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A phenome-wide association study of polygenic scores for attention deficit hyperactivity disorder across two genetic ancestries in electronic health record data

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Abstract

Testing the association between genetic scores for Attention Deficit Hyperactivity Disorder (ADHD) and health conditions, can help us better understand its complex etiology. Electronic health records linked to genetic data provide an opportunity to test whether genetic scores for ADHD correlate with ADHD and additional health outcomes in a health care context across different age groups. We generated polygenic scores (ADHD-PGS) trained on summary statistics from the latest genome-wide association study of ADHD ($N = 55{,}374$) and applied them to genome-wide data from 12,383 unrelated individuals of African-American ancestry and 66,378 unrelated individuals of European ancestry from the Vanderbilt Biobank. Overall, only Tobacco use disorder (TUD) was associated with ADHD-PGS in the African-American ancestry group (Odds ratio [95% confidence intervals] = 1.23[1.16–1.31], $p = 9.3 \times 10^{-09}$). Eighty-six phenotypes were associated with ADHD-PGS in the European ancestry individuals, including ADHD (OR[95%CIs] = 1.22[1.16–1.29], $p = 3.6 \times 10^{-10}$), and TUD (OR[95%CIs] = 1.22[1.19–1.25], $p = 2.8 \times 10^{-46}$). We then stratified outcomes by age (ages 0–11, 12–18, 19–25, 26–40, 41–60, and 61–100). Our results suggest that ADHD polygenic scores are associated with ADHD diagnoses early in life and with an increasing number of health conditions throughout the lifespan (even in the absence of ADHD diagnosis). This study reinforces the utility of applying trait-specific PGSs to biobank data, and performing exploratory sensitivity analyses, to probe relationships among clinical conditions.

1 | INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder, diagnosed in approximately 2–6% of children worldwide (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Visser et al., 2014) and is clinically characterized by difficulty controlling attention resulting in alternating hyper-attentional focus as well as inattentiveness, hyperactivity, and impulsivity. Unsupported ADHD can be associated with multiple adverse behavioral and psychosocial outcomes, including under employment and low income (Biederman & Faraone, 2006), substance use (Groenman et al., 2013), and obesity (Cortese, Faraone, Bernardi, Wang, & Blanco, 2013).

Similar to other neurodevelopmental conditions, ADHD is multifactorial, heterogeneous, and highly heritable (70–80%) (Faraone & Larsson, 2019), and both common and rare genetic variants are involved (Hamshere et al., 2013; Stergiakouli et al., 2012). The focus of our study is on common genetic variants. Genome-wide association studies (GWAS), have shown that thousands of genetic variants with small effect sizes are likely to contribute to ADHD (Demontis et al., 2019). Although individual loci have small effects, when aggregated into the form of genetic scores, their cumulative effect is greater (Purcell et al., 2009). On average, individuals with ADHD have higher genetic scores for ADHD compared with those without an ADHD diagnosis (Stergiakouli et al., 2012). Moreover, studies using information from the largest genome wide association (GWA) meta-analysis of ADHD (20,183 cases vs. 35,191 controls) found that high genetic scores for ADHD are also associated with a variety of other conditions including higher BMI, neuroticism, anxiety, depression, alcohol use, smoking, cognition (Du Rietz et al., 2018), bipolar disorder (Grigoroiu-Serbanescu et al., 2020), and eating disorder symptoms (Yao et al., 2019). Such findings suggest that genetic factors may be shared between these traits. However, it is also important to note that phenotypic hitchhiking (Dennis et al., 2019) and nongenetic influences on outcomes (such as socioeconomic status or experiences of discrimination), can also be reflected in genetic data (Abdellaoui et al., 2018) thus cautious interpretation of genetic scores is warranted.

Although polygenic scores (PGS) may eventually be implemented in clinical settings to aid in differential diagnostics and risk stratification (Middeldorp & Wray, 2018), the majority of studies have tested performance of PGS in highly ascertained research populations. Outside of research populations, one study examined associations between ADHD-PGS and health conditions in the Penn Medicine Biobank (Kember et al., 2021) by performing a phenome wide association study (PheWAS) (Denny et al., 2013) in an adult (>18 years) population. ADHD-PGS was positively associated with Tobacco Use Disorder (TUD) and its sequela, as well as type 2 diabetes, but was negatively associated with myopia, and health screenings for malignant neoplasms of the skin. It is possible that the negative associations with myopia and health screenings were due to potential confounding by socio-economic status.

Moreover, previous studies have tested the ADHD-PGS only in participants of European ancestry because the ADHD discovery GWAS was performed in European samples. The proportion of phenotypic variance explained of most PGSs is lower in populations that differ, even modestly, from the discovery population used to train the PGS. Poor cross-ancestry performance in turn raises concerns about exacerbating health inequalities (Palk, Dalvie, De Vries, Martin, & Stein, 2019). This is a challenge facing the genetics field, given that the majority of GWASs have been conducted in participants of European ancestry. It is therefore imperative to include non-European populations in GWAS and to develop new tools that maximize the accuracy of the PGS in populations of different ancestries (Davis, 2021).

We constructed ADHD-PGS using the latest ADHD GWAS summary statistics (Demontis et al., 2019) 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). This study had three aims including (1) confirmation of the association between ADHD-PGS and ADHD diagnosis in a pediatric and adult Electronic Health Records (EHR) setting; (2) identification of the medical conditions that are associated with ADHD-PGS across age; and (3) conditional analyses to determine whether these associations remain after adjusting for socioeconomic and clinical risk factors. With regards to the age-stratified analyses, we expected to identify differences in associations with medical phenotypes for which age is an important risk factor (i.e., cardiometabolic traits), but stability among diagnostic rates for mental health conditions.

