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Putative Proximal and Distal Effects between Smoking and Alcohol Consumption: Causal Inference from Models Integrating Polygenic Scores with Longitudinal Data

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Tobacco smoking and alcohol consumption often show moderate to high correlations in epidemiological studies. Here, we examined whether potential reciprocal causal effects contribute to their comorbidity, using structural equation modeling with longitudinal data and polygenic scores (PGSs). We analyzed two waves of repeated assessments (three years apart) in 4,895 adult unrelated European-ancestry individuals from the Netherlands Twin Register. At each wave, self-reported smoking was operationalized as an ordinal scale (never vs. former vs. current smoking). Alcohol consumption was assessed on a seven-point Likert scale of drinks/week. Results from a cross-lagged panel model (CLPM) indicated a statistically significant lagged effect of smoking status on drinks/week (b=0.062, S.E.=0.027) but a non-significant reverse effect (b=0.018, S.E.=0.011). We then added PGSs of smoking and drinks/week to the model, using the IV-CLPM approach to estimate both the lagged (i.e., temporally “distal”) and the bidirectional cross-sectional (i.e., “proximal”) effects at each wave. The model accounted for the correlation between PGSs to partly accommodate background genetic confounding between smoking and drinks/week. The best-fitting IV-CLPM showed a significant *proximal* effect of drinks/week on smoking status (b=0.196, S.E.=0.094), along with a *distal* effect of smoking on drinks/week assessed three years later (b=0.065, S.E.=0.027). These results suggest a complex bidirectional causal relationship between smoking status and alcohol consumption, involving a near-term causal effect of drinks/week on smoking, which, in turn, likely has a relatively more persistent feedback effect on drinks/week. Future research should examine similar models between alcohol consumption and different aspects of smoking behavior (initiation, cessation, and heaviness).