Package: mr.pivw (via r-universe)

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Type Package

Title Penalized Inverse-Variance Weighted Estimator for Mendelian
Randomization

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Description The penalized inverse-variance weighted (pIVW) estimator
is a Mendelian randomization method for estimating the causal
effect of an exposure variable on an outcome of interest based
on summary-level GWAS data. The pIVW estimator accounts for
weak instruments and balanced horizontal pleiotropy
simultaneously. See Xu S., Wang P., Fung W.K. and Liu Z. (2022)
<doi:10.1111/biom.13732>.

Depends R (>= 3.5.0), methods

License GPL-2

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Description

The penalized inverse-variance weighted (pIVW) estimator is a Mendelian randomization method for estimating the causal effect of an exposure variable on an outcome of interest based on summary-level GWAS data. The pIVW estimator accounts for weak instruments and balanced horizontal pleiotropy simultaneously.

Usage

```
mr_pivw(
  Bx,
  Bxse,
  By,
  Byse,
  lambda = 1,
  over.dispersion = TRUE,
  delta = 0,
  sel.pval = NULL,
  Boot.Fieller = NULL,
  n.boot = 1000,
  alpha = 0.05
)
```

Arguments

Bx	A numeric vector of beta-coefficient values for genetic associations with the exposure variable.
Bxse	The standard errors associated with the beta-coefficients Bx.
By	A numeric vector of beta-coefficient values for genetic associations with the outcome variable.
Byse	The standard errors associated with the beta-coefficients By.
lambda	The penalty parameter in the pIVW estimator. It plays a role in the bias-variance trade-off of the estimator. It is recommended to choose lambda=1 to achieve the smallest bias and valid inference. By default, lambda=1.
over.dispersion	Should the method consider overdispersion (balanced horizontal pleiotropy)? Default is TRUE.
delta	The z-score threshold for IV selection. delta should be greater than or equal to zero. By default, delta=0 (i.e., no IV selection will be conducted). See 'Details'.

sel.pval	A numeric vector containing the P-values of the SNP effects on the exposure, which will be used for the IV selection. `sel.pval` should be provided when `delta` is not zero. See 'Details'.
Boot.Fieller	If `Boot.Fieller=TRUE`, then the P-value and the confidence interval of the causal effect will be calculated based on the bootstrapping Fieller method. Otherwise, the P-value and the confidence interval of the causal effect will be calculated from the normal distribution. By default, `Boot.Fieller=TRUE` when `Condition` is smaller than 10 (see 'Details'), and `Boot.Fieller=FALSE` otherwise .
n.boot	The number of bootstrap samples used in the bootstrapping Fieller method. It will be used only when `Boot.Fieller=TRUE`. By default, `n.boot=1000`. A larger value of `n.boot` should be provided when a more precise P-value is needed.
alpha	The significance level used to calculate the confidence intervals. The default value is 0.05.

Details

The penalized inverse-variance weighted (pIVW) estimator accounts for weak instruments and balanced horizontal pleiotropy simultaneously in two-sample MR with summary statistics, i.e., an exposure sample (with IV-exposure effect `Bx` and standard error `Bxse`) and an outcome sample (with IV-outcome effect `By` and standard error `Byse`).

The pIVW estimator also allows for IV selection in three-sample MR, where weak IVs are screened out using an extra sample (with IV-exposure effect `Bx*` and standard error `Bxse*`) independent of the exposure sample and outcome sample. Generally, the P-value for `Bx*` can be computed By `sel.pval=2*pnorm(abs(Bx*/Bxse*), lower.tail = FALSE)`, Given `sel.pval` and a z-score threshold `delta`, the variants kept in the analysis will be those with `sel.pval<2*pnorm(delta,lower.tail = FALSE)`.

The `mr_pivw` function outputs a measure `Condition` that needs to be large for reliable asymptotic properties of the pIVW estimator. We also refer to `Condition` as effective sample size, which is a function of a measure of IV strength and the number of IVs. When `delta` is zero (i.e., no IV selection), `Condition = (average F-statistic -1)*sqrt(# snps)`. When `delta` is not zero (i.e., IV selection is conducted), `Condition = [(average F-statistic -1)*sqrt(# snps)]/c`, where the numerator is computed using the selected variants, and the denominator `c` involves the selection probabilities of all variants (see more details in the paper https://doi.org/10.1111/biom.13732). We suggest that `Condition` should be greater than 5 for the pIVW estimator to achieve reliable asymptotic properties.

Value

The output from the function is a `PIVW` object containing:

Over.dispersion	
	TRUE if the method has considered balanced horizontal pleiotropy, FALSE otherwise.
Boot.Fieller	TRUE if the bootstrapping Fieller method is used to calculate the P-value and the confidence interval of the causal effect, FALSE otherwise.

N.boot	The number of bootstrap samples used in the bootstrapping Fieller method.
Lambda	The penalty parameter in the pIVW estimator.
Delta	The z-score threshold for IV selection.
Estimate	The causal point estimate from the pIVW estimator.
StdError	The standard error associated with `Estimate`.
CILower	The lower bound of the confidence interval for `Estimate`, which is derived from the bootstrapping Fieller method or normal distribution. For the bootstrapping Fieller's interval, if it contains multiple ranges, then lower limits of all ranges will be reported.
CIUpper	The upper bound of the confidence interval for `Estimate`, which is derived from the bootstrapping Fieller method or normal distribution. For the bootstrapping Fieller's interval, if it contains multiple ranges, then upper limits of all ranges will be reported.
Alpha	The significance level used in constructing the confidence interval.
Pvalue	P-value associated with `Estimate`, which is derived from the bootstrapping Fieller method or normal distribution.
Tau2	The variance of the balanced horizontal pleiotropy. `Tau2` is calculated by using all IVs in the data before conducting the IV selection.
SNPs	The number of SNPs after IV selection.
Condition	The estimated effective sample size. It is recommended to be greater than 5 for the pIVW estimator to achieve reliable asymptotic properties. See 'Details'.

References

Xu S., Wang P., Fung W.K. and Liu Z. (2022). A Novel Penalized Inverse-Variance Weighted Estimator for Mendelian Randomization with Applications to COVID-19 Outcomes. Biometrics. Available at https://doi.org/10.1111/biom.13732.

Examples

```
mr_pivw(Bx = Bx_exp, Bxse = Bxse_exp, By = By_exp, Byse = Byse_exp)
```

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