2 | MATERIALS AND METHODS

2.1 | Vanderbilt University medical center (VUMC) sample

The project was approved by the VUMC Institutional Review Board (IRB #190418). The study was conducted using the Synthetic Derivative (SD) database at VUMC, a de-identified version of the entire VUMC EHR, including records of 3.2 million individuals. DNA has been collected from over 250,000 of these participants, extracted from discarded blood and linked to de-identified clinical data that is deposited in BioVU (Vanderbilt's Biobank) (Roden et al., 2008).

2.2 | Genotyping and quality control

Individuals included in our sample were genotyped on the MEGA^{EX} platform. The quality control process has been described elsewhere (Dennis et al., 2021). Genotype imputation was performed using the Michigan Imputation Server (Das et al., 2016) and the Haplotype Reference Consortium (HRC) reference panel. Variants with low imputation quality (i.e., $R^2 < 0.3$) were removed. Single Nucleotide Polymorphisms (SNPs) with a minor allele frequency <0.005 were removed, as well as SNPs with genotyping rates <0.98, and individuals with call rates <0.98. We also removed SNPs with a Hardy–Weinberg Equilibrium P value $<10e^{-10}$. We filtered the sample for cryptic relatedness by removing one individual of each pair for which pihat > 0.2. Ancestry components were calculated to define individuals of primarily European or African ancestry. This resulted in a total of 12,383 African American ancestry and 66,378 European ancestry samples for analysis.

2.3 | Polygenic scores

We generated PGS trained on the latest ADHD GWAS from the Psychiatric Genomics Consortium for each individual in BioVU (Demontis et al., 2019). Training data included 20,183 cases and 35,191 controls of European ancestry. The BioVU sample included 12,383 individuals (39% males, median age of record [SD] = 38.5 [21.1]), of African American Ancestry and 66,378 individuals (44% males, median age of record [SD] = 48.2 [22.3]) of European ancestry. The PGS per individual was computed by applying a continuous shrinkage prior (CS) to SNP effect sizes using the PRS_CSx software (Ruan et al., 2022) for the African American ancestry individuals, and the PGS_CS software for the European ancestry individuals (Ge, Chen, Ni, Feng, & Smoller, 2019). We chose the PRS_CS, and its extension, the PRS_CSx software because they have been shown to outperform other approaches for a variety of traits, and different genetic architectures (Ge et al., 2019; Ruan et al., 2022). Moreover, PRS_CSx, has also been shown to robustly improve the predictive accuracy of the PGS in non-European populations, by jointly modeling the GWAS summary statistics from different populations (Ruan et al., 2022).

2.4 | Phenotypes

We mapped International Classification of Diseases 9th and 10th edition (ICD-9 and ICD-10) billing codes in the EHR to 1,533 phecodes, which represent higher order phenotypic categories, according to the Phecode map 1.2b1 (Denny et al., 2010). ADHD was defined by the phecode 313.1, and TUD was defined by the phecode 318. We used the PheWAS R package version v 0.99.5-2. We required each phecode to have a sample size of at least 50 cases for inclusion in the analysis. The PheWAS package also generates phecode groups, which are combinations of ICD-9 and ICD-10 codes that represent groups that are more closely related in terms of disease and etiology. For details see: https://phewascatalog.org and (Denny et al., 2010).

To covary for socioeconomic status we included the Area Deprivation Index (ADI) variable (Liu et al., 2021). The variable was derived using six different census-related variables: (1) the fraction of households with income below poverty level, (2) the median household income, (3) fraction of population 25 and older with at least a high school graduation or General Education Diploma equivalency, (4) fraction of population without insurance coverage, (5) fraction of households that receive public assistance income or food stamps or Supplemental Nutrition Assistance Program, and (6) fraction of houses that are vacant (Brokamp et al., 2019).

2.5 | Statistical analysis

We standardized the ADHD PGS to have a mean of 0 and a standard deviation of 1 and used it as the predictor variable in PheWAS analyses. We covaried each analysis for sex, median age of the patients' medical record, current age (to adjust for cohort effects), and the first 10 principal components calculated from genetic data (to adjust for genetic ancestry). Results were considered statistically significant if they passed Bonferroni correction ($p < 2.1 \times 10^{-05}$) for $n = 2{,}419$ tests ($n = 886$ tests in the African American Ancestry population and 1,533 in the European ancestry population). We did not perform any further analyses in the African American ancestry sample, given a lack of significant associations.

For the European ancestry sample, we performed follow-up conditional analyses adjusting for (1) ADHD diagnosis and commonly used ADHD medications (i.e., amphetamine, dextroamphetamine, lisdexamfentamine, dexmethylephenidate, methamphetamine, methylphenidate [and their respective brand names]), (2) tobacco use disorder, and (3) ADI.

We then performed sensitivity analyses to examine associations within different age groups and by sex. In the first sensitivity analysis we stratified the sample to the following age bins: 0–11 (childhood), 12–18 (adolescence), 19–25 (young adulthood, and college-age students), 26–40 (adulthood), 41–60 (middle age), 61–100 (older adulthood), and adjusted for sex, median age across the EHR, current age, and the first 10 principal components of genetic ancestry. We separated adolescence from young adulthood using 18 and 19 years old as the threshold, to reflect the change from pediatric to adult clinics.

Next, we performed a sex-stratified PheWAS in the European ancestry and African American ancestry samples. From this set of results, we prioritized phenotypes with a main effect in at least one sex and returned to the sex-combined analysis to test whether there were significant differences in the ORs between males and females by performing an interaction test (Sex * PGS).

