Advancing the Prediction of Adolescent Alcohol Use Onset by Deriving PolyeXposure Alcohol Risk Scores using the ABCD Study

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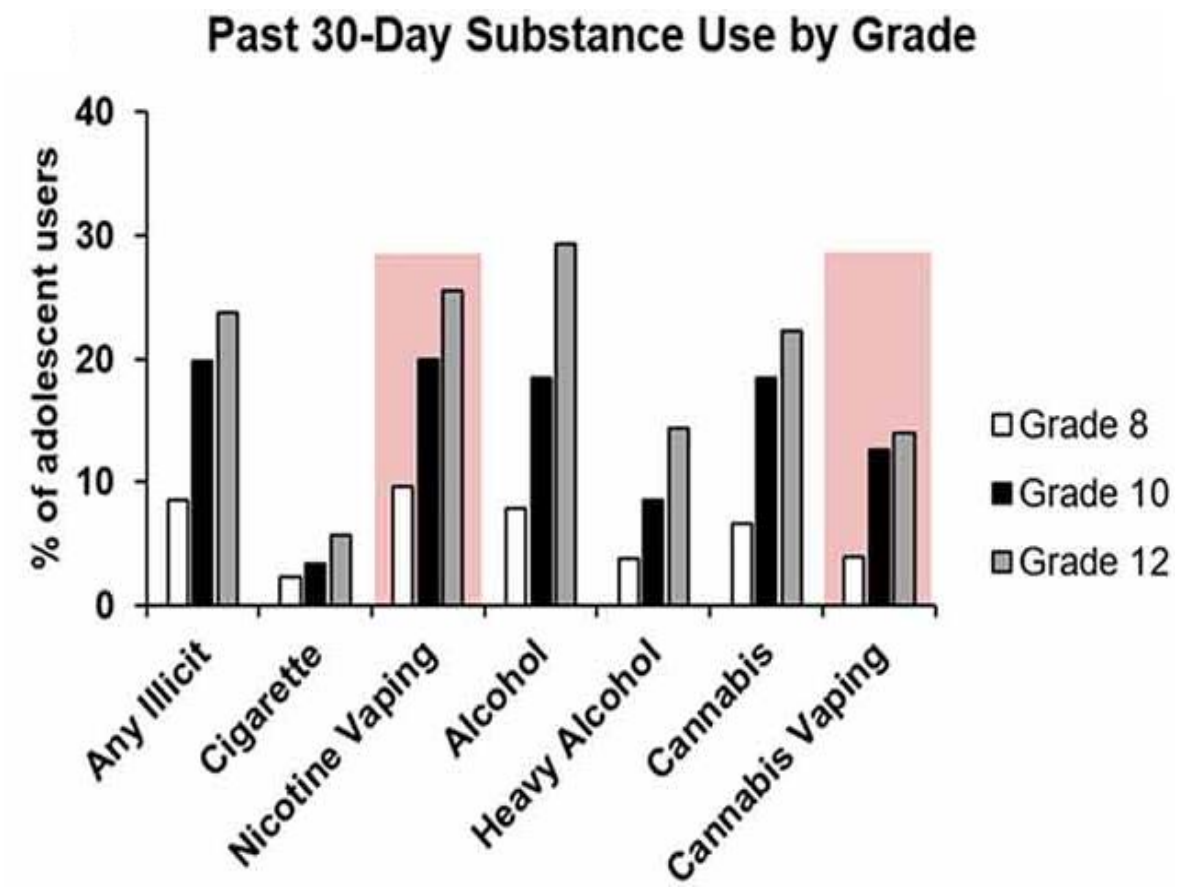
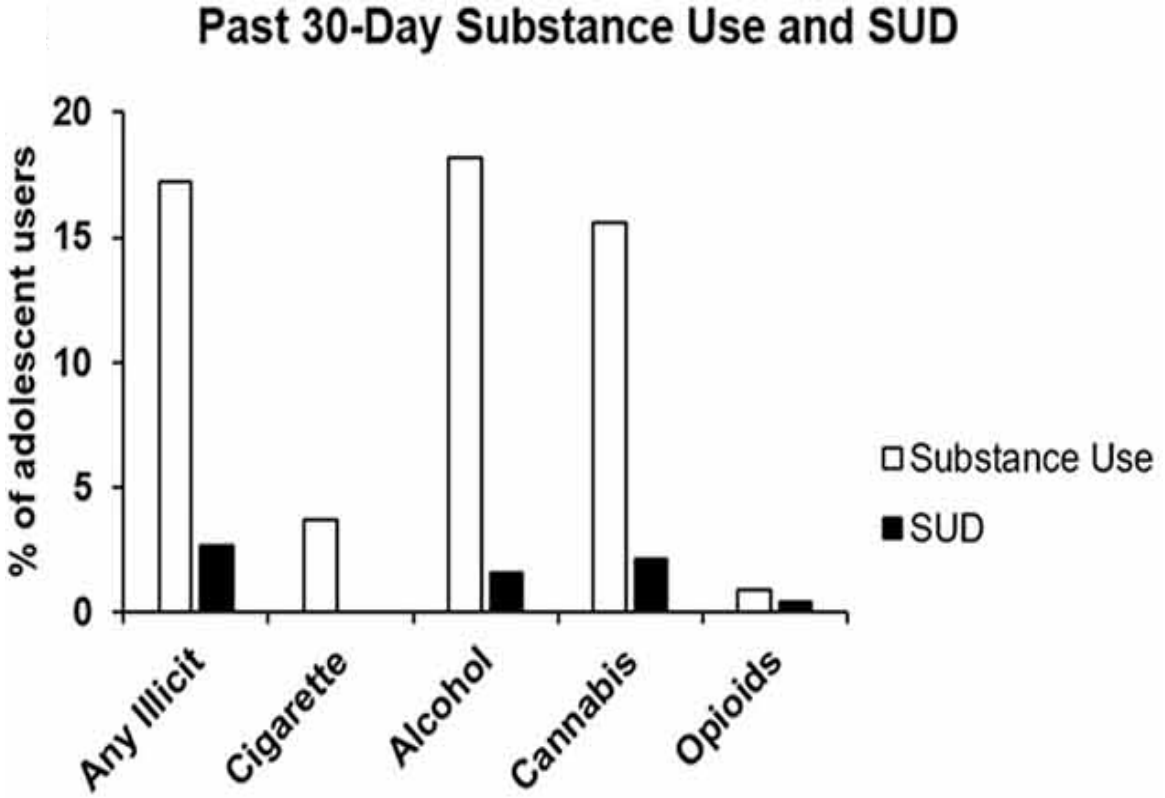
Mount Sinai

