MRBEE corrects measurement error and sample overlap biases in multivariable Mendelian Randomization

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INTRO

- MR can estimate causal relationships between phenotypes using GWAS summary statistics
- **Classic MR estimators are vulnerable to weak instrument, measurement error (ME), and sample overlap biases**
- **Bias in IVW:**

$$\underbrace{\left(\frac{m}{M}\Sigma_{\beta\beta}+\frac{1}{m}\sum_{i=1}^{m}\Sigma_{UUi}\right)^{-1}}_{\text{weak instrument bias}}\underbrace{\frac{1}{m}\left(\sum_{i=1}^{m}\Sigma_{UVi}-\Sigma_{UUi}\Theta\right)}_{\text{ME \& sample overlap bias}}$$

- **MRBEE is the first MR estimator to correct for these biases and allows multiple exposures and outcomes**

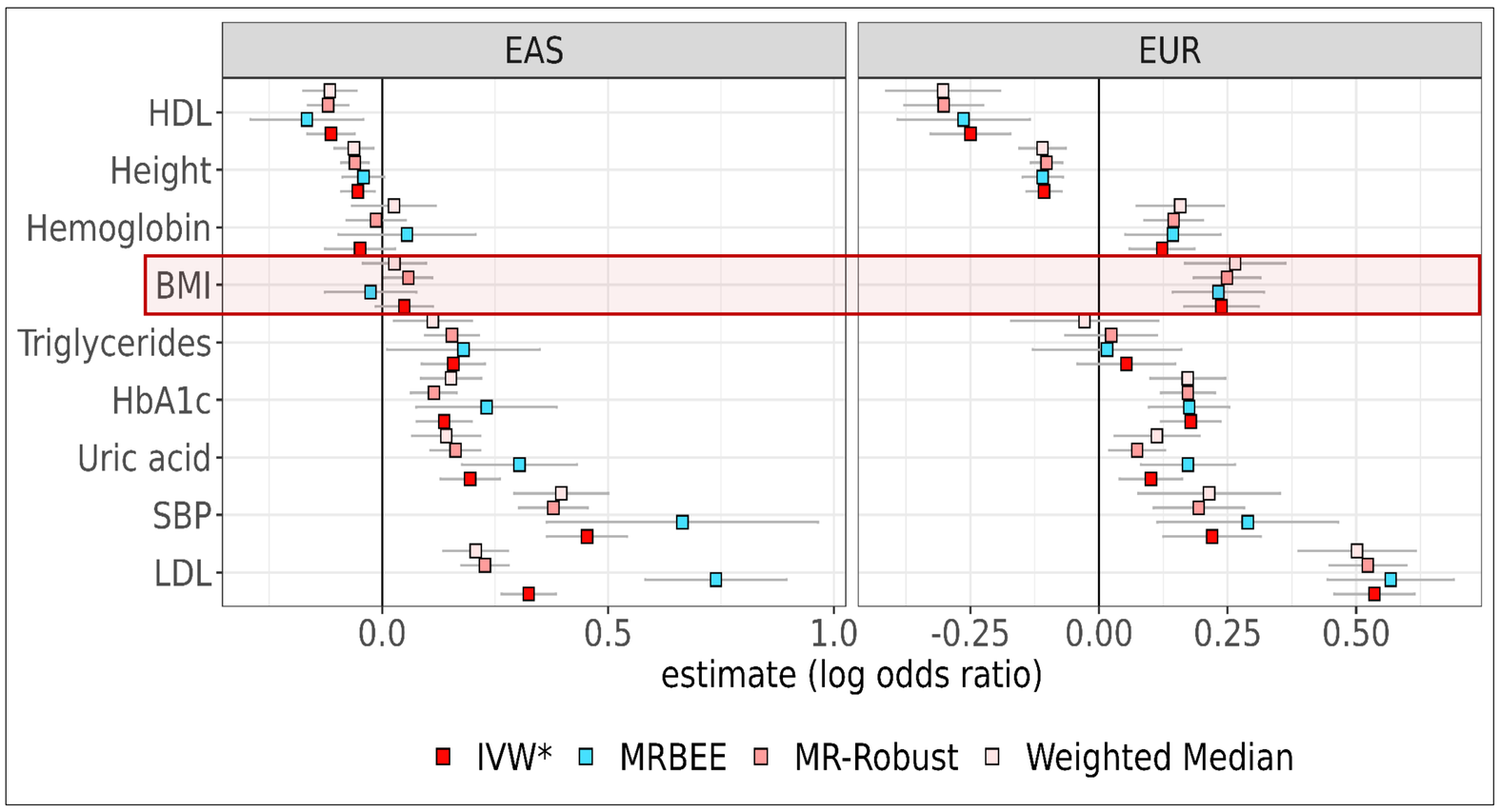
METHODS

