Mendelian Randomization Accounting for Correlated and Uncorrelated Pleiotropy Using Genome Wide Summary Statistics

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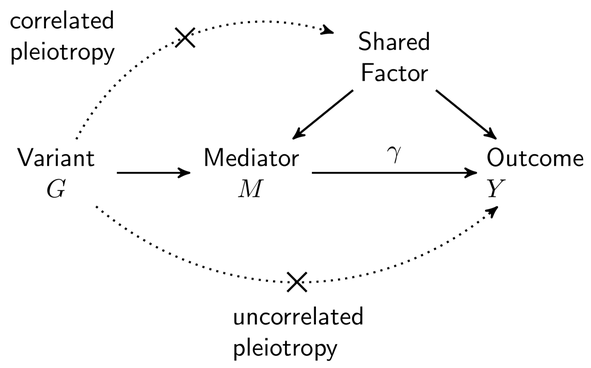
Mendelian Randomization

Mendelian randomization (MR) uses genetic variants as instrumental variables to estimate the causal effect of a mediator on an outcome.

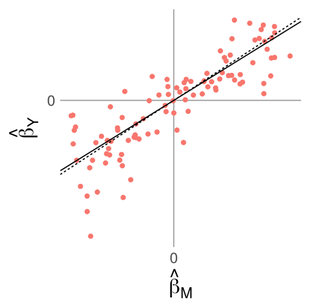
Most MR methods rely on strong assumptions:

1. Variants included must be causally associated with M.
2. Variants do not exhibit horizontal pleiotropy: Effects on Y that are not mediated by M.
   - Correlated pleiotropy occurs when G affects a factor affecting both M and Y.
   - Uncorrelated pleiotropy occurs when G affects Y through separate mechanisms.



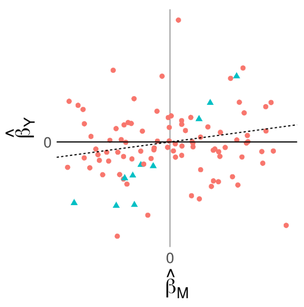
Correlated Pleiotropy Leads to False Positives

If MR assumptions hold, γ can be estimated by regressing variant associations with M on variant associations with Y.



Simulated effect estimates with a true causal effect of M on Y. The regression slope estimates the causal effect.

Even a small number of variants associated with a shared heritable factor can create a false positive.



Simulated effect estimates with no causal effect. 10% of variants exhibit correlated pleiotropy resulting in an IVW estimate significantly different from zero.

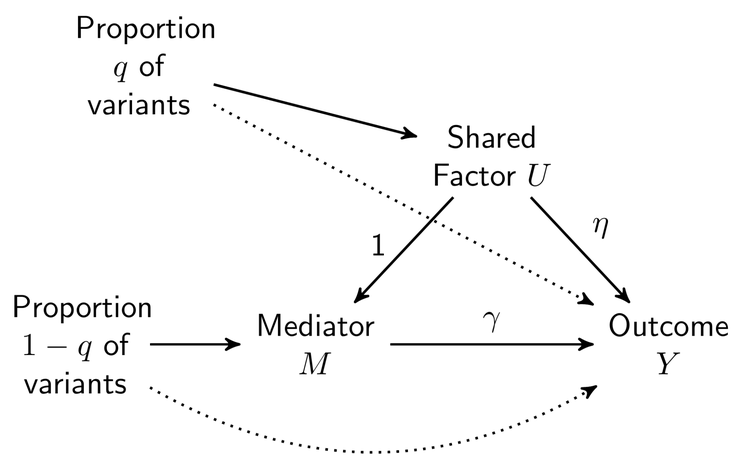
Detecting Causal Signatures by Modeling an Unobserved Shared Factor
CAUSE: Causal Analysis Using Summary Statistics

Model Features and Assumptions:

- Some variants affect the mediator through an unobserved heritable shared factor U.
- The proportion of variants acting through U is small.
- All variants may have additional mean zero pleiotropic effects on Y.
- Effects are assumed sparse and all variants are included.

Parameters:

- q: Proportion of variants that act through the shared factor
- γ: Causal effect of M on Y
- η: Shared factor effect of U on Y



Estimation

- The model defines a likelihood for summary statistics.
- Effect prior distributions are estimated empirically.
- Posterior distributions for q, γ, and η are obtained from the prior and likelihood.

Testing:

- Fit two nested models:
  - **Sharing Model:** γ is fixed at zero
  - **Causal Model:** γ can be non-zero
- Compare fit of posterior distributions using ELPD.
- If the Causal Model is a significantly better fit, the data are consistent with a causal effect.
- Otherwise, the data can be adequately explained with only a shared factor.

Examples

LDL Cholesterol → Coronary Artery Disease

P-value comparing causal and sharing models: 6.1×10^{-11}
Posterior medians and 95% credible intervals:

Model	γ	η	q
Sharing		0.40 (0.33, 0.47)	0.79 (0.66, 0.89)
Causal	0.36 (0.30, 0.42)	-0.01 (-0.67, 0.57)	0.03 (0.00, 0.25)

The data are consistent with a causal effect of LDL cholesterol on risk of CAD.