Addressing Substance Use in Youth





DeWit, D. J., et al. (2000)
Monitoring the Future Study (2022)

Risk Factors for Substance Use Onset

- Genetic predisposition (i.e., family history of substance use, and polygenic liability measured by polygenic risk scores)
- Environmental risk factors including low parental monitoring, school engagement, neighborhood stressors and cultural norms

Gaps in the Field

- Limited generalizability in genetics due to focus on European participants
- Environmental studies use a “pick and choose” approach
- Existing analytical approaches overlook the co-occurring and interactive effects

Non-Genetic “Exposome” Risk Scores

- **Exposome:** totality of the environment i.e., all “non-genetic” factors
- Utility of ***Exposome-Wide Association Study (ExWAS)***; analogous to genome-wide association study (GWAS)
- Captures the total contribution of several exposome variables, while accounting for inter-exposure correlations; akin to polygenic risk scores
- Improves the prediction accuracy of Type 2 Diabetes by **3-folds** compared to that of PRS

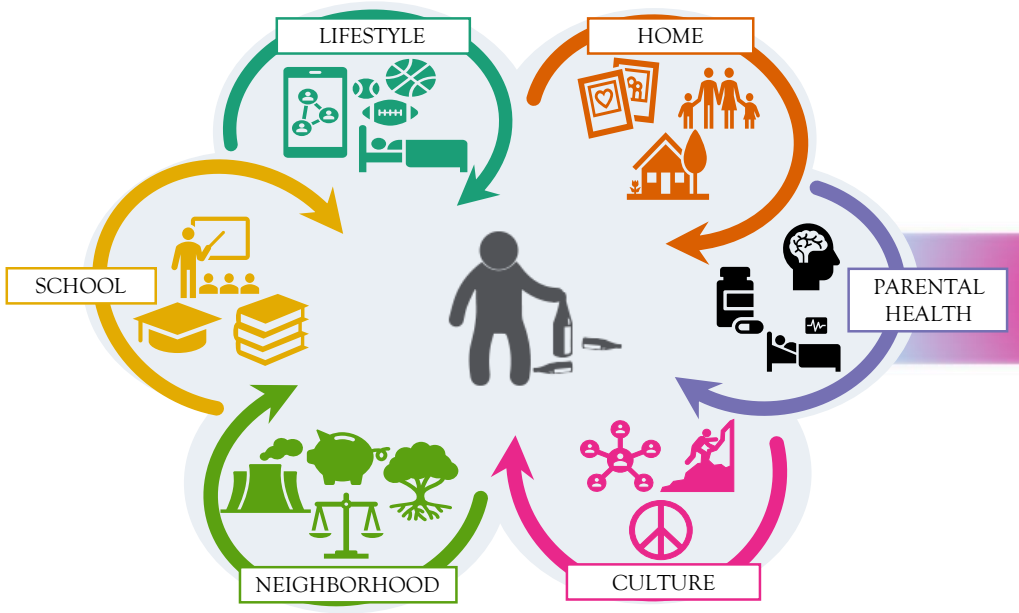
Conduct a robust exposomic characterization and develop a ***PolyeXposure Risk Score (PXS)*** to capture individual-level exposomic risk factors for substance use onset, independent of genetic factors.

Study Aims

Aim 1: Conduct an Exposome-Wide Association Study **(ExWAS)** to evaluate the exposomic associations with substance onset in youth.

Aim 2: Derive PolyExposure Risk Score **(PXS)** to assess the additive and cumulative exposomic risks on substance use onset.

The ABCD Exposome



Study Population

n = 11,835 ABCD Participants

“Full Drug Use→ SU"

Yes → n = 609; **No** → n = 11,226

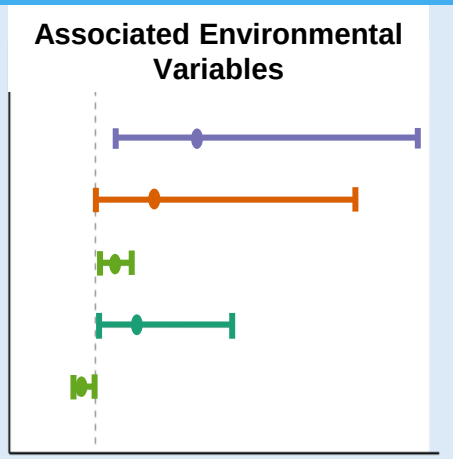
Time to SU Onset ranged from:

~ 4 – 15 years old

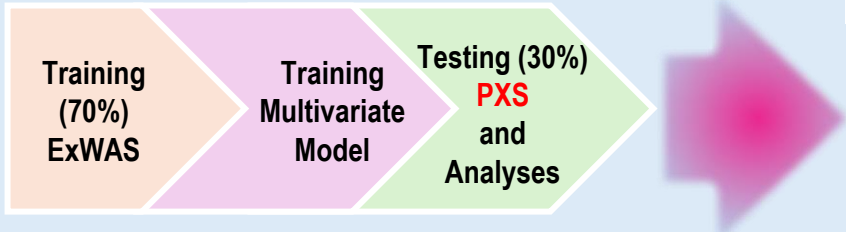
Exposome-Wide Association Study (ExWAS)