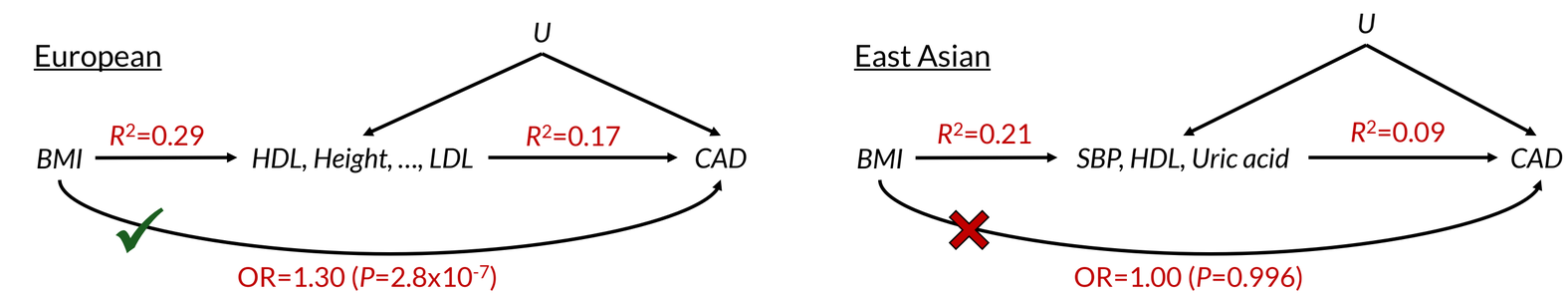
- We developed MRBEE, a multivariable MR estimator that adjusts for all known sources of bias in MR
- We demonstrate MRBEE in real data analysis
  - Cardiometabolic risks of CAD in EAS and EUR
  - Causal mediation tests using MRBEE
  - Pleiotropy testing to identify pathways through which genes associate with CAD
- Data:
  - GWAS summary statistics mainly from UKBB, BBJ
  - Pleiotropy testing to identify pathways of genetic association with CAD

	East Asian		European	
	GWAS *n*	h^2_{SNP}	GWAS *n*	h^2_{SNP}
CAD	212k	0.13	194k	0.08
Height	159k	0.41	361k	0.42
BMI	158k	0.17	695k	0.17
HbA1c	43k	0.11	361k	0.18
LDL	73k	0.07	1.3M	0.10
Triglycerides	106k	0.12	1.3M	0.18
SBP	137k	0.08	758k	0.14
Hemoglobin	109k	0.07	361k	0.15
Uric acid	109k	0.14	361k	0.16
HDL	71k	0.16	1.3M	0.22

