A Phenome-wide Association study of polygenic scores for Attention Deficit Hyperactivity Disorder 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 3-6% of children world wide
- 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 (Middeldorp 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 10,183 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 1 diabetes, but also with low risk for myopia, benign neoplasms of skin, and screening for malignant neoplasms of the skin.

Study questions

1. Is ADHD-PRS associated with ADHD in BioVU?
2. What are the medical problems associated with ADHD-PRS?
3. Do these associations remain after adjusting for ADHD diagnosis and socioeconomic factors (measured by the Area Deprivation Index)?
4. What medical problems are associated with ADHD-PRS in different age categories?

Methods

PRS

We generated PRS for each individual in BioVU using the latest ADHD GWA study from the Psychiatric Genomics Consortium (Demontis, Walters et al. 2017) as the discovery sample. Our BioVU sample included **66,378** unrelated individuals (44% males, median age of record(SD)=48.2 (22.3)) of European ancestry.

Phenome Wide Association Study (PheWAS)

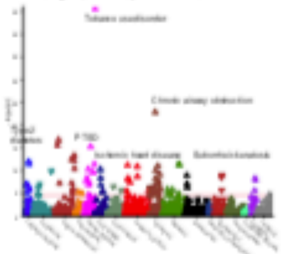
We standardized the ADHD PRS to have a mean of 0 and a standard deviation of 1 and used it as the predictor variable in the PheWAS. We required phecodes to have at least 50 cases and included covariates for sex, median age across the EHR, current age, and the first ten principal components of ancestry. Results were considered statistically significant if they passed Bonferroni correction ($p<3.3 \times 10^{-05}$).

PheWAS results

The ADHD-PRS was significantly associated with higher risk for ADHD (Odds Ratio (OR)=1.22, $p=3.22 \times 10^{-14}$)

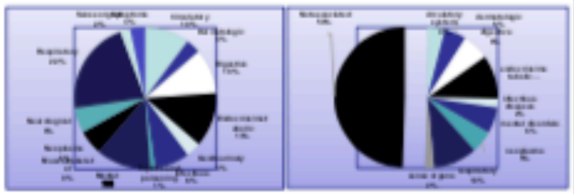
92 phecodes were significantly associated with ADHD-PRS ($p<3.3 \times 10^{-5}$)

Figure 1. PheWAS plot of ADHD-PRS risk in the Electronic Health Records. Phecode categories are on the x axis, P value (-log10) on the y axis, the triangles are the specific phecodes within the phecode categories. If the direction of the effect is positive, the arrow points upwards, if the direction of the effect is negative, the arrow points downwards.

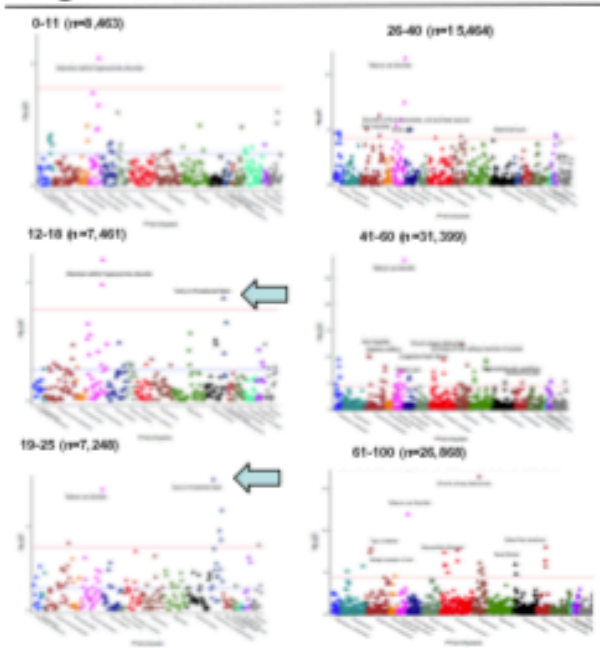


When we adjusted for tobacco use disorder (TUD) only half of the associations remained significant (Figures 2A and 2B)

Figure 2. Phecode categories associated with genetic liability to ADHD A) unadjusted and B) adjusted for Tobacco Use Disorder



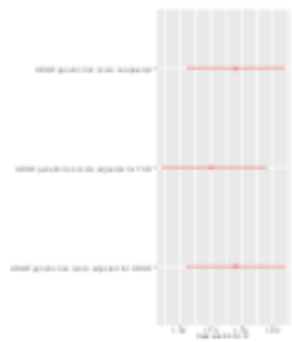
Age-stratified



Follow-up analyses

We aimed to further explore the associations with pregnancy complications for the ages 12 to 18, and 19 to 25, and restricted our analyses to females. We pulled together the females aged 12 to 24 and also examined the phecode categories 'Early threatened labor' and 'Known or suspected fetal abnormality' as one variable. The association of the ADHD risk score remained when we adjusted for tobacco use.

Figure 3. Odds ratios of the association between ADHD genetic risk score and pregnancy complications for females aged 12 to 25.



Overall, there was no evidence that ADHD diagnosis was associated with pregnancy complications (OR=1.02, p=0.88).

Discussion

Genetic liability to ADHD was associated with many medical diagnoses in the Vanderbilt biobank, including ADHD itself

Replicated previous associations in research ascertained samples, including associations with smoking, higher BMI, Type 2 diabetes and major depressive disorder, while we also identified novel associations, including associations with pneumonia, sepsis, HIV, and PTSD.

Most findings remained significant when we adjusted for the diagnosis of ADHD, indicating that genetic liability to ADHD is associated with varying health outcomes, over and above the clinical diagnosis.

After adjusting for TUD, only half of the associations remained significant, possibly due to direct or indirect associations with TUD

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.

Genetic liability to ADHD was associated with pregnancy complications, over and above ADHD and TUD diagnosis. Whether these associations are a result of pleiotropy remains to be examined.

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

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