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Phenome Wide Association Study of Polygenic Risk Scores for Substance Use Disorders in The Adolescent Brain and Development Study

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A fundamental gap in our understanding of substance use disorder (SUD) etiology lies in our inability to disentangle reciprocal effects between substance use and putative etiologic factors. Longitudinal data, specifically those that capture youth behavior prior to and following the onset of substance use, can inform the extent to which correlates may plausibly represent predispositional risk factors and/or a consequence of substance involvement. Here, in a sample of 5,556 and 1,456 adolescents whose genomes most closely resemble those of persons from Europe (Eur) and sub-Saharan Africa (AA), respectively, we developed polygenic scores based on the current largest GWAS of alcohol (*N Eur* = 903,147; *N* AA = 122,571), tobacco (*N Eur* = 739,895, *N AA* = 114,420), cannabis (*N Eur* = 886,025, *N AA* = 123,208), opioid (*N Eur*= 321,312, *N AA* = 91,407) use disorders, and on a large GWAS of the generalized genetic liability to all 4 disorders (*N Eur* = 1,025,550, *N AA* = 92,630). We examined the association between these polygenic scores and 1,271 measures of bio-psycho-social factors and behavior from ages 9-11 and measures of substance initiation from ages 9-15 in the Adolescent Brain and Cognitive Development study. Preliminary Eur findings show that genetic liability to SUDs is associated with sensation-seeking/fun-seeking, sleep problems, neighborhood disadvantage, and a family history of mental health disorders, all prior to onset of substance use. These data highlight that many behavioral and environmental correlates of substance involvement may represent predispositional risk factors associated with genetic liability.

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