp1 Effect size in GWAS (I) after Rao-Blackwellization to eliminate the winner's curse

se1 Standard errors in GWAS (I) after Rao-Blackwellization to eliminate the winner's curse

weights The weights for each SNP. If smoothing is False, weights are the same for each SNP.

References

Xinwei Ma, Jingshen Wang, Chong Wu. (2023). Breaking the Winner's Curse in Mendelian Randomization: Rerandomized Inverse Variance Weighted Estimator <https://projecteuclid.org/journals/annals-of-statistics/volume-51/issue-1/Breaking-the-winners-curse-in-Mendelian-randomization/10.1214/22-AOS2247.full>.

pre_selection	<i>Supplementary function for MAGIC to conduct rerandomization and Rao-Blackwellization in GWAS (I) and GWAS (III).</i>
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Description

Take GWAS (I) ($\hat{\beta}_{X_j}, \sigma_{X_j}$) as an example, here $\hat{\beta}_{X_j, \text{RB}} = \hat{\beta}_{X_j} - \frac{\sigma_{X_j}}{\eta} \left(\phi(A_{j,+}) - \phi(A_{j,-}) \right) \left(\frac{1_{(j \in S_x)}}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} - \frac{1_{(j \notin S_x)}}{\Phi(A_{j,+}) - \Phi(A_{j,-})} \right)$, $\hat{\sigma}_{X_j, \text{RB}}^2 = \sigma_{X_j}^2 \left(1 - \frac{1}{\eta^2} \frac{A_{j,+} \phi(A_{j,+}) - A_{j,-} \phi(A_{j,-})}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} + \frac{1}{\eta^2} \left(\frac{\phi(A_{j,+}) - \phi(A_{j,-})}{1 - \Phi(A_{j,+}) + \Phi(A_{j,-})} \right)^2 \right)$, and $\phi(\cdot)$ is the density function of standard normal distribution, $\Phi(\cdot)$ is the cumulative function of standard normal distribution.

Usage

```
pre_selection(
  gamma1.exp,
  se1.exp,
  gamma2.exp,
  se2.exp,
  etamean1 = 0.5,
  etamean2 = 0.5,
  pthr = c(5e-05, 5e-05),
  seed = 0
)
```

Arguments

gamma1.exp	SNP effect size's vector of the exposure variable (GWAS(I))
se1.exp	SNP effect size's standard errors of beta.exposure
gamma2.exp	SNP effect size's vector of the mediator variable (GWAS(III))
se2.exp	SNP effect size's standard errors of beta.mediator
etamean1	rerandomized scale of exposure variable. Default is 0.5.
etamean2	rerandomized scale of mediator variable. Default is 0.5.
pthr	A vector of specified pre-screening threshold in the ordering of (exposure, mediator). Default is (5e-5, 5e-5). (corresponding λ is 4.06)
seed	The value of the random seed. Default is 0.

Value

A list

filter1 Indexs of selected relevant IVs in S_x

filter2 Indexs of selected relevant IVs in S_m

gamma_exp1 Effect size in GWAS (I) after Rao-Blackwellization to eliminate the winner's curse

se1 Standard errors in GWAS (I) after Rao-Blackwellization to eliminate the winner's curse

gamma_exp2 Effect size in GWAS (III) after Rao-Blackwellization to eliminate the winner's curse

se2 Standard errors in GWAS (III) after Rao-Blackwellization to eliminate the winner's curse

gamma_exp1.carve Effect size in GWAS (I) after Rao-Blackwellization to eliminate the loser's curse

gamma_exp2.carve Effect size in GWAS (III) after Rao-Blackwellization to eliminate the loser's curse

References

Rita Qiuran Lyu, Chong Wu, Xinwei Ma, Jingshen Wang (2023). Mediation Analysis with Mendelian Randomization and Efficient Multiple GWAS Integration. <https://arxiv.org/abs/2312.10563>.

RIVW

Main function for conducting RIVW estimator.

Description

Conventional two-sample Mendelian randomization methods often employ the same sample for selecting relevant genetic variants and for constructing final causal estimates. Such a practice often leads to biased causal effect estimates due to the well-known "winner's curse" phenomenon. To address this fundamental challenge, we propose a novel framework that not only systematically breaks the winner's curse but also provides an unbiased estimate of the genetic association effect after selection. Built upon the proposed framework, we introduce a novel randomized inverse variance weighted (RIVW) estimator that is provably consistent when selection and parameter estimation are conducted on the same sample.

Usage

```
RIVW(
  beta.exposure,
  beta.outcome,
  se.exposure,
  se.outcome,
  Conf.level = 0.95,
  smoothing = FALSE,
  pval.select = 5e-05,
  eta = 0.5,
  seed = 0
)
```

Arguments

<code>beta.exposure</code>	SNP effect size's vector of the exposure variable (GWASI)
<code>beta.outcome</code>	SNP effect size's vector of the outcome variable (GWASII)
<code>se.exposure</code>	SNP effect size's standard errors of <code>beta.exposure</code>
<code>se.outcome</code>	SNP effect size's standard errors of <code>beta.outcome</code>
<code>Conf.level</code>	Confidence level. Default is 0.95.
<code>smoothing</code>	Whether to use smoothing to decrease variance. Default is FALSE.
<code>pval.select</code>	The specified pre-screening threshold. Default is 5e-5. (corresponding λ is 4.06)
<code>eta</code>	A vector of rerandomized scale. Default is 0.5.
<code>seed</code>	The value of the random seed. Default is 0.

Value

A list

beta.rerand Exposure dataset effect size after rerandomization.

se.rerand Exposure dataset standard errors after rerandomization.

beta.hat Estimated direct effect from exposure to outcome variable

beta.se Standard error of `beta.hat`

IV The index of IVs selected in `Sx`

n.IV Number of IVs used in exposure dataset

F The value of F-statistic

p.val The p-value of estimated causal effect

Conf.Interval Confidence interval of the causal effect given `Conf.level`

References

Xinwei Ma, Jingshen Wang, Chong Wu. (2023). Breaking the Winner's Curse in Mendelian Randomization: Rerandomized Inverse Variance Weighted Estimator <https://projecteuclid.org/journals/annals-of-statistics/volume-51/issue-1/Breaking-the-winners-curse-in-Mendelian-randomization/10.1214/22-AOS2247.full>.

Index

MAGIC, [1](#)

pre_screening, [3](#)

pre_selection, [4](#)

RIWV, [5](#)