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A Phenome-wide Association study of polygenic risk for Attention Deficit Hyperactivity Disorder across two genetic ancestries in the electronic health record data

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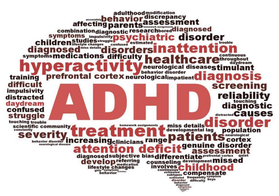
Attention Deficit Hyperactivity Disorder (ADHD)



- Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable childhood-onset neurodevelopmental disorder, which affects approximately 2-6% of children worldwide
- Individuals with ADHD have a higher polygenic risk for ADHD (ADHD-PRS) compared to controls
- High genetic risk for ADHD is also associated with higher BMI, neuroticism, anxiety, depression, alcohol use, smoking, anxiety, depression, and lower general cognitive ability (Du Rietz, Coleman et al. 2018).
- Although, PRS can be eventually implemented in clinical settings to improve diagnostics and risk stratification (Middeldrop and Wray 2018), the majority of studies focus on highly ascertained research populations.
- Data from large Biobanks can overcome these limitations.
- In a sample of 10,182 European ancestry individuals in the Penn Medicine Biobank, the ADHD PRS was not associated with ADHD. There were, however, significant associations with high risk for Tobacco Use Disorder (TUD), chronic airway obstruction, and type 2 diabetes, but also with low risk for myopia, benign neoplasm of skin, and screening for malignant neoplasms of the skin.

Study questions

This study had three aims:

1) Confirmation of the association between ADHD-PGS and ADHD diagnosis in a pediatric and adult EHR setting
2) Identification of the medical conditions that are associated with ADHD-PGS across developmental epochs
3) Conditional analyses to determine whether these associations remain after adjusting for socioeconomic and clinical risk factors

Methods

PRS

We constructed ADHD-PGS using the latest ADHD GWAS summary statistics (Demontis et al. 2017) for 12,383 unrelated subjects of African American Ancestry, and 66,378 unrelated subjects of European Ancestry in the Vanderbilt University Medical Center Biobank (BioVU).

Phenome Wide Association Study (PheWAS)

We standardized the ADHD PRS to have a mean of 0 and a standard deviation of 1 and used it as the predictor variable in the PheWAS. We required phecodes to have at least 50 cases and included covariates for sex, median age across the EHR, current age, and the first ten principal components of ancestry. Results were considered statistically significant if they passed Bonferroni correction ($p<2.1 \times 10^{-05}$). We did not perform conditional analyses in the African American ancestry sample, due to the lack of significant associations in the PheWAS.

PheWAS results

In the African American ancestry sample, the ADHD PGS was significantly associated with Tobacco Use Disorder (OR(95%CI)=1.23 (1.16 to 1.31), $p=9.3 \times 10^{-9}$. No other associations reached phenome-wide significance.

In the European ancestry sample, the most statistically significant association was TUD (OR(95%CI)=1.22(1.19 to 1.25, $p=2.8 \times 10^{-46}$). The ADHD PGS was also significantly associated with the diagnosis of ADHD (OR(95%CI)=1.22(1.16 to 1.29, $p=3.6 \times 10^{-10}$). Overall, 86 phecodes were significantly associated with ADHD-PGS ($p<2.1 \times 10^{-5}$).

Figure 1. PheWAS plot of genetic liability to ADHD in subjects of African American genetic ancestry

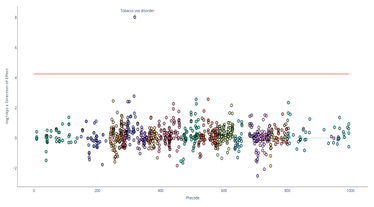
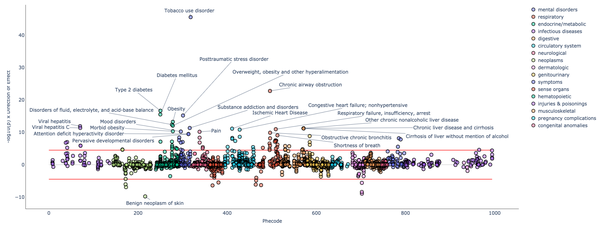
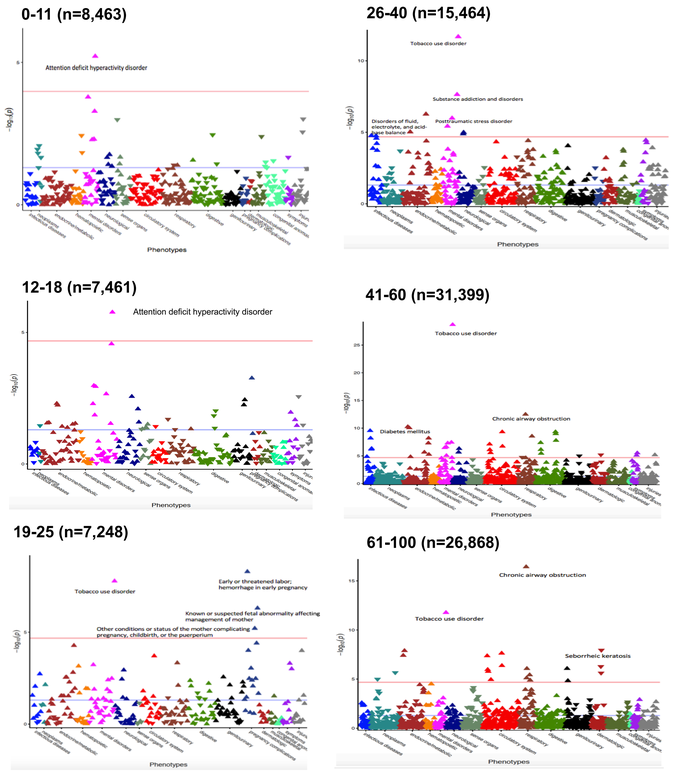