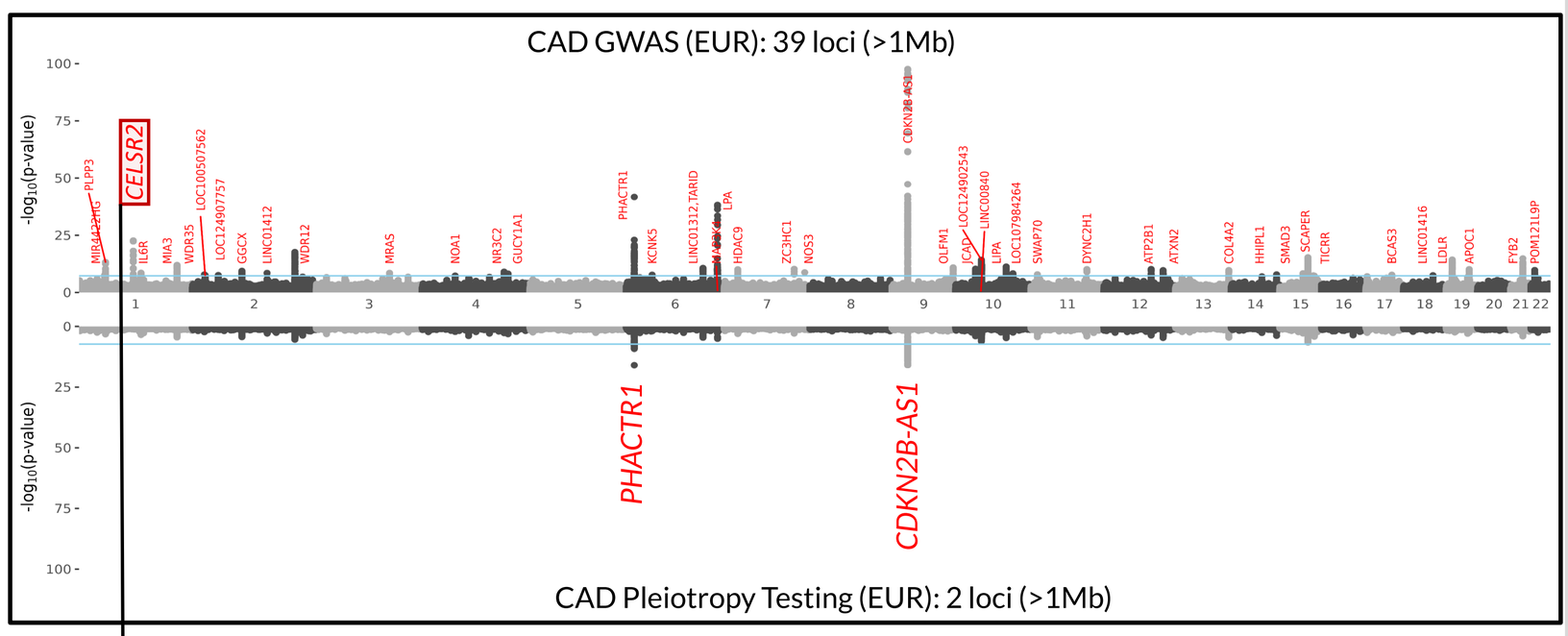
DISCUSSION

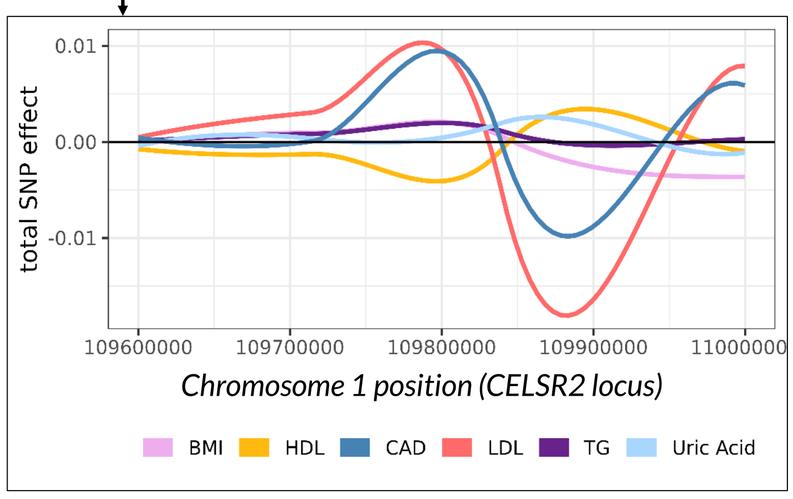
- MR methods used in practice are subject to bias for which no explicit correction has existed
- MRBEE is a multiple-exposure MR method that can adjust for known sources of bias in MR

