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LEVERAGING LOCAL DISTRIBUTIONS IN MENDELIAN RANDOMIZATION: UNCERTAIN OPINIONS ARE INVALID

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Abstract: Mendelian randomization (MR) considers using genetic variants as instrumental variables (IVs) to infer causal effects in observational studies. However, the validity of causal inference in MR can be compromised when the IVs are potentially invalid. In this work, we propose a new method, MR-Local, to infer the causal effect in the existence of possibly invalid IVs. By leveraging the distribution of ratio estimates around the true causal effect, MR-Local selects the cluster of ratio estimates with the least uncertainty and performs causal inference within it. We establish the asymptotic normality of our estimator in the two-sample summary-data setting under either the plurality rule or the balanced pleiotropy assumption. Extensive simulations and analyses of real datasets demonstrate the reliability of our approach.

Key words and phrases: Causal inference, instrumental variable, Mendelian randomization, pleiotropy.

1. Introduction

The instrumental variable (IV) approach is widely used to infer causal effects in the existence of unmeasured confounders. It relies on the valid IV assumption that instruments only affect the outcome through the exposure of interest. In epidemiology and biological studies, genetic variants are often utilized as IVs to detect causal relationships between phenotypes. Such causal studies are known as Mendelian randomization (MR) and gain popularity in various disciplines (Davey Smith and Ebrahim, 2003). However, the statistical foundations of MR are still evolving due to concerns regarding the potential invalidity of genetic instruments.

The large availability of genome-wide association studies (GWAS) has made genetic variants, particularly single nucleotide polymorphisms (SNPs), a popular choice of IVs. However, the exclusion restriction assumption, a key assumption in conventional IV methods, may not be credible when using genetic instruments. Many genetic variants exhibit pleiotropic effects, meaning that they can affect multiple phenotypes simultaneously (Davey Smith and Hemani, 2014). Hence, a variant can affect the outcome through more than one pathway, violating the

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