We further explored a sex-specific association with pregnancy complications detected in the sensitivity analysis. We first constructed a variable that included individuals with at least one pregnancy complication ICD code (https://www.questdiagnostics.com/dms/Documents/Other/ICD-10-CPT-2015/38365-v1-ICD_9-10_Codes_for_OBGYN-MI3859-090915.pdf). We then restricted the sample to EHR recorded female sex between the ages of 12–25 (representing the age bins from the PheWAS in which the association was detected) and performed three separate logistic regression analyses. We fitted a logistic regression model to the data to test the relationship between ADHD genetic risk and pregnancy complications after adjusting for median age at record, age at delivery, and the top 10 principal components generated from genetic data. We then performed additional analyses to account for ADHD diagnosis, and ADHD medication.

3 | RESULTS

3.1 | Phenome wide association study

A total of 12,383 unrelated individuals (39% males, median age of record [SD] = 38.5 [21.1]), of African American ancestry, were including in the PheWAS. The ADHD-PGS was significantly associated with TUD (Odds ratio [95% confidence intervals] = 1.23 [1.16–1.31], $p = 9.3 \times 10^{-09}$) (Supplementary Table 1). No other associations

reached phenome-wide significance. However, there was a strong correlation in the magnitude and direction of ORs for nominally associated phenotypes ($p = .05$) identified in the African ancestry analysis compared with the European ancestry analysis (Spearman Rho = 0.30, $p = 9.6 \times 10^{-08}$).

Further, we separately analyzed data from 66,378 unrelated individuals (44% males, median age of record [SD] = 48.2 [22.3]) of European ancestry. Similar to the African American ancestry sample, the most statistically significant association was TUD (OR[95% CI] = 1.22[1.19–1.25], $p = 2.8 \times 10^{-46}$). The ADHD-PGS also significantly associated with the diagnosis of ADHD (OR[95%CI] = 1.22 [1.16–1.29], $p = 3.6 \times 10^{-10}$) (Supplementary Table 2). Overall, 86 phecodes (5.6% of the phenome) were significantly associated with ADHD-PGS ($p < 2.1 \times 10^{-5}$) (Figures 1–3 and Table 1). The largest effect size was observed for posttraumatic stress disorder (PTSD) (OR[95%CI] = 1.30[1.23–1.36], $p = 6.2 \times 10^{-16}$). Other significant associations included type 2 diabetes (OR[95%CI] = 1.11[1.08–1.13], $p = 2.3 \times 10^{-17}$), obesity (OR[95%CI] = 1.11[1.08–1.14], 5.8×10^{-14}), and chronic airway obstruction (OR[95%CI] = 1.18 [1.14–1.21], $p = 1.5 \times 10^{-23}$). Table 2 shows the top associations per phecode group. For instance, type 2 diabetes was the strongest association in the Endocrine/Metabolic group of diagnoses, TUD was the

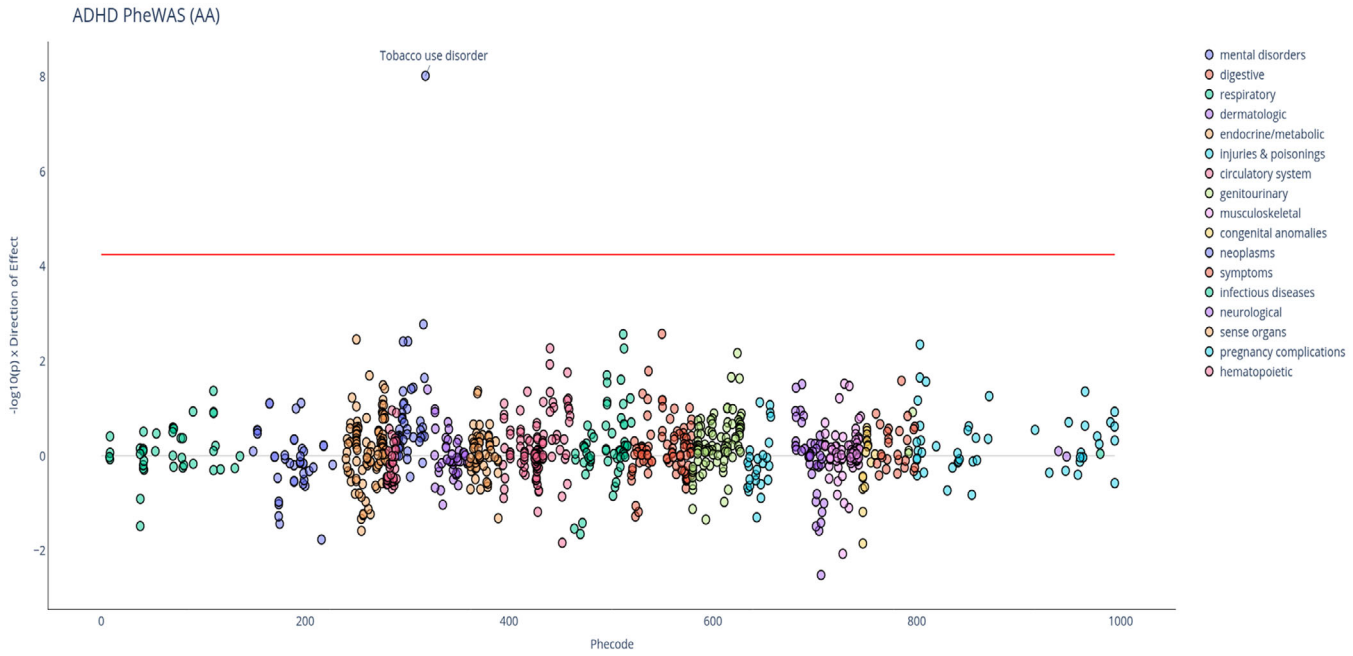

FIGURE 1 PheWAS plot of genetic liability to ADHD in subjects of African American genetic ancestry

