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Genetic liability for tobacco use disorder predicts adolescent nicotine and cannabis use in the Adolescent Brain Cognitive Development (ABCD) Study

Background: Early initiation of nicotine and cannabis use predicts later substance use disorders and related psychiatric outcomes. Polygenic scores (PGS) derived from genome-wide association studies (GWAS) index genetic liability prior to clinical onset. However, the extent to which genetic liability for tobacco use disorder (TUD) predicts early substance use initiation across adolescence and ancestry groups remains unclear.
Methods: Youth- and parent-reported substance use was drawn from the Adolescent Brain Cognitive Development (ABCD) Study (Release 5.1; baseline N=10,977). TUD PGS were generated using PRS-CSx from a recent multi-ancestry GWAS meta-analysis of TUD (N=653,790) conducted across European (EUR), African (AFR), and Admixed American (AMR) ancestry groups within the PsycheMERGE Consortium (Toikumo et al., 2024). Multivariable logistic regression and Cox proportional hazards models examined associations between TUD PGS and the likelihood and timing of nicotine and cannabis initiation from ages 9-10 through 15-16 years. Models adjusted for sociodemographic factors, prenatal substance exposure, and ancestry-informative principal components, and were stratified by ancestry.
Results: Among EUR youth, higher TUD PGS was associated with increased odds and earlier initiation of nicotine (OR=1.65; HR=1.68; both p<.0001) and cannabis use (OR=1.93; HR=1.74; both p<.0001). In AMR youth, TUD PGS was associated with increased odds and earlier nicotine initiation (OR=1.30; HR=1.31; both p=.004) and increased odds of cannabis use (OR=1.34; p=.02), though earlier cannabis initiation did not reach statistical significance (HR=1.25; p=.062). No significant associations were observed in AFR youth.
Conclusions: Genetic liability to TUD is associated with increased risk for adolescent nicotine and cannabis initiation among EUR and AMR youth. The absence of significant associations in AFR youth may reflect reduced predictive performance in smaller or ancestrally underpowered samples, highlighting the need for continued expansion of diverse GWAS discovery efforts. Future work should integrate shared genetic liability and environmental exposures to refine developmentally informed risk stratification.

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