Attention Deficit Hyperactivity Disorder (ADHD)

- Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable childhood-onset neurodevelopmental disorder, which affects approximately 2-4% 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, neurocognition, anxiety, depression, alcohol use, smoking, anxiety, depression, and lower general cognitive ability (Du Rietz, Coleman et al. 2018).
- Although PGS can be eventually implemented in clinical settings to improve patient care, it remains to be seen whether this will be feasible given the current state of evidence.
- 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. However, significant associations with high risk for Tobacco Use Disorder (TUD) chronic obstructive pulmonary disease, and type 2 diabetes, but with low risk for epilepsy, benign neoplasm of skin, and screening for malignant neoplasms of the skin.

Methods

PSRs

We constructed ADHD-PRS using the latest ADHD GWAS summary statistics (Demontis et al. 2017) for 12,383 unrelated subjects of African American Ancestry, and 64,378 unrelated subjects of European Ancestry in the Vanderbilt University Medical Center Biobank (BioVU). We stratified the population by sex, median age across the EHR, current age, and the first ten principal components of 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 phenocodes 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 not considered statistically significant if they passed Bonferroni correction (p<2.1 x 10^-10).

Study questions

This study had three aims:

1. Confirmation of the association between ADHD-PRS and ADHD diagnosis in a pediatric and adult EHR setting.
2. Identification of additional conditions associated with ADHD-PRS across developmental stages.
3. Conditional analyses to determine whether these associations remain after adjusting for socioeconomic and clinical risk factors.

PheWAS results

In the African American ancestry sample, the ADHD-PRS was significantly associated with Smoking Behavior Disorder (OR(95%CI)=2.13 (1.16 to 1.21), p=9.3 x 10^-5). 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 x 10^-4). The ADHD-PRS was also significantly associated with the diagnosis of ADHD (OR(95%CI)=2.25 (1.16 to 2.94), p=1.8 x 10^-3). Overall, 66 phenocodes were significantly associated with ADHD-PRS (p<2.1 x 10^-10).

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, 16% of the associations remained virtually unchanged. However, when we adjusted for TUD, we observed a dramatic decrease in disease associations with ADHD-PRS, with only half of the associations remaining significant suggesting that the results are primarily driven by ADHD genetics.

Medication treatment for ADHD has been associated with minor mean elevations in blood pressure and heart rate (Hamerness 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-PRS 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.

Discussion

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

Medication treatment for ADHD has been associated with minor mean elevations in blood pressure and heart rate (Hamerness 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-PRS 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.

Acknowledgements

The project described was supported by the National Center for Research Resources, Grant U1I RR024975-01, and is now at the National Center for Advancing Translational Sciences, Grant 2 U1I TR000445-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.