Debiased Inverse-Variance Weighted Estimator in Two-Sample Summary-Data Mendelian Randomization

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Abstract: Recently, Mendelian randomization has become a popular approach to study the effect of a modifiable biomarker or exposure on an outcome of interest using genetic variants from pre-existing genome-wide association studies as instruments. A challenge of using genetic variants as instruments is that each individual genetic variant usually explains a relatively small proportion of variance in the exposure and there are many such instruments, a setting known as many weak instruments. Unfortunately, some popular estimators in Mendelian Randomization are developed under the strong instruments setting and only empirical studies have shown that they are biased under the many weak instruments setting. In this paper, we study the theoretical properties of the two most popular estimators in Mendelian Randomization, the inverse-variance weighted (IVW) estimator and pre-screened IVW estimator using strong instruments selected from a selection dataset. We provide a full characterization of these estimators with many weak instruments by using a measure of average instrument strength. Based on our theoretical investigations, we propose a debiased IVW estimator, a simple modification of the IVW estimator, that is robust to many weak instruments and requires no pre-screening. When a selection dataset is available, we propose two principled ways to determine the p-value cutoff for pre-screening to improve efficiency of the debiased IVW estimator. An extension of debiased IVW estimator to the balanced horizontal pleiotropy is also discussed. We conclude by demonstrating our results in simulated and real datasets.