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Bidirectional causal modeling with instrumental variables and data from relatives

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Establishing (or falsifying) causal associations is an essential step towards developing effective interventions for psychiatric and substance use problems. While randomized controlled trials (RCTs) are considered the gold standard for causal inference in health research, they are impossible or unethical in many common scenarios. Mendelian randomization (MR) can be used where RCTs are not feasible, but it requires stringent assumptions that can be fundamentally flawed when applied to complex traits. Some assumptions of MR can be avoided with using structural equation modeling. In this paper we developed an extension of the Direction of Causation twin model *(Neale 1994)* that includes two polygenic risk scores in the specification, as an approach to avoid some inherent restrictions of both MR and RCT. We hypothesize that adding a second PRS will generate a more flexible model in terms of identification, whilst maintaining reasonable power and allowing for bidirectional causation. OpenMx software is used to explore the power of such a model and its identification. We arrive at an extension of the Direction of Causation model that can be used both in a twin design or in a extended family design, but at the same time relaxing some of MRs assumptions. We further report the model is well powered enough for current data set sizes (from around 13000 observations or less, depending on the variance of the instruments), and in a range of additive, shared and environmental variances found in common clinical scenarios.