De-biased multivariable Mendelian Randomization and its implementation

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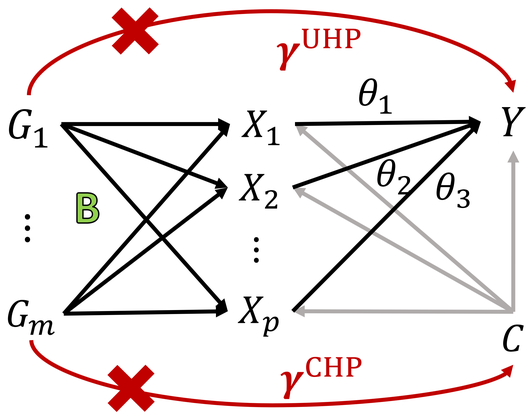
Background



$$(G_1, \ldots, G_m) \xrightarrow{\alpha} Y$$

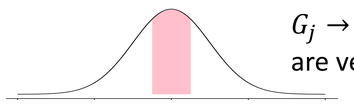
$$\alpha_j = \beta_j^\top \theta + \gamma_j^{UHP} + \gamma_j^{CHP}$$

Estimated from GWAS

Outliers that can bias $\widehat{\theta}$

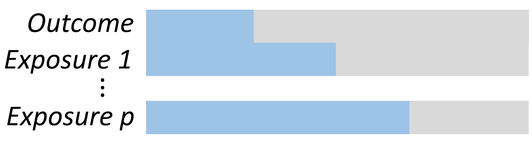
Current methods estimate θ with bias due to

Weak IVs

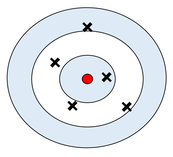


$G_j \to X_k$ effects are very small

GWAS sample overlap



GWAS estimation error



True $G_j \to X_k$ and $G_j \to Y$ effects measured with sampling error

$$(\widehat{\beta}_j, \hat{\alpha}_j) = (\beta_j, \alpha_j) + (\mathbf{u}_j, v_j)$$

MRBEE Software (R & Python*)

Input Data

`data`
- *Merged data set of all standardized exposure, outcome GWAS summary statistics*
  - *effect sizes*
  - *standard errors*
  - *unique SNP identifier (e.g., rsID)*

`IVInds`
- *Row index positions of IVs in* `data`

`leadSNPs`
- *Row index positions of lead outcome SNPs (optional)*

Preparing Data

`biasTerms()`
- *Bias-correction terms*
- *Harmonised alleles*

`prepData()`
- *Simplify data format for all analyses*

Example code

```
bT=biasTerms(data,dNames)
pD=prepData(bT,IVInds,oi)
```

`dNames`: Named list of effect size, SE, and effect allele column name vectors in `data`, e.g.: `list(est=<x>,se=<x>,allele=<x>)`

`oi`: "outcome index"; index position of `dNames` vector elements corresponding to outcome

Performing MR

`MRBEE.IMRP()`
`MRBEE.Median()`
`MRBEE.Mix()`
`MRBEE.IPOD()`
`MRBEE.MLqe()`

(Correct biases in multivariable MR)

Visualizing causality

`causalPlot()`
- *Display causal estimates*

Example code

```
fit<x>=MRBEE.<x>(pD)
causalPlot(fit<x>,eNames)
```

`eNames`: Vector of exposure names, order corresponding to orders in `dNames$<x>` e.g.: `c(<x>, …, <x>)`

Pleiotropy analysis

`Spleio()`
- *Horizontal pleiotropy test*

`genomePleio()`
- *Genome-wide* `Spleio()`

Visualizing pleiotropy

`residualPlot()`
- *Assess pleiotropy in MR*

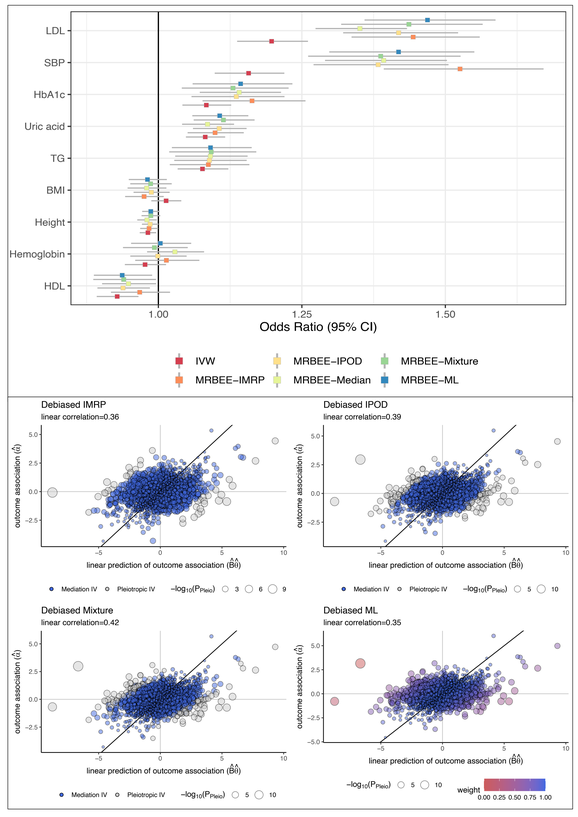
`gwPleioPlot()`
- *Assess pleiotropy in genome*

