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TITLE: Developmental pathways connecting polygenic risk of smoking initiation to adolescent and young-adult substance use

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## ABSTRACT:

**Background:** A recent genome-wide association study identified genetic variants associated with regular tobacco smoking. However, the developmental pathways through which this polygenic liability is manifested are unclear. Drawing on research that identifies risk factors for problematic substance use, we tested whether associations between polygenic risk of smoking initiation and substance use were mediated by (a) behavioral disinhibition, (b) negative emotionality, (c) cognitive ability, or (d) family socioeconomic status (SES).

**Methods:** We analyzed data from two longitudinal twin studies (N = 2054) in which participants provided molecular genetic data and completed repeated, prospective measures of nicotine, cannabis, and alcohol use from early adolescence into young adulthood (ages 11 to 24 years). Multi-informant measures of behavioral disinhibition and negative emotionality, WISC-R IQ scores, and multiple indicators of family SES were collected at age 11, when all participants were substance-naïve. We used twin participants' molecular genetic data to calculate a genome-wide polygenic score for smoking initiation and tested whether it was associated with each putative mediator assessed at age 11. We further tested whether these individual and family characteristics mediated associations between polygenic risk and subsequent cumulative substance use in later adolescence and young adulthood using structural equation modeling (SEM).

**Results:** Higher polygenic risk of smoking initiation was associated with greater use of nicotine, cannabis, and alcohol in adolescence and young-adulthood (ages 14 to 24 years). Age-11 behavioral disinhibition, IQ, and family SES all emerged as partial mediators of this effect; however, SEM mediation paths through IQ and family SES were modest, significant only for nicotine use, and were reduced to non-significance in models that also included mediation paths through disinhibition. In contrast, behavioral disinhibition mediated associations between polygenic risk and cumulative use of each individual substance as well as a broader latent factor capturing general propensity to substance use, even controlling for the effects of other putative mediators.

**Conclusions:** Polygenic risk of smoking initiation captures more than simply genetic propensity towards nicotine use. In addition to predicting a broader substance-use phenotype, these scores also capture variation in early-adolescent behavioral disinhibition, and—to a lesser extent—cognitive ability and aspects of the family environment. Our results suggest the testable hypothesis that helping children to increase their self-regulatory capacity may help to partly mitigate genetic risk.

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