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Describing Polygenic Associations for Alcohol Use, ADHD Symptoms, Cigarette Use, and Educational Attainment: A Within-Family Comparisons Study.

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Polygenic scoring has emerged as a way to characterize multiple genetic influences on substance use and related behaviors. Typically, polygenic associations are interpreted as causal, such that carrying more trait- or disorder-associated alleles increases risk. Yet, these associations may be confounded by familial factors, such as socioeconomic status. To address this, we integrated a twin design with polygenic scoring to evaluate whether differences in polygenic load between dizygotic (DZ) twins, who share their rearing environment and half their genetic variation, predict phenotypic differences for several substance-related traits, including alcohol misuse, Attention Deficit Hyperactivity Disorder (ADHD), educational attainment, and cigarette use. In a sample of Finnish twins (FinnTwin12; N = 1299; 54% female), we evaluated associations of each polygenic score (derived from PGC, SSGAC, and GSCAN summary statistics and selected based on highest R² using the pruning-and-thresholding method) with its discovery phenotype in conventional between-family analyses, using the plm package in R with age and sex as covariates. We observed significant polygenic associations for alcohol consumption, educational attainment, and lifetime smoking (ps < .01). Polygenic associations were not significant for alcohol dependence or ADHD (ps > .11). We then limited analyses to DZ twins (N = 765; 53% female) for within-family comparisons with sex as a covariate. Polygenic associations for alcohol consumption, educational attainment, and lifetime smoking were no longer significant (ps > .08), consistent with familial confounding. By employing between- and within-family methods, our analyses lend greater insight into the nature of polygenic associations for substance-related behaviors.