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## **Phenotypic and Genetic relationship between ADHD and SUDs in the Yale-Penn cohort**

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**Background:** Attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUDs) commonly co-occur and have overlapping genetic liabilities. Little is known regarding either the phenomenology or the genetics of ADHD in cohorts enriched for SUDs or the influence of genetic liability for ADHD on the risk of developing SUDs when controlling for SUD-related genetic risk.

**Methods:** We used data from the Yale-Penn cohort, which comprises ~14,000 individuals ascertained for SUDs and/or as controls. Polygenic risk scores (PRS) were developed for ADHD and multiple SUDs using summary statistics from large genome-wide association studies (GWAS). Regressions were run to determine the association between ADHD PRS and multiple SUDs, controlling for specific SUD PRS when feasible. Associations of different SUD PRS on ADHD were also determined.

**Results:** Participants who met DSM-IV Criteria for ADHD (n=444) had significantly increased odds for every DSM-5 SUD analyzed, greater polysubstance use, and younger age of onset of substance use. ADHD PRS was significantly associated with multiple DSM-5 SUD phenotypes controlling for SUD-specific PRS among participants of both European and African ancestry. Of the SUD and substance trait PRS, only one (smoking initiation) was significantly associated with ADHD diagnosis, and only among individuals of European ancestry.

**Discussion:** In this sample, enriched for SUDs, ADHD was associated with increased risk for SUDs and earlier onset of substance use. Additionally, genetic liability to ADHD was independently associated with SUDs. Further studies in large, diverse populations are needed to enhance our understanding of these associations.