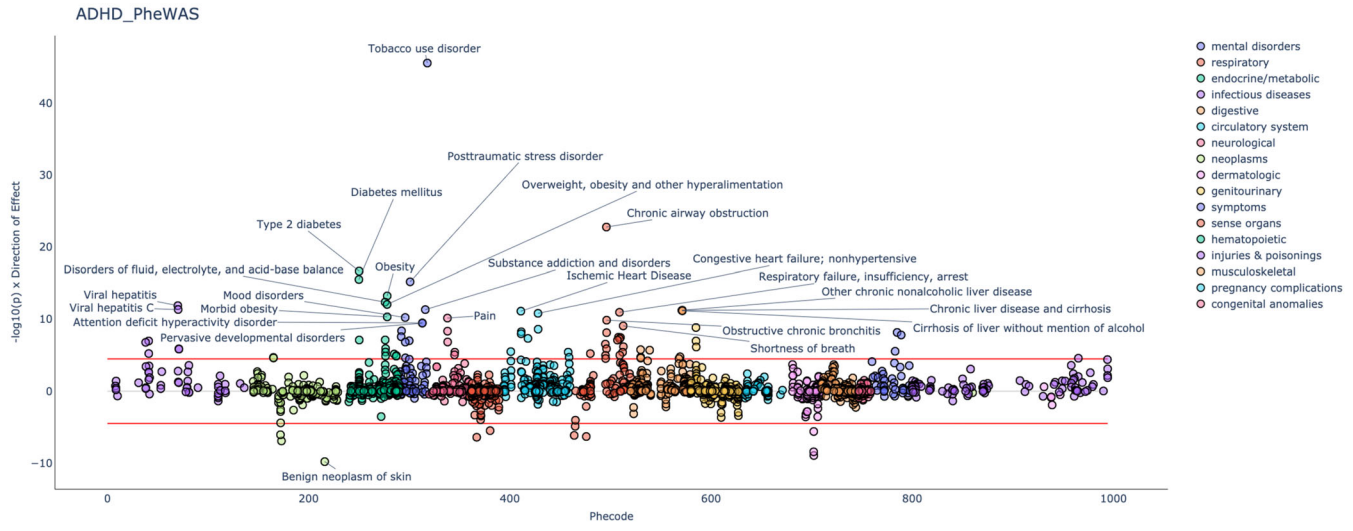

FIGURE 2 PheWAS plot of genetic liability to ADHD in subjects of European genetic ancestry

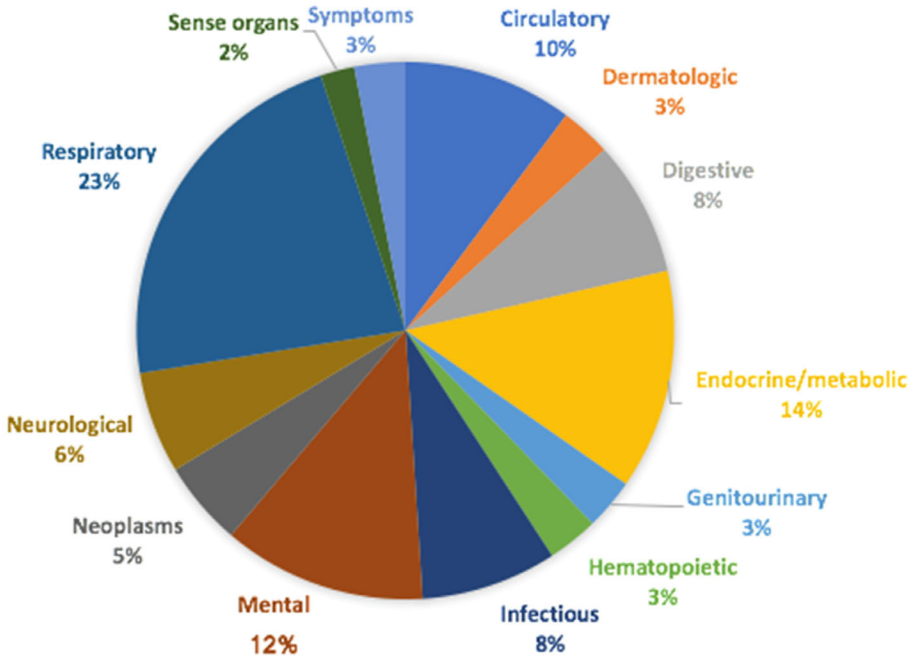

FIGURE 3 Pie chart of phecode groups associated with genetic liability to ADHD

TABLE 1 Summary of number of diseases per phecode group

Genetic liability to ADHD was associated with higher risk of the following medical problems:
9 diseases of the circulatory system (e.g., ischemic heart disease, hypertension)
7 diseases of the digestive system (e.g., bariatric surgery, diseases of the esophagus)
11 diseases of the endocrine/metabolic system (e.g., type 2 diabetes, obesity)
3 diseases of the genitourinary system (e.g., renal failure)
7 infectious diseases (e.g., viral hepatitis, septicemia)
10 mental disorders (e.g., tobacco use disorder, mood disorders)
5 neurological disorders (e.g., chronic pain, convulsions)
19 disorders of the respiratory system (e.g., asthma, pneumonia)
3 symptoms (e.g., nausea and vomiting, abdominal pain)
3 hematopoietic (e.g., thrombocytopenia, acute posthemorrhagic anemia)
Genetic liability to ADHD was associated with lower risk of the following medical problems:
3 dermatologic diseases (e.g., seborrheic keratosis, actinic keratosis)
2 diseases affecting the sense organs (i.e., myopia, impacted cerumen)
3 neoplasms (i.e., benign neoplasm of skin, neoplasm of uncertain behavior or skin)