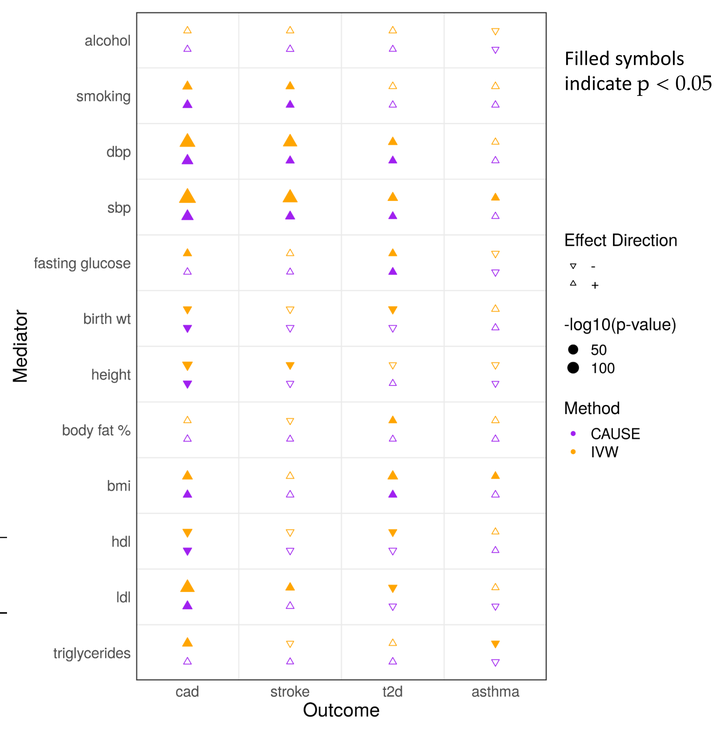
Birth Weight → Type 2 Diabetes

P-value comparing causal and sharing models: 0.07
Posterior medians and 95% credible intervals:

Model	γ	η	q
Sharing		-0.98 (-3.13, 0.00)	0.12 (0.01, 0.39)
Causal	-0.27 (-0.47, -0.08)	-0.03 (-2.30, 2.10)	0.04 (0.00, 0.26)

The data are not consistent with a causal effect but there is genetic sharing that leads to significant genetic correlation.

Anthropometric and Metabolic GWAS Traits

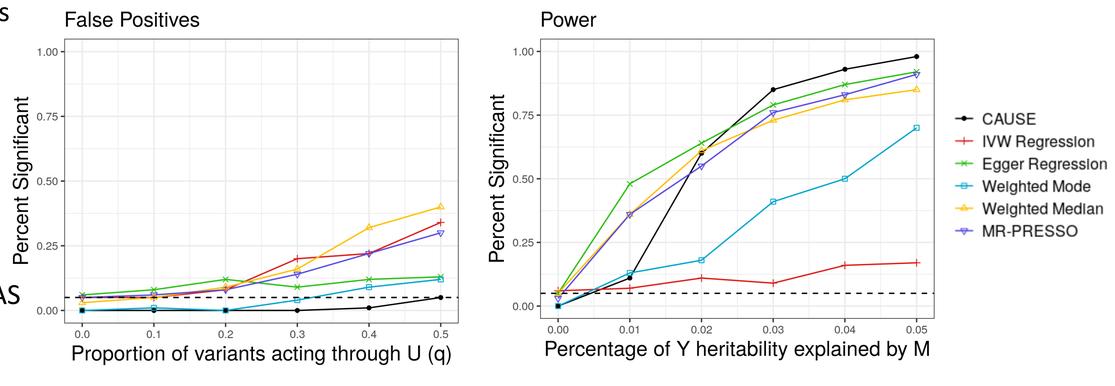


- CAUSE rejects the sharing model for plausibly causal trait pairs: LDL → CAD, BMI → CAD, Blood pressure → Stroke
- IVW identifies several pairs that are likely false positives: BMI → Asthma, Triglycerides → Asthma
- Both methods falsely identify HDL → CAD. These traits have a very high proportion of shared variants that is beyond what CAUSE can accommodate.

Learn More, Use CAUSE!
Pre-Print: BioRxiv 682237
R package: github.com/jean997/cause
Website: jean997.github.io/cause/
Contact: jeanm@uchicago.edu

CAUSE is Robust to Confounding While Retaining Power in Simulations

- Summary statistics simulated with LD patterns estimated from 1K Genomes.
- With small amounts of correlated pleiotropy, CAUSE controls the false positive rate below the nominal level.
- CAUSE has a better false positive rate than other methods for all levels of correlated pleiotropy.
- CAUSE has the best advantage when the GWAS for trait M has low power (results shown).
- Check the website for full simulation results!



References:
MR Review, IVW: Burgess, S., Dudbridge, F., & Thompson, S. G. (2016). *Stat Med*, *35*(11), 1880–1906.
ELPD: Vehtari, A., Gelman, A. & Gabry, *J Stat Comput* (2017) 27: 1413
Egger Regression: Bowden, J., Smith, G. D., & Burgess, S. (2015). *Int J Epidemiol*, (June), 512–525.
MR-PRESSO: Verbanck, M., Chen, C., Neale, B., & Do, R. (2018). *Nat Gen*, *50*(May).
Weighted Median: Bowden, J., Fabiola Del Greco, M., Minelli, C., Smith, G. D., Sheehan, N. A., & Thompson, J. R. (2016). *Int J Epidemiol*, *45*(6), 1961–1974.
Weighted Mode: Hartwig, F. P., Smith, G. D., & Bowden, J. (2017). *Int J Epidemiol*, *46*(6), 1985–1998.