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Mendelian randomization analyses under case-control sampling

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Mendelian randomization studies use inherited genetic variants as instrumental variables to infer the causal effect of an intermediate phenotype on a disease outcome. For relative rare dichotomous disease outcomes, case-control sampling is efficient and commonly used to ascertain genetic variants. In this article, we assess the impact of case-control sampling on Mendelian randomization analyses with a dichotomous disease outcome and a continuous intermediate phenotype, and we focus on the two-stage least squares (2SLS) estimation. We show that the 2SLS procedure, though merely an approximation in this setting, provides a valid test and a generally conservative estimate of the causal effect. Under case-control sampling, the first stage of the 2SLS procedure becomes estimation of secondary trait association. Through theoretical development and simulations, we compare the naïve estimator, the inverse probability weighted (IPW) estimator and the maximum likelihood (ML) estimator for the secondary trait association, and more importantly, the resulting 2SLS estimates of the causal effect. We also include in our comparison the causal odds ratio estimate derived from structural mean models (SMM), a consistent estimator that are estimated via generalized methods of moments (GMM). Our results suggest that the naive estimator is substantially biased under the alternative, yet unbiased under the null hypothesis of no causal effect; for small to moderate sample size, the ML estimator yields smaller variance and mean squared error than both the IPW estimator and the GMM estimator; the GMM estimator delivers the smallest bias, but generally larger variance, and sometimes it has issues in algorithm stability and convergence.

Biography

James Y Dai has graduated from Department of Biostatistics, University of Washington, Seattle, in 2007. He is associate member in Fred Hutchinson Cancer Research Center and affiliate Associate Professor in Department of Biostatistics, University of Washington. He has been actively publishing in methodological research on genome-wide genetic association, gene-environment interactions, and adaptive algorithms. As part of his research interest, he has been working in causal mediation analysis, Mendelian randomization, and estimation direct and indirect effects in genetic epidemiology.

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