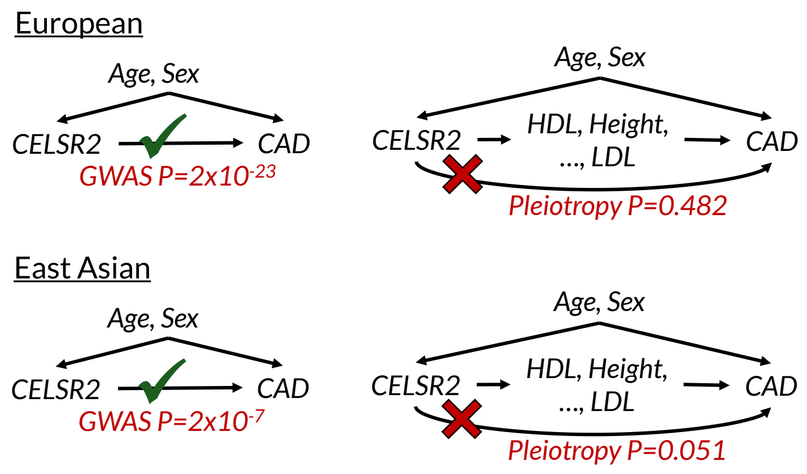




Causal effect of BMI on CAD fully mediated by other phenotypes in East Asians but not Europeans







MRBEE

- Where the IVW estimating equation is S_{IVW},

$$S_{MRBEE} = S_{IVW} - \text{bias}(S_{IVW})$$

- MR estimates causal effects Θ in $\hat{B}_i = \Theta^T \hat{A}_i + U_i$

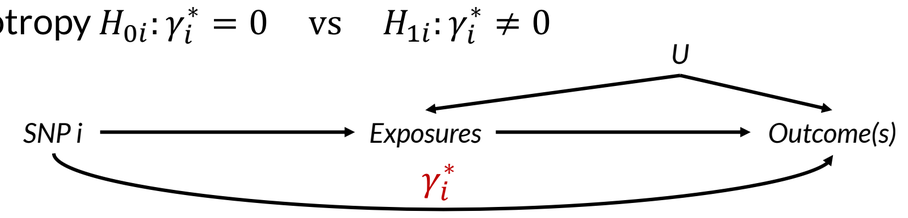
$$\vec{\hat{\Theta}}_{MRBEE} \xrightarrow{D} N\left(\Theta^0, \frac{1}{m}P^{-1}VP^{-1}\right)$$

Advantages

- Reduces confounding potential by including multiple exposures
- Robust to weak instrument, measurement error, sample overlap, and pleiotropy biases

Pleiotropy test

- Pleiotropy $H_{0i}: \gamma_i^* = 0$ vs $H_{1i}: \gamma_i^* \neq 0$



- Purpose:
  1. Reduce bias in MR (remove pleiotropy)
  2. Identify pathways of genetic effects
- Can be performed genome-wide
- A SNP significant in GWAS testing but not pleiotropy testing affects CAD through the exposures

Software
`github.com/noahlorinczcomi/MRBEE`

References (PMIDs)
(GWAS data) 34594039, 30239722, 34887591, 34887591, 30224653
(MR methods) 33226062, PMC6659377

Acronyms
MR: Mendelian Randomization
IVW: Inverse-variance weighted
*IVW**: Pleiotropy-adjusted IVW
CAD: Coronary artery disease
EAS, EUR: East Asian, European
MRBEE: MR with bias-corrected estimating equations
UKBB: UK Biobank
BBJ: Biobank Japan