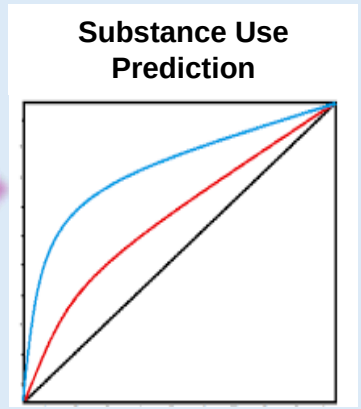
Single Exposure Modeling (Cox Regression)

Surv (Time to SU, Event) =
Exposure + Sex + Race/Ethnicity + Pubertal Score + Site ID + Family ID

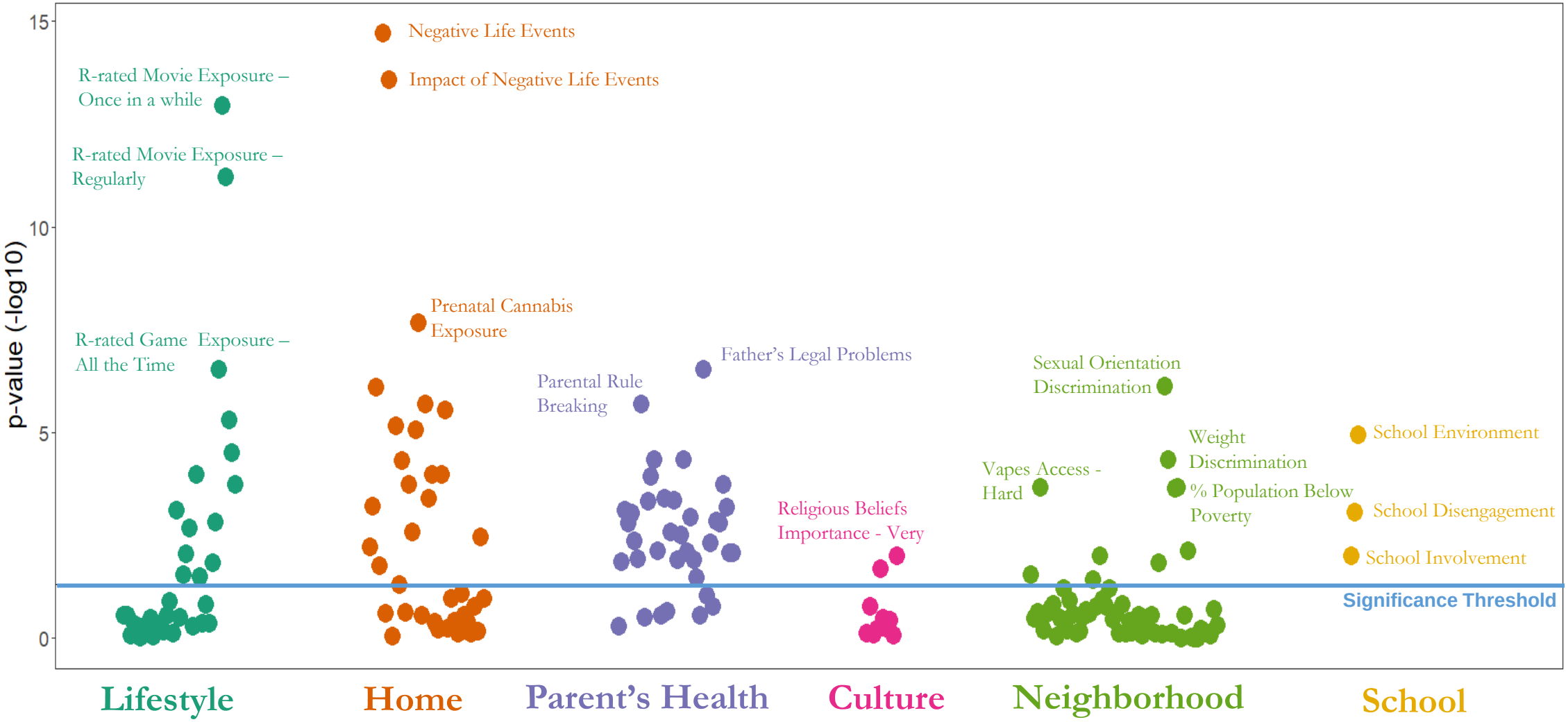


PXS Development

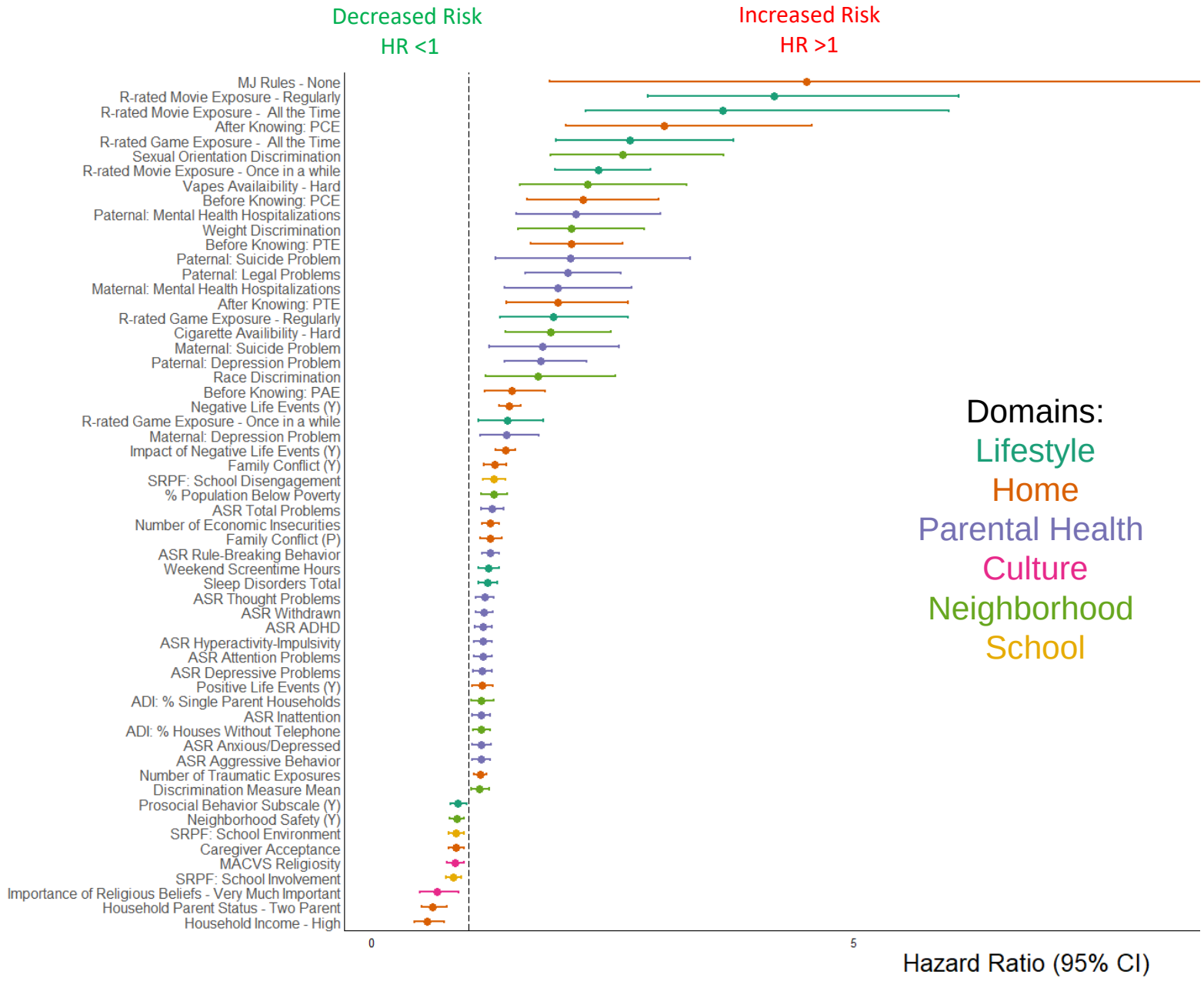