strongest in the mental health group of diagnoses, and chronic airway obstruction was the strongest in the respiratory group of diagnoses. Negative associations were also observed, replicating previous results including reduced diagnosis of benign neoplasm of skin (OR[95% CI] = 0.86[0.82–0.91], $p = 1.6 \times 10^{-10}$), seborrheic keratosis (OR [95%CI] = 0.88[0.84–0.92], $p = 1.2 \times 10^{-09}$), and myopia (OR[95% CI] = 0.87[0.82–0.93], $p = 3.9 \times 10^{-07}$).

3.2 | Conditional PheWAS

To determine whether the phenome-wide ADHD-PGS associations were influenced by (a) treatment for ADHD, (b) confounding with socio-economic variables, or (c) comorbidity, we repeated the PheWAS with additional covariates for (a) ADHD diagnosis and medications commonly prescribed for ADHD (see Methods for the complete list), (b) ADI, and (c) TUD. These analyses were only conducted in the European ancestry sample. After controlling for the ADHD diagnosis and medications, 90% ($N = 77$) of the associations remained virtually unchanged (Figure 4a and Supplementary Table 3). After adjustment for ADI, two thirds of the original associations remained unchanged. The remaining one third of the associations that changed, include but are not limited to hypertension, and myopia which were no longer significantly associated with the ADHD-PGS (Supplementary Table 4) after controlling for ADI. Finally, when adjusting 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 4b and Supplementary Table 4). Among the findings that remained significantly associated were type 2 diabetes (OR[95%CI] = 1.09[1.07–1.12], $p = 1.4 \times 10^{-12}$), PTSD (OR[95%CI] = 1.25[1.18–1.32], $p = 3.9 \times 10^{-10}$), obesity (OR[95%CI] = 1.10[1.07–1.13], $p = 4.5 \times 10^{-10}$) and pervasive developmental disorders (OR[95% CI] = 1.19[1.13–1.24], $p = 9.3 \times 10^{-10}$). On the other hand, mood

TABLE 2 Top associations per phecode group

Group	Diagnosis	OR	Lower 95% CI	Upper 95% CI	*p* value
Circulatory system	Ischemic heart disease	1.09	1.06	1.11	8.1×10^{-12}
Dermatologic	Seborrheic keratosis	0.88	0.84	0.92	1.2×10^{-09}
Digestive	Other chronic nonalcoholic liver disease	1.14	1.10	1.17	5.4×10^{-12}
Endocrine/metabolic	Type 2 diabetes	1.11	1.08	1.13	2.3×10^{-17}
Genitourinary	Renal failure	1.08	1.05	1.10	1.3×10^{-09}
Infectious diseases	Viral hepatitis	1.22	1.16	1.27	1.4×10^{-12}
Mental disorders	Tobacco use disorder	1.22	1.19	1.25	2.8×10^{-46}
Hematopoietic	Acute posthemorrhagic anemia	1.08	1.04	1.11	6.8×10^{-06}
Neoplasms	Benign neoplasm of skin	0.86	0.82	0.91	1.6×10^{-10}
Neurological	Pain	1.08	1.06	1.11	7.3×10^{-11}
Respiratory	Chronic airway obstruction	1.18	1.14	1.21	1.5×10^{-23}
Sense organs	Myopia	0.87	0.82	0.93	3.9×10^{-7}
Symptoms	Abdominal pain	1.06	1.04	1.08	7.9×10^{-9}

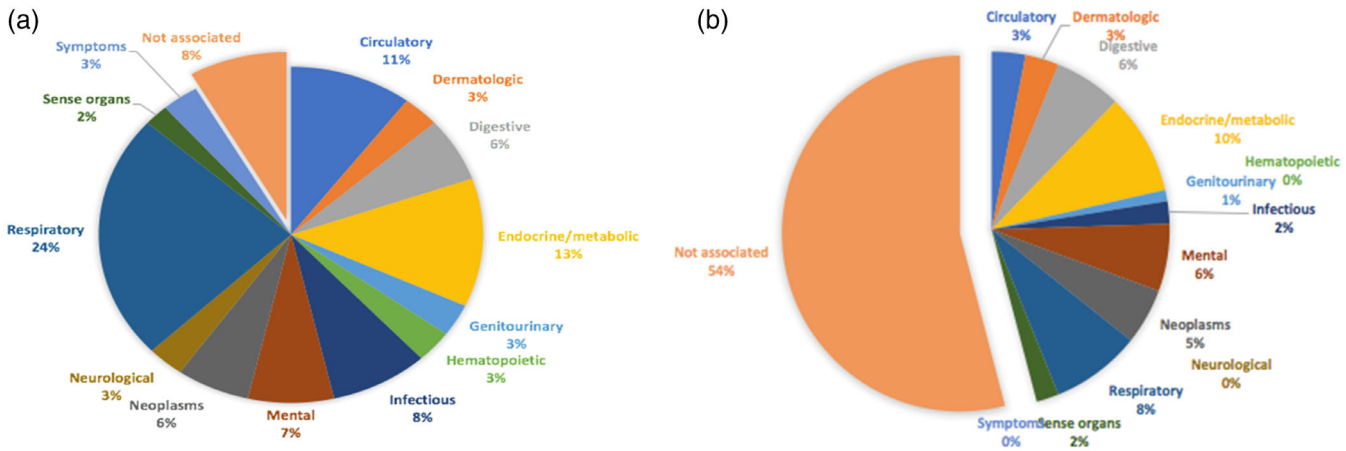

FIGURE 4 Pie charts of phecode categories associated with genetic liability to ADHD, (a) adjusted for ADHD diagnosis and medication; and (b) adjusted for TUD

disorders and substance addiction disorders were no longer significant associated with ADHD-PGS.

3.3 | Age-stratified PheWAS

To test the associations between ADHD-PGS and medical phenotypes present during different ages, we stratified phecodes from each medical record by age at code assignment. It is important to note that the different age groups may include overlapping samples. For example, data from a 30-year old with 15 years-worth of medical records would be included in the 12–18, 19–25, and 26–40 age bins, but only the codes that they received during those ages would be included in each respective age binned analysis. This is an approach that allows us to test for associations of ADHD PGS with age.

3.3.1 | 0–11 years old

A total of 8,463 individuals were included in this analysis (50% males, median age of record[SD] = 8.5[6.4]). For the ages 0 to 11, the ADHD-PGS was significantly associated with ADHD (OR[95% CI] = 1.27[1.16–1.37], $p = 7.5 \times 10^{-6}$). No other significant associations were identified (Supplementary Table 6 and Supplementary Figure 1).

3.3.2 | 12–18 years old

For the patients between the ages of 12 and 18, a total of 6,921 individuals were included (41% males, median age of record[SD] = 16.1 [6.4]). Again, the ADHD-PGS was only significantly associated with

ADHD (OR[95%CI] = 1.31[1.20–1.42], $p = 1.7 \times 10^{-6}$) (Supplementary Table 7 and Supplementary Figure 2).

3.3.3 | 19–25 years old

A total of 7,248 individuals (31% males, median age of record [SD] = 24.1[6.6]) were included in the analysis. Early or threatened labor; hemorrhage in early pregnancy was the most significant association observed (OR[95%CI] = 1.38[1.27–1.49], $p = 5.0 \times 10^{-09}$), followed by TUD (OR[95%CI] = 1.49[1.35–1.63], $p = 1.6 \times 10^{-08}$) (Supplementary Table 8 and Supplementary Figure 4). While ADHD was not significantly associated with the ADHD-PGS in this age group, the OR (95% CI) of 1.30 (1.12–1.48) was similar to that observed at younger ages (Supplementary Table 12).

3.3.4 | 26–40 years old

A total of 15,464 individuals (32% males, median age of record = 36.5 [8.4]) were included in the analysis. TUD was the most significant association (OR[95%CI] = 1.29[1.22–1.36], $p = 2.1 \times 10^{-12}$). Pregnancy complications were no longer associated, and complex chronic diseases and psychiatric disorder associations began to emerge, including type 2 diabetes (OR[95%CI] = 1.19[1.11–1.27], $p = 9.6 \times 10^{-06}$) and PTSD (OR[95%CI] = 1.33[1.21–1.44], $p = 1.0 \times 10^{-6}$) (Supplementary Table 9 and Supplementary Figure 4). Within this age group, ADHD was not associated with ADHD-PGS (OR[95%CI] = 1.05[0.09–1.20], $p = 5.25 \times 10^{-01}$) (Supplementary Table 12).

3.3.5 | 41–60 years old

A total of 31,399 individuals (44% males, median age of record [SD] = 53.6[8.9]) were included in the analysis. The ADHD-PGS was associated with 39 phecodes. TUD remained the strongest association in the age-group (OR[95%CI] = 1.25[1.21–1.29], $p = 2.1 \times 10^{-29}$) (Supplementary Table 10 and Supplementary Figure 5). Other significant associations included chronic airway obstruction (OR[95%CI] = 1.22[1.16–1.27], $p = 3.3 \times 10^{-13}$), type 2 diabetes (OR[95%CI] = 1.12[1.08–1.15], $p = 9.0 \times 10^{-11}$), viral hepatitis C (OR[95%CI] = 1.24[1.17–1.30], $p = 2.9 \times 10^{-10}$), and chronic liver disease and cirrhosis (OR[95%CI] = 1.16[1.11–1.20], $p = 4.6 \times 10^{-10}$). Associations with the largest effect sizes were opiates and related narcotics causing adverse effects in therapeutic use (OR[95%CI] = 1.34[1.22–1.47], $p = 6.7 \times 10^{-06}$), PTSD (OR [95%CI] = 1.34[1.23–1.44], $p = 5.0 \times 10^{-08}$), and HIV infection symptomatic (OR[95%CI] = 1.27[1.18–1.36], $p = 4.8 \times 10^{-07}$). Within this age group, ADHD was not associated with ADHD-PGS (OR[95%CI] = 1.16[1.01–1.31], $p = 5.91 \times 10^{-02}$) (Supplementary Table 12).

3.3.6 | 61–100 years old

A total of 26,868 individuals (49% males, median age of record [SD] = 68.8[8.2]) were included in the analysis. The ADHD-PGS was associated with 21 phecodes. Among the top significant associations were Chronic airway obstruction (OR[95%CI] = 1.18[1.14–1.22], $p = 3.8 \times 10^{-17}$), TUD (OR[95%CI] = 1.17[1.12–1.21], $p = 1.7 \times 10^{-12}$), type 2 diabetes (OR[95%CI] = 1.09[1.06–1.12], $p = 1.3 \times 10^{-08}$), ischemic heart disease (OR[95%CI] = 1.09[1.06–1.11], $p = 4.3 \times 10^{-08}$), myocardial infarction (OR[95%CI] = 1.12 [1.07–1.16], $p = 1.1 \times 10^{-06}$) (Supplementary Table 11 and Supplementary Figure 6). Obstructive chronic bronchitis yielded the largest effect size (OR[95%CI] = 1.21[1.13–1.28], $p = 8.5 \times 10^{-07}$), along with chronic airway obstruction, (OR[95%CI] = 1.18[1.14–1.22]) ($p = 3.8 \times 10^{-17}$). There were fewer than 50 patients with an ADHD diagnosis within this age group, thus ADHD was not assessed due to low power.

3.4 | Investigation of ADHD-PGS association with pregnancy complications

Given the novelty of the findings, we further explored associations between ADHD-PGS and pregnancy complications observed in the age bins 12–18, and 19–25. We restricted to female sex, combined the data from 12 to 25 years and combined the phecodes "Early threatened labor: hemorrhage in early pregnancy" and "Known or suspected fetal abnormality" into a single "pregnancy complications" factor. Motivated by prior literature, (Leppert et al., 2020), we found that ADHD-PGS was associated with younger age at delivery (adjusting for 10 PCs), ($b = -0.02$, $p = 2.4 \times 10^{-05}$). Based on this, we included an additional covariate for age at delivery which attenuated the association between ADHD-PGS and pregnancy complications (OR[95% CI] = 1.22[0.98–1.52], $p = .07$). We then further adjusted for ADHD diagnosis and ADHD medication (OR[95%CI] = 1.20[0.96–1.50], $p = .10$) which again, further reduced the association between ADHD-PGS and pregnancy complications.

3.5 | Sex-stratified PheWAS and interaction tests in the African American Ancestry and European Ancestry Samples

The ADHD-PGS was significantly associated with TUD in males of African American Ancestry (OR = 1.30, 95% CI: 1.19–1.41) (Supplementary Table 13). There were no phenome-wide significant associations between the ADHD PGS and the medical phenotypes tested within females. Furthermore, the interaction test yielded no significant differences.

Although the ADHD-PGS was significantly associated with a number of medical phenotypes within females and males in the European Ancestry group, after accounting for the different baseline

prevalence of these phenotypes, there were no significant differences in the strength of the associations between males and females (Supplementary Table 14).

4 | DISCUSSION

We generated polygenic scores of ADHD trained on summary statistics from the most recent Psychiatric Genomics Consortium (PGC) GWAS of ADHD and applied them to 12,383 individuals of African American ancestry and 66,378 unrelated individuals of European ancestry from the Vanderbilt Biobank. Within the African American ancestry group, which was significantly smaller than the EU ancestry sample, the only association that exceeded correction for multiple testing was tobacco use disorder. Within the European Ancestry group, 86 phenotypes (5.6% of the total medical phenome) were associated with the ADHD-PGS, including ADHD itself. We replicated previous findings observed in research ascertained samples, including associations with smoking, higher BMI (Du Rietz et al., 2018), and type 2 diabetes (Demontis et al., 2019).

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., 2021) and UK Biobanks (Leppert et al., 2020). Although we observed 86 phenotypes associated with the PGS in the European ancestry sample, TUD was the only significant association in the African-American ancestry population. The most likely explanation for the lack of associations in the African-American ancestry population, is that the sample size was approximately five times smaller than that of the European ancestry population. Potential loss of power can also be attributed to the lack of large GWAS of ADHD in an African ancestry sample and the failure of European ancestry GWAS to fully capture linkage disequilibrium (LD) patterns specific to non-European populations. Future studies, in larger samples are needed to replicate our findings and to examine whether there may be other medical phenotypes that may be related with ADHD-PGS in participants of African American ancestry.

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 including type 2 diabetes, obesity, and PTSD, while associations to mood disorders, and substance addiction disorders were no longer significant.

Medication treatment for ADHD has been associated to minor mean elevations in blood pressure and heart rate (Hammerness, Karampahtsis, Babalola, & Alexander, 2015). Safety concerns have been raised related to risk for adverse cardiovascular outcomes, including myocardial infarction (MI) and stroke (Westover & Halm, 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 myocardial infarction, and hypertension and when we adjusted for ADHD medication, the associations did not change. However, when we adjusted for TUD, the ORs for myocardial infarction and hypertension dropped from 1.11 and 1.05 unadjusted, to 1.07 and 1.02, respectively. These results indicate that smoking may be a greater risk factor for MI and hypertension than stimulant medication use, in our hospital population.

Finally, we also identified novel associations, with phenotypes including pregnancy complications, respiratory illness, and PTSD, and replicated the findings from a previous study in the Penn Biobank (Kember et al., 2021), including negative associations with myopia. On conditional analysis we found that the association with pregnancy complications were primarily explained by age of the mother at delivery, respiratory illness was explained by tobacco use, and myopia was explained by area-level deprivation. These findings suggest that some PGS associations are likely to be health consequences of risk factors that can be correlated with diagnosed or undiagnosed ADHD (i.e., smoking, underemployment and lower socioeconomic status), while others may be due to pleiotropic genetic risk.

