

A

Compared MR methods

Summary-level data-based MR methods

1. IVW-class

- IVW (fixed)
- IVW (random)

3. Model-based

- Egger
- RAPS
- CAUSE
- MR-APSS
- MRMix
- MR-ConMix
- MRCUE

2. Outlier detection and removal

- MR-PRESSO
- cML-MA
- MR-Lasso

4. Outlier robust

- MR-Robust,
- Weighted-median
- Weighted-mode

B

Steps of run MR methods

Input: GWAS summary-level data of exposure and outcome

Step 1: Conduct quality control

- Keep Hapmap3 SNPs
- Remove duplicates/missing/MHC /ambiguous /poor imputed / MAF <0.01 SNPs

Step 2: Harmonise SNP effects

- Ensure SNP-exposure and SNP-outcome effect estimates refer to the same allele

Step 3: IV selection and extract IV effects

- SNPs associated with exposure (p-value < IV threshold)
- Plink LD clumping: $r^2 < 0.001$, 1Mb

Step 4: Run MR methods

Change IV threshold from 5×10^{-8} , 5×10^{-7} , 5×10^{-6} to 5×10^{-5}

C

Performance evaluation

1. Type I error control

- **Confounding scenario (a)**
Population stratification

Dataset

1130 exposure-outcome trait pairs
No causal effect

- **Confounding scenario (b)**
Pleiotropy

Dataset

77 exposure-outcome trait pairs
No causal effect

- **Confounding scenario (c)**
Family-level confounders

Dataset

82 exposure-outcome trait pairs
No causal effect

2. Accuracy of causal effect estimates

Dataset

Six exposure-outcome pairs
True casual effect = 1

3. Replicability

Case study

LDL-C (six GWASs) and CAD