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Presentation preference: Oral presentation.

Cross-Lagged Mendelian Randomization: Integrating Genomic Data with Repeated-Measures Designs to Strengthen Causal Inference

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Background. Mendelian Randomization (MR) employs randomly-segregated alleles as instrumental variables to discern causality in observational studies. Here, we combine one-sample MR with a repeated-measures design to further strengthen MR's causal inference by integrating it with longitudinal Granger causality.

Method. Building on a two-trait, two-timepoint Cross-Lagged Panel Model (CLPM) with simulated phenotypes, we add to the model the polygenic score of both phenotypes as genetic instruments. Additionally, we estimate bidirectional instantaneous paths between the traits. This bidirectional Cross-Lagged MR (CL-MR) model statistically controls for within-trait autoregression, within-assessment confounding between the traits, and any correlation between the genetic instruments (e.g., due to Linkage Disequilibrium).

Results. The bidirectional CL-MR model renders identified both lagged and instantaneous causal paths. Simulations indicate that the power to detect either causal path increases with stronger genetic instruments, though the power to reject the null hypothesis of no causation is higher for the lagged effect than for the instantaneous one. Fitting simpler, unidirectional models with one genetic instrument does not enhance the power. The method requires MR's assumption of no horizontal pleiotropy; however, this assumption can be assessed via sensitivity analyses by fixing additional regression paths to particular values from either genetic instrument to the opposite trait.

Conclusion. Cross-lagged MR allows longitudinal MR analysis, decomposing the longitudinal causal effect into potential direct and indirect effects (via the instantaneous paths). This model has broad applicability for unraveling the causal relationships between substance use phenotypes and their epidemiological correlates, using large-scale biobanks and Electronic Health Records with repeated assessments.

Acknowledgment/Funding. The authors are grateful for support from NIH Grants R01DA049867 and T32MH-20030.