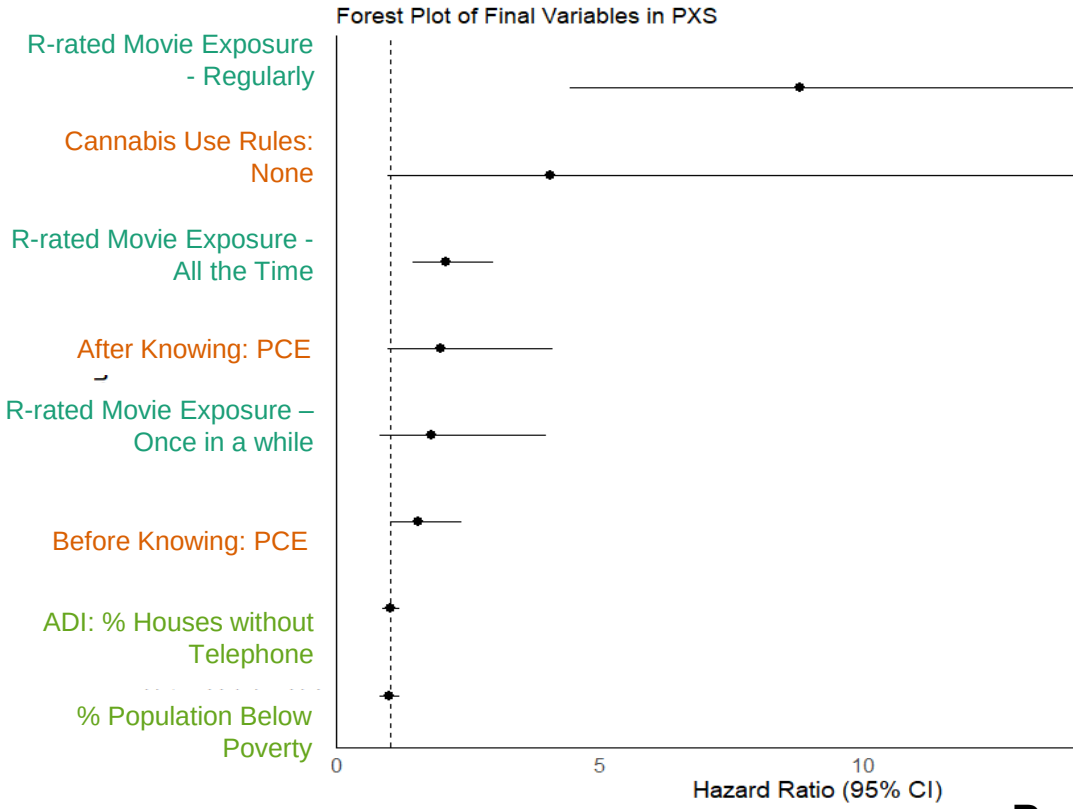
ExWAS revealed 74 exposomic features independently associated with time to substance use onset.

