Asymptotic Theory for Two-Sample Instrumental Variables Estimators

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Two-sample instrumental variable (IV) methods are widely used in Mendelian randomisation, where researchers estimate causal effects using summary statistics from independent samples. While the inverse variance weighted (IVW) estimator is the standard approach, existing asymptotic theory largely focuses on settings with a growing number of instruments, and its validity can require strong conditions in the presence of many weak instruments. We develop asymptotic theory for two-sample IV estimators by establishing consistency and asymptotic normality of both IVW and debiased IVW (dIVW) when the number of instruments is fixed, complementing existing many-instrument theory. We show that IVW and dIVW have the same first-order asymptotic variance in this setting. We then compare IVW and dIVW with the profile score (PS) estimator across fixed- and many-instrument regimes. Under standard variance assumptions, dIVW and PS require the same rate of collective instrument strength but impose different additional restrictions on instrument growth and the concentration of instrument strength, so their theoretical guarantees favour different asymptotic regimes. Under a common variance-ratio condition, we further show that dIVW has strictly smaller asymptotic variance than PS in the fixed-instrument setting, while their relative variance difference vanishes as the sample size increases.
These results provide a unified theoretical comparison of the commonly used two-sample IV estimators and clarify how instrument strength, instrument growth, and the concentration of instrument strength determine their validity and relative efficiency.

References:

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