EXPLORING THE PATHWAYS LINKING PARENTAL ALCOHOL AND SUBSTANCE MISUSE, GENETIC RISK, AND CHILD ADHD: A GRAPH-BASED MEDIATION APPROACH

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Background

ADHD is a prevalent neurodevelopmental disorder with both genetic and environmental interplay. Parental alcohol and substance misuse are environmental risk factors that may affect child ADHD outcomes. To study how parental alcohol and substance misuse, together with a child's genetic predisposition (PRS), impacts a child's attention-deficit/hyperactivity disorder (ADHD) risk. A graph-based mediation method was developed, and this framework provides a holistic, data-driven way to explore these pathways.

Data and Methods

We utilized individuals data from the Adolescent Brain Cognitive Development (ABCD) study[1], selecting parental factors indicative of alcohol or substance misuse from the Adult Self-Report/Adult Behavior Checklist. We focused on the second-year follow-up as the only time point where all relevant variables were consistently available. Polygenic Risk Scores (PRS) for ADHD were computed using publicly available genome-wide association study findings[2] for 4,698 Caucasian adolescents.

- **Identify parental factors** We utilized the ABCD dataset, focusing on parental alcohol/substance misuse items extracted from the ASR/ABCL inventories via relevant alcohol/substance-related keywords. Preliminary linear regressions identified which parental factors correlated most strongly with child ADHD scores.
- **Calculate genetic predisposition** We obtained summary-level results from a genome-wide association study (GWAS) of ADHD. Individual polygenic risk scores (PRS) values were computed as genetic predisposition for participants of Caucasian ancestry to minimize population-stratification bias.
- **Graph-Based Model Construction** We modeled parental factors, child PRS, and ADHD symptom severity within a directed acyclic graph (DAG). To capture the strongest pairwise relationships, we applied a minimum spanning tree (MST) approach using mutual information before finalizing the DAG structure.
- **Mediation and Moderation Analyses** We tested whether parental factors influence ADHD symptoms directly or indirectly through child PRS (i.e., mediation). Potential moderating effects of child gender were evaluated to determine if pathways differ between males and females.

Parental and Gene Influence Factors

Variable	Description	P-Value (Regression with ADHD)
ADHD_P	Parents ADHD T-score	0.0
Parents_AUD	Parents Alcohol Use Disorder	0.18e-05
Parents_SUD	Parents Substance Use Disorder	1.75e-15
Parents_Druguse_self	Parents Drug Use Self-evaluate	8.99e-08
Parents_Druguse	Parents Drug Use	1.73e-06
Parents_Alcohol_Overus_self	Parents Alcohol Use Self-evaluate	1.14e-06
Parents_Alcohol_Overuse	Parents Alcohol Use	1.25e-09
Parents_TUD	Parents Tobacco (T-Score)	0.45e-23
Parents_Tobacco_Use	Parents Tobacco Use	2.67e-14
Child_PRS	Children's PRS Score	2.9e-11

Table 1. Preliminary linear regressions for all kinds of factors correlated with child ADHD scores.

Genetic Predisposition

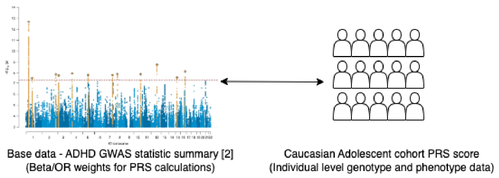


Figure 1. Using ADHD GWAS statistic summary for Caucasian adolescent cohort's PRS calculation

Graph-Based Mediation Model

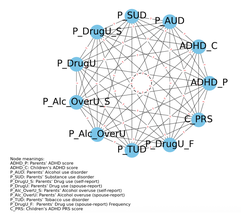


Figure 2. Study how all these factors interplay within a graph structure

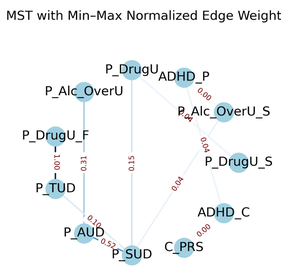


Figure 3. Using Maximum Spanning Tree (MST) to capture correlations.

