Robust Mendelian Randomization in the Presence of Many Weak Instruments and Widespread Horizontal Pleiotropy

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ABSTRACT

Mendelian randomization (MR) has become a popular approach to studying the effect of a modifiable exposure on an outcome by using genetic variants as instrumental variables (IVs). Two distinct challenges persist in MR: (i) each genetic variant explains a relatively small proportion of variance in the exposure and there are many such variants, a setting known as many weak IVs; and (ii) many genetic variants may have direct effects on the outcome not through the exposure, or in genetic terms, when there exists widespread horizontal pleiotropy. To address these two challenges simultaneously, we propose a novel estimator, the debiased inverse-variance weighted (dIVW) estimator for summary-data MR and we establish its statistical properties. An extension to the multivariable MR will also be discussed.