Sparse Causal Effect Estimation using Two-Sample Summary Statistics in the Presence of Unmeasured Confounding

Shimeng Huang, Niklas Pfister, and Jack Bowden

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Motivation

In genetic epidemiology, Mendelian randomization (MR)—instrumental variable estimation (IV) with genetic variants being the instruments—is often used to estimate causal effects, which accounts for unmeasured confounding.

- Only summary-level data from two samples are available: estimated marginal associations from large-scale genome-wide association study (GWAS).
- Not enough strong & valid instruments for all covariates, but also not all covariates may have a direct causal effect on the response.

Setting

Assume the underlying SCM is linear and we observe two-sample summary statistics

- Estimated association between Z and Y from sample 1 $(\widehat{\pi}, \widehat{\Sigma}_{\pi})$
- Estimated association between Z and X from sample 2 $(\widehat{\Pi}, \widehat{\Sigma}_{\Pi})$

The goal is to identify the average causal effect of X on Y.

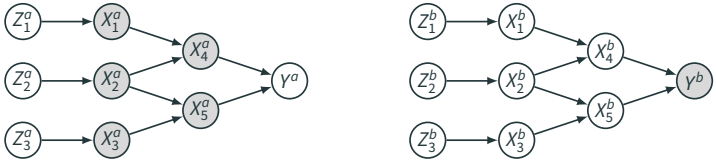


Figure 1: Example: A two-sample IV scenario that is considered as underidentified in the usual sense. *Hidden confounders between X and Y are omitted.* Unobserved variables are in gray.

Methods

Pfister and Peters (2022) discuss identifiability conditions of sparse causal effects, and propose an estimator (spaceIV) based on one-sample individual-level data using subset selection.

In this work, we consider the two-sample summary-statistics counterpart using

- **Subset selection** (L0) for which we show consistency
- **Lasso-type estimation** (L1) as a computational speed-up

Methods

Q statistic (Theorem 2.2, HPB, 2024)

Assume certain regularity conditions hold. For all $\beta \in \mathbb{R}^d$, define the Q statistic as

$$Q(\beta) := (\widehat{\pi} - \widehat{\Pi}\beta)^\top (\tfrac{1}{n_a}\widehat{\Sigma}_\pi + \tfrac{1}{n_b}\widehat{\Sigma}_\Pi(\beta))^{-1}(\widehat{\pi} - \widehat{\Pi}\beta),$$

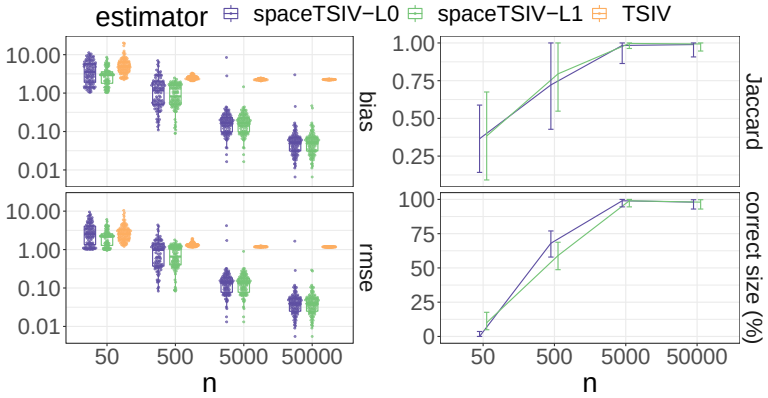
where $\widehat{\Sigma}_\Pi(\beta) := \xi(\beta)\widehat{\Sigma}_\Pi\xi^\top(\beta)$ with $\xi(\beta) := \beta^\top \otimes I_m$. Then it holds for all $\beta \in \mathbb{R}^d$ and all $r \in (0, \infty)$ that

$$\lim_{\substack{n_a, n_b \to \infty \\ n_a/n_b \to r}} \sup_{t \in \mathbb{R}} \sup_{\substack{P \in \mathcal{P}: \\ \beta \in \mathcal{B}^{\text{sum}}(P)}} \left| \mathbb{P}_P \left(Q(\beta) \leq t \right) - \kappa_m(t) \right| = 0,$$

where κ_m is the CDF of the χ^2 distribution with m-degrees of freedom.

Simulation

Data-generating processes: A linear SCM corresponding to Figure 1.



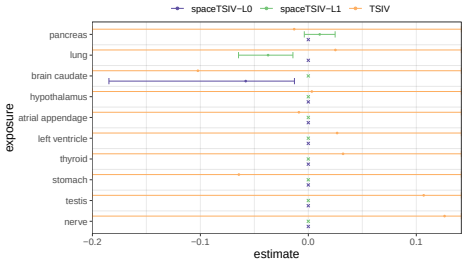
Application

We apply sparse MVMR to the tissue-specific GLP1R expression on the risk of coronary artery disease (Patel et al., 2024).

Table 1: Top 5 ranked models and corresponding posterior probabilities from MR-BMA (Patel et al., 2024, Table 2).

Rank	Tissues	Posterior probability (%)
1	Brain-caudate	45.9
2	Stomach	14.8
3	Nerve	8.0
4	Testis	6.6
5	Brain-hypothalamus	5.4

Figure 2: spaceTSIV using 17 genetic variants as instruments. Error bars represent 90% CIs constructed by inverting Q test.



Discussions

Future directions:

- Variable selection on the instruments as well
- Overlapping samples
- Heterogeneous samples
- Inference of the spaceTSIV estimator (post-selection inference)

References

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