Example code

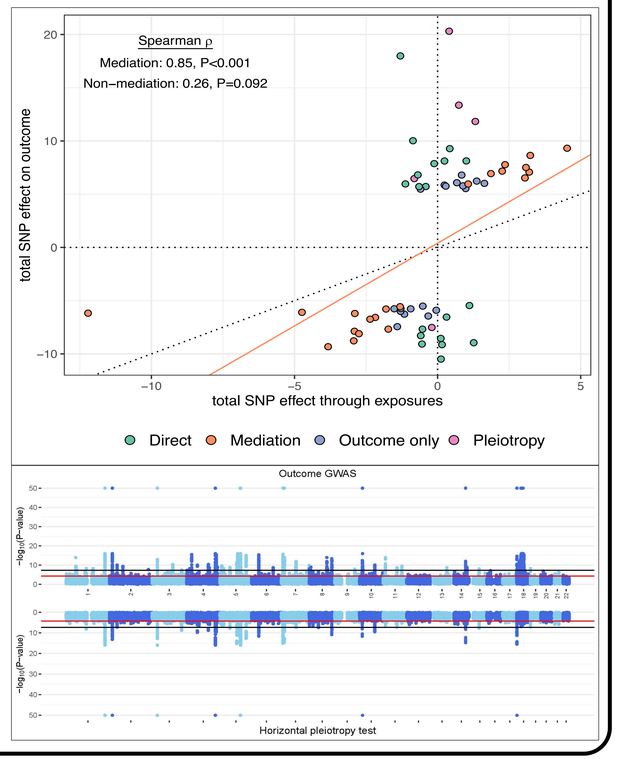
```
sP<x>=Spleio(pD,fit<x>)
gP<x>=genomePleio(pD0,fit<x>)
residualPlot(fit<x>)
gwPleioPlot(gP<x>,leadSNPs,CHR_BP)
```

```
pD0=prepData(bT,oi=oi)
leadSNPs: Vector of row indices in data of lead SNPs in outcome GWAS tagging independent loci
CHR_BP: Vector of positions as <CHR>_<BP>
```

Causal effect estimates and model fit[1]



Classifying outcome loci using horizontal pleiotropy [1]



Methods

MR using **B**ias-corrected **E**stimating **E**quations

$$S_{\text{MRBEE}}(\boldsymbol{\theta}) = \mathbf{0} = \sum_{j=1}^{m} \rho\left(\hat{\alpha}_j - \widehat{\boldsymbol{\beta}}^\top \boldsymbol{\theta}\right) - \Gamma(\boldsymbol{\theta}, \boldsymbol{\Sigma})$$

$$\overset{[4]}{=} \sum_{j=1}^{m} w_j \widehat{\boldsymbol{\beta}}(\hat{\alpha}_j - \widehat{\boldsymbol{\beta}}^\top \boldsymbol{\theta}) - \Gamma(\boldsymbol{\theta}, \boldsymbol{\Sigma})$$

ρ: Loss function robust to (γ^{CHP}, γ^{UHP})

- `MRBEE.IMRP()`: Removes UHP/CHP IVs
- `MRBEE.Median()`: assumes <50% UHP/CHP IVs
- `MRBEE.Mix()`: Mixture of valid & UHP/CHP IVs
- `MRBEE.IPOD()`: Penalized outliers
- `MRBEE.MLqe()`: Likelihood-weighted IVs

Compare methods using residual plots

$\Gamma(\boldsymbol{\theta}, \boldsymbol{\Sigma})$: Bias-correction terms

- $\mathrm{m}^{-1}\Gamma(\boldsymbol{\theta}, \boldsymbol{\Sigma}) \overset{[2]}{=} \mathrm{Cov}(\mathbf{u}_j)\boldsymbol{\theta} - \mathrm{Cov}(v_j, \mathbf{u}_j)$
- Estimated using full GWAS summary statistics[3]
- Necessary for valid statistical inference[2]

Conclusion

MRBEE software performs

a) Bias-correction for $\Gamma(\boldsymbol{\theta}, \boldsymbol{\Sigma})$
   - Commonly nonzero in practice

b) Bias-protection against UHP/CHP
   - Many methods user can choose
   - Chosen method is setting-specific

Download software

R: https://github.com/noahlorinczcomi/MRBEE
Python*: In progress

References

[1]: Lorincz-Comi et al (2023) **PMID: 36778480**
[2]: Yang et al (2023) ***arXiv:2301.05130***
[3]: Zhu et al (2015) **PMID: 25500260**
[4]: She & Owen (2011) ***JASA 106*(494), 626-639**