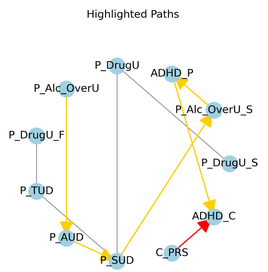
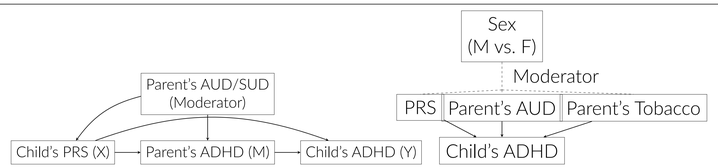
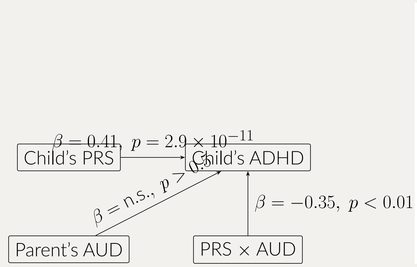


Figure 4. Building a DAG to find optimized paths to the target.

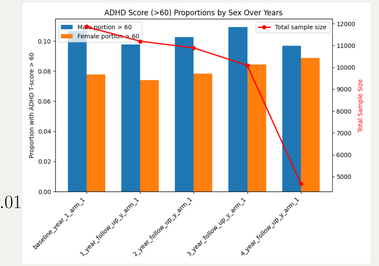
Mediation and Moderation Analyses



Results



(a) Direct and moderation effects.



(b) ADHD sex proportions with sample size.

Figure 5. **(a)** Simplified diagram illustrating direct and moderation effects, **(b)** ADHD sex proportions by sample size.

i. There could be a modification between Parents' AUD and child PRS

A child's PRS showed a direct effect on ADHD ($\beta = 0.41, p = 2.9 \times 10^{-11}$). Parent's alcohol use disorder alone was nonsignificant ($p > 0.5$), but the PRS × AUD interaction was significant ($\beta = -0.35, p < 0.01$), indicating a moderation effect.

ii. Girls tend to be affected by parents' AUD and TOD

In the combined sample, sex*PRS, sex*AUD, and sex*Toc showed no significant interactions. However, separate analyses revealed parents' alcohol and tobacco disorders affect girls more than boys. Furthermore, boys across age groups exhibit higher ADHD prevalence than girls, aligning with existing literature. More further analysis of sex differences in ADHD will be done in the future.

Discussion&Conclusions

We built a graph-based model to examine how multiple factors interact to influence a child's ADHD. Through path analysis, we found that parents' alcohol use disorder (AUD) negatively modifies the child's polygenic risk score (PRS) and thereby impacts ADHD. A stratified analysis showed that this negative effect emerges only in the low- and high-risk PRS groups, not in the middle-risk group. We also observed that girls are more affected by parents' alcohol/tobacco use disorders than boys when analyzed separately; however, in the combined sample, PRS and alcohol/tobacco use disorder interactions were nonsignificant, possibly due to PRS having limited explanatory power. Additional correlation (linear and nonlinear) and hierarchical regressions (adding each factor stepwise) indicated that PRS, parents' ADHD, sex, tobacco use disorder, and AUD × PRS were all significantly related to a child's ADHD, though overall explainability remained modest. These findings suggest the need for broader, more intricate modeling, as a graph-based approach could incorporate all relevant factors simultaneously and clarify how they jointly contribute to ADHD.

References

[1] Adolescent Brain Cognitive Development (ABCD) Study Consortium.
Data usage and terms and conditions of the data use certification.
`https://abcdstudy.org`.

[2] Ditte Demontis, Walters, et al.
Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder.
Nature Genetics, 51(1):63–75, 2019.