Figure 2. PheWAS plot of genetic liability to ADHD in subjects of European genetic ancestry



Age-stratified



Conditional analyses

We repeated the PheWAS with additional covariates for (a) ADHD diagnosis and medications commonly prescribed for ADHD, and (b) TUD. After controlling for ADHD diagnosis and medications, 90% of the associations remained virtually unchanged. However, when we adjusted for TUD, we observed a dramatic decrease in disease associations with ADHD-PGS as only half of the associations remained significant, suggesting that tobacco use rather than ADHD genetics are primarily contributing to these observed health problems.

Figure 3. Pie chart of phecode categories associated with genetic liability to ADHD

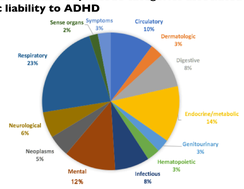


Figure 4. Pie chart of phecode categories associated with genetic liability to ADHD adjusted for ADHD diagnosis and medication

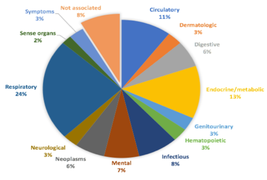
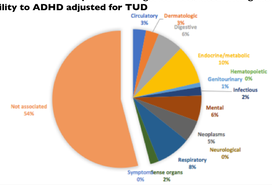


Figure 5. Pie chart of phecode categories associated with genetic liability to ADHD adjusted for TUD



Discussion

ADHD-PGS was associated with many diagnoses in the Vanderbilt biobank, including ADHD itself.

We replicated previous associations in research ascertained samples, including associations with smoking, higher BMI, (Du Rietz et al. 2018) Type 2 diabetes and major depressive disorder (Demontis et al. 2017).

ADHD-PGS was strongly associated with TUD, for both European and African American ancestries, similar to what was identified in both the Penn (Kember et al. 2019) and UK Biobanks (Beate Leppert et al. 2019). Given that many of the PheWAS associated health outcomes could be sequela related to smoking (e.g., chronic obstructive pulmonary disease), we further adjusted the PheWAS for TUD. After accounting for TUD, only half of the prior observed associations remained significant.

Medication treatment for ADHD has been associated to minor mean elevations in blood pressure and heart rate (Hammerness et al 2015). Safety concerns have been raised related to risk for adverse cardiovascular outcomes, including myocardial infarction (MI) and stroke (Westover et al.2012), but two large studies reported no evidence for such risks (Cooper et al., 2011, Habel et al., 2011). In our data, ADHD-PGS was initially associated with MI and hypertension and when we adjusted for ADHD medication the associations did not change. However, when we adjusted for TUD, the effect sizes for MI and hypertension dropped from 1.11 and 1.05 unadjusted, to 1.07 and 1.02 respectively. These results indicate that smoking is a great risk factor for MI and hypertension than stimulant medication use, in our hospital population.

Our study is the first to examine the associations of ADHD genetic risk with health outcomes over the lifespan in a clinical setting.

We found that the number of associations with adverse health outcomes increased with age, indicating that the effects of genetic liability to ADHD may have long term effects on health. However, it is also likely that these findings are a result of horizontal pleiotropy (i.e., shared genetic variants across disorders), or due to better power, taking into account that BioVU has older individuals compared to the general population.

Our findings further reinforce the utility of applying trait-specific PGSs to biobank data to probe relationships amongst clinically-related conditions

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