

Biomarkers and Disease Progression in Precision Medicine: Causal Insights from a Large-Scale Taiwanese Cohort

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Abstract

Mendelian Randomization (MR) is widely applied to strengthen causal inference. However, standard two-sample MR may be biased by correlated exposures, temporal variation, and pleiotropy. Extensions such as multivariable MR (MVMR) and time-varying MR (TVMR) address these challenges. We evaluated their methodological performance and clinical relevance by investigating the causal role of glycated hemoglobin (HbA1c) in microvascular complications. Using data from the Taiwan Biobank, we used HbA1c as the exposure, while microvascular biomarkers were the outcomes. Causal estimates were compared across two-sample MR, MVMR, and TVMR. This study demonstrates that advanced MR frameworks can jointly address methodological biases and generate clinically meaningful insights. Our findings provide evidence that long-term glycemic exposure contributes causally to microvascular outcomes. Moreover, we also point to the need for integrating methodological advances with clinical application.

Keyword: Mendelian Randomization; Taiwan Biobank; HbA1c