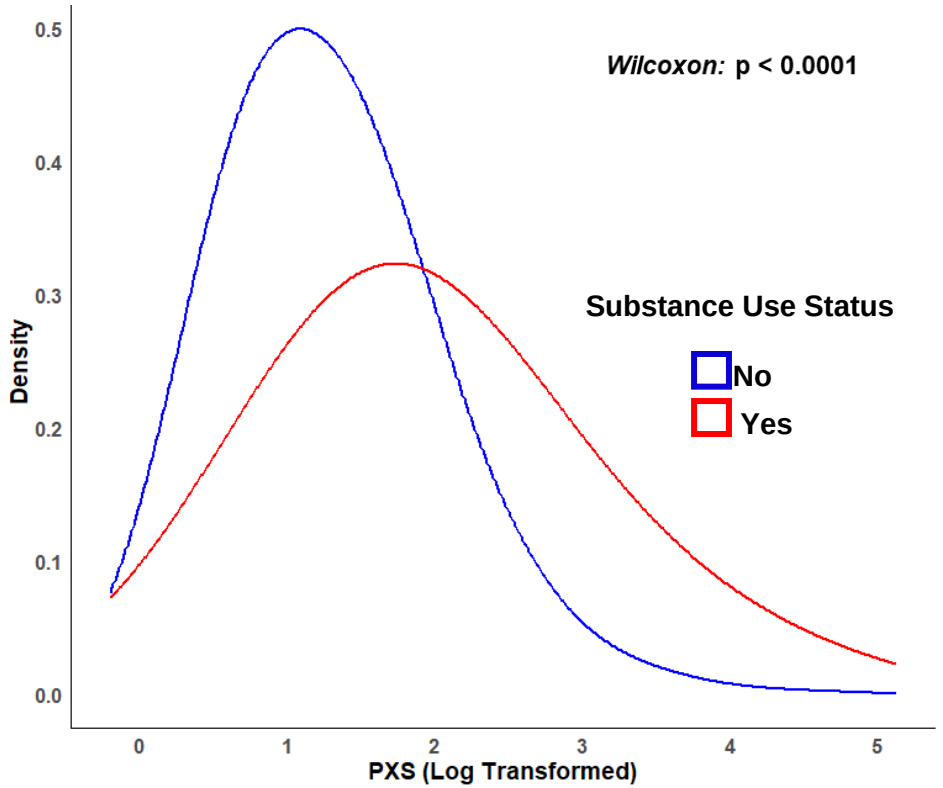


Among them, were risk (HR >1) and protective factors (HR <1) associated with time to substance use onset in youth.



PXS included factors from Lifestyle, Home, and Neighborhood domains, differing in substance naïve and substance exposed youth.





Prediction Accuracy

Change in AUC: 0.032 (0.01, 0.0.053)

Model 1 [covariates only] AUC: 0.668 (0.647, 0.732)

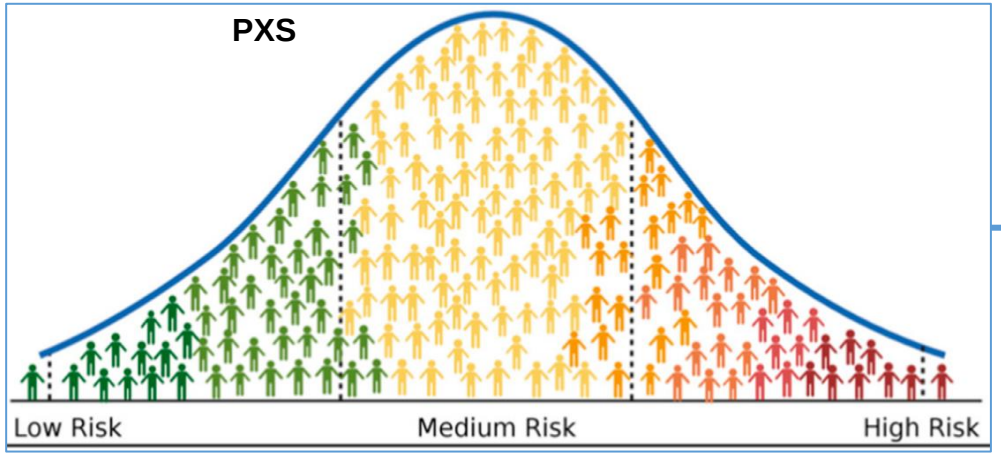
Model 2 [covariates + PXS] AUC: 0.700 (0.685, 0.764)

Limitations

- Measurement error and recall bias
  - Misreporting of actual events
    - self-reported environmental variables
    - reported age of onset
  - Underreporting of alcohol use among youth

Future Directions

- Compare PXS to genetic risk factors (FHD and PRS)
- Explore the neurobiological correlates for substance onset in youth



Reward Processing
Response Inhibition
Emotion Regulation

Broader Implications

- Identification of exposomic factors; some that may be modifiable and targeted for clinical interventions for substance use onset

- Application of non-genetic “exposome” risk scores to other behavioral outcomes in the ABCD study

START

Scientific Training in Addiction Research Techniques