5 | ADHD GENETIC RISK ACROSS THE LIFESPAN

Our study is the first to examine associations between ADHD genetic scores and health outcomes over the lifespan in a clinical setting. As expected, we found that ADHD genetic score was most strongly associated with ADHD diagnosis in childhood. The lack of significant associations with ADHD in the adult groups is most likely due to lack of power in these age groups as the number of adults with an ADHD diagnosis drops almost in half this of the pediatric sample (Supplementary Table 12). Moreover, decreases in the OR are not observed until middle age when the number of cases proportional to controls drops by an order of magnitude.

Furthermore, we found that the number of associations between ADHD-PGS and adverse health outcomes increased with age, indicating that the effects of genetic liability to ADHD may have direct and indirect long-term effects on health. Our results suggest that ADHD genetic liability may increase risk for health concerns even in the absence of an ADHD diagnosis, given that when we adjusted for ADHD diagnosis and medication, 90% of the associations remained unchanged. However, only 33% of the total patient sample with ADHD were assigned an ICD ADHD code at some point in adulthood and many adults in our sample do not have childhood records available. Therefore, the ADHD covariate may not be equally informative across age groups. The long term consequences of ADHD include risk for substance and tobacco use (Lee, Humphreys, Flory, Liu, & Glass, 2011), mood disorders (Chen et al., 2014) as well as obesity (Hodgkins et al., 2012; Kaisari, Dourish, & Higgs, 2017), all of which were associated with high ADHD-PGS in our study. Finally, as expected, we found differences by age in associations with medical phenotypes that increase in prevalence with age. For instance, congestive heart failure only appeared as a significant association in individuals over 40 years old. On the other hand, mental health diagnoses were consistently associated with ADHD-PGS across age groups.

6 | CLINICAL IMPLICATIONS

Individuals with ADHD are more likely to smoke regularly (Lambert & Hartsough, 1998; Pomerleau, Downey, Stelson, & Pomerleau, 1995), start smoking earlier (Kollins, McClernon, & Fuemmeler, 2005; Milberger, Biederman, Faraone, Chen, & Jones, 1997), have more severe nicotine dependence (Wilens et al., 2008), have greater difficulty quitting smoking (Covey, Manubay, Jiang, Nortick, & Palumbo, 2008), and experience more intense withdrawal symptoms (Rhodes et al., 2016) than individuals without ADHD. There are several explanations consistent with these findings, including genetic pleiotropy, or bidirectional causality (Treur et al., 2019). For instance, there are genetic correlations between ADHD and smoking (Demontis et al., 2019; Vilar-Ribó et al., 2021) as well as nicotine dependence (Vink, Treur, Pasman, & Schellekens, 2020). Moreover, there is evidence that specific variants within the neuronal nicotinic-acetylcholine receptor (nAChR) complex genes that are associated with smoking are also related to ADHD (Lee, Fuemmeler, McClernon, Ashley-Koch, & Kollins, 2013; Polina et al., 2014). It has been further hypothesized that individuals with ADHD may receive therapeutic benefit from nicotine (Bekker, Böcker, van Hunsel, van den Berg, & Kenemans, 2005; Gray & Upadhyaya, 2009; Poltavski & Petros, 2006) which may increase rates of smoking and negatively impact cessation efforts. Our study suggests that the linkages between smoking and ADHD may extend beyond diagnosed ADHD to also include those with high genetic liability to ADHD.

Our findings underscore the importance of considering neurodiversity in a general medicine clinical setting. For instance, smoking cessation programs that are tailored for individuals with ADHD or a broader neurodiverse population could have a significant impact on reducing health disparities among individuals with differences in neurodevelopment. Our finding that two-thirds of the health conditions were no longer significant after adjusting for TUD highlights the broad sequelae and health risks may be primarily driven by high rates of smoking in individuals with ADHD and suggests benefit to providing tailored smoking cessation strategies to support individuals with ADHD, subclinical ADHD symptoms, and even high ADHD-PGS. Finally, the fact that that genetic liability for ADHD was associated with 6% of the medical phenome provides further evidence towards the importance of including mental health in treatment and intervention designs to adopt strategies that work for all.

7 | STUDY LIMITATIONS

Given that ADHD genetic score is associated with different psychiatric conditions during the course of human development, it is useful to adopt a developmental perspective in the genetic epidemiology of psychiatric conditions (Thapar & Riglin, 2020). One limitation of our study is that BioVU is not representative of the general population, as genotyped participants are typically ascertained for health care usage and tend to be older and insured. Also, although we attempted to test the associations between ADHD PGS and diagnoses registered in the EHR in the African American ancestry sample, our sample size is still relatively small especially compared with the sample size for the European Ancestry populations. Another limitation is that there were sample size differences across the age groups, which could have affected our power to detect associations in the younger compared with the older groups. Our results are impacted by power limitations, both in the discovery sample GWAS and the target sample. Finally, we did not test rare genetic influences, as these are not captured by the PGS.

8 | CONCLUSIONS

ADHD-PGS was associated with many diagnoses in the Vanderbilt biobank, including ADHD itself. We found that many associations with adverse health outcomes were mediated by smoking, which is a modifiable risk factor. Finally, our findings also suggest that smoking cessation strategies tailored for neurodiverse populations are needed and may improve outcomes even in individuals without an ADHD diagnosis.

AUTHOR CONTRIBUTIONS

Study conception and design: Maria Niarchou, Lea K. Davis. Data analysis: Maria Niarchou, Julia M. Sealock, Peter Straub. Interpretation of results: all authors. Draft manuscript preparation: Maria Niarchou, Lea K. Davis. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Due to data sharing restrictions related to privacy concerns in the EHR, the datasets generated from our hospital population will not be publicly available, however, all scripts used in the study are available upon request.

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SUPPORTING INFORMATION

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