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Associations between attention-deficit hyperactivity disorder genetic liability and ICD-10 medical conditions in adults: utilizing electronic health records in a Phenome-Wide Association Study

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Abstract

Background. Attention-deficit hyperactivity disorder (ADHD) is often comorbid with other medical conditions in adult patients. However, ADHD is extremely underdiagnosed in adults and little is known about the medical comorbidities in undiagnosed adult individuals with high ADHD liability. In this study we investigated associations between ADHD genetic liability and electronic health record (EHR)-based ICD-10 diagnoses across all diagnostic categories, in individuals without ADHD diagnosis history.

Methods. We used data from the Estonian Biobank cohort ($N = 111\,261$) and generated polygenic risk scores (PRS) for ADHD (PRS_{ADHD}) based on the ADHD genome-wide association study. We performed a phenome-wide association study (PheWAS) to test for associations between standardized PRS_{ADHD} and 1515 EHR-based ICD-10 diagnoses in the full and sex-stratified sample. We compared the observed significant ICD-10 associations to associations with (1) ADHD diagnosis and (2) questionnaire-based high ADHD risk analyses.

Results. After Bonferroni correction ($p = 3.3 \times 10^{-5}$) we identified 80 medical conditions associated with PRS_{ADHD}. The strongest evidence was seen with chronic obstructive pulmonary disease (OR 1.15, CI 1.11–1.18), obesity (OR 1.13, CI 1.11–1.15), and type 2 diabetes (OR 1.11, CI 1.09–1.14). Sex-stratified analysis generally showed similar associations in males and females. Out of all identified associations, 40% and 78% were also observed using ADHD diagnosis or questionnaire-based ADHD, respectively, as the predictor.

Conclusions. Overall our findings indicate that ADHD genetic liability is associated with an increased risk of a substantial number of medical conditions in undiagnosed individuals. These results highlight the need for timely detection and improved management of ADHD symptoms in adults.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a highly heritable common neurodevelopmental disorder with a worldwide prevalence of about 5% among school-aged children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Although the onset of ADHD is typically in childhood, ADHD often persists in adulthood. It has been shown that at least 15% of children with ADHD meet diagnostic criteria for ADHD also in adulthood (Faraone, Biederman, & Mick, 2006). The average prevalence of ADHD in adults has been found to be 3–4% (Fayyad et al., 2007). However, ADHD in adults is often underdiagnosed and/or untreated, which may lead to negative psychosocial and health consequences (Ginsberg, Quintero, Anand, Casillas, & Upadhyaya, 2014). Evidence from previous studies has shown substantial comorbidity between ADHD and both psychiatric and somatic medical conditions, e.g. hypertension, migraine, obesity, and type 2 diabetes, in adulthood (Brikell, Burton, Mota, & Martin, 2021; Chen et al., 2018; Kittel-Schneider et al., 2022). Yet, the comorbidities in undiagnosed or subclinical ADHD populations are less clear.

Although shared genetic factors have been implicated in explaining the link between ADHD and psychiatric outcomes (Brikell et al., 2021), little is known about the role of shared genetic mechanisms in ADHD and medical conditions. ADHD is highly heritable with an average heritability of 76% in twin studies (Faraone & Larsson, 2019; Faraone et al., 2005) and the heritability attributed to single nucleotide polymorphisms (SNPs) identified in large

genome-wide association studies (GWAS), e.g. SNP-heritability of 22% (Demontis et al., 2019). The genetic correlations based on the results of ADHD GWAS showed significant genetic overlap between ADHD and several mental health (e.g. depression, autism, subjective well-being, and neuroticism), as well as physical health traits and conditions (e.g. body mass index (BMI), obesity, HDL cholesterol, and type 2 diabetes) (Demontis et al., 2023, 2019). Another approach to investigate shared genetics across traits and disorders is by using polygenic risk scores (PRSs), which capture an individuals weighted sums of risk alleles as detected with a large-scale, independent GWAS (Lewis & Vassos, 2020). Currently, PRS for ADHD (PRS_{ADHD}) based on the GWAS explains up to 5.5% of variance in ADHD and individuals in the top 10% of this PRS show five times higher odds of ADHD compared to individuals in the lowest PRS decile (Demontis et al., 2019). Although many individuals with high PRS_{ADHD} will not have ADHD diagnosis, PRS_{ADHD} has still great potential to identify individuals with high ADHD genetic liability in populations with low ADHD prevalence, potentially expressing a higher degree of ADHD-like traits (e.g. impulsivity, inattention).

Despite the strong advantage of exploiting electronic health records (EHR) in medical genetics research in biobanks (Abul-Husn & Kenny, 2019) there are currently few available reports on the associations between PRS_{ADHD} and EHR-based medical diagnoses. Such studies would help to generate hypothesis about potential underlying mechanisms, e.g. shared genetic etiology, confounding, or causal effects seen in studies of ADHD and somatic health comorbidities. A phenome-wide association study (PheWAS) is a hypothesis-free approach that can be used to test associations between a single predictor (e.g. genetic variants, PRS, and diagnosis) and a wide range of phenotypes, such as the EHR data (Pendergrass et al., 2011). A PheWAS based on UK Biobank questionnaire and diagnosis data showed that PRS_{ADHD} was associated with several health-related traits (e.g. physical abuse, younger age at first sexual intercourse, smoking behavior, obesity, higher BMI, and several blood measures) (Leppert et al., 2020). Another EHR-based PheWAS in 10 000 Penn Medicine Biobank Cohort participants using more than 1800 phecodes over 6,6 years on average also found PRS_{ADHD} associations with medical conditions (e.g. tobacco use disorder, chronic airway obstruction, and type 2 diabetes) (Kember et al., 2021).

We aimed to take the hypothesis-free PheWAS approach in a large population-based biobank (Estonian Biobank; EstBB) to identify the associations between ADHD genetic liability and lifetime history of medical conditions based on ICD-10 diagnoses from EHRs in individuals without a history of ADHD diagnosis (PRS_{ADHD} analysis). Considering the sex differences in the prevalence of ADHD (Biederman, Faraone, Monuteaux, Bober, & Cadogen, 2004; Gaub & Carlson, 1997), we also investigated potential sex differences for the associations between PRS_{ADHD} and medical conditions. Additionally, we compared the direction and strength of the identified ICD-10 associations that passed multiple corrections to the associations between these medical conditions and EHR-based ADHD diagnosis (ADHD diagnosis analysis) as well as to the high ADHD risk based on an adult ADHD brief screening instrument (questionnaire-based ADHD analysis). Although existing evidence shows substantial comorbidity and genetic correlation between ADHD and depression, as well as depression and other medical conditions (Carney & Freedland, 2017; Demontis et al., 2023, 2019; Kan et al., 2016; Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017; Levey et al., 2021; Rajan et al., 2020), it is unknown to what degree depression may mediate ADHD-medical condition link in adults. Therefore, our secondary aim was to explore the mediation effect of depression in the identified PRS – medical condition associations.

Methods and materials

Study population

The Estonian Biobank (EstBB) is a large data-rich population-based biobank (Leitsalu et al., 2015), covering approximately 20% of the adult population in Estonia ($N = \sim 210\,000$; 66% females; mean birth year 1971). All EstBB participants have signed an informed consent form and provided blood samples for genotyping. The EHR data is regularly retrieved by linking to the national health databases and registries, such as the National Health Insurance Funds (NHIF) database, cause of death register, and hospital records. Estonia has universal health care, covering more than 95% of the population. The research project has obtained approval from the Estonian Council on Bioethics and Human Research. More details about the recruitment of participants can be found in Supplementary information.

Phenotype data

Medical conditions via ICD-10 diagnoses

Medical diagnosis data was drawn from the EHRs based on the NHIF´s database covering the period from 2004 to 2020. NHIF´s database is a nationwide system integrating data from all healthcare providers in Estonia. EHR data included 2004 ICD-10 codes, of which 489 were excluded as these were not medical diagnoses or were in a very low prevalence (online Supplementary Table S1). In total, 1515 phenotypes from all ICD-10 disease categories (online Supplementary Table S2) were included in the analyses. ADHD diagnosis was defined by ICD-10 diagnosis code F90 (including diagnoses F90.0, F90.1, F90.8, and F90.9).

High ADHD risk based on adult ADHD self-report scale

As a sensitivity analysis, we included self-reported ADHD symptoms score, measured with the modified Estonian version of Adult ADHD Self-Report Scale (ASRS v1.1) part A (Kessler et al., 2005). ASRS part A is a brief six-item screening questionnaire and items are assessed on Likert scale ranging from 0 to 4: 0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = very often. A score cutoff of 14 out of 24 represents individuals with higher risk for ADHD (Kessler et al., 2007). ASRS data in EstBB is available for 86 245 participants (Ojalo et al., 2024).

ADHD polygenic risk scores

To compute the PRS, the PRS-CS-auto algorithm was first used to apply a Bayesian regression framework to infer posterior effect sizes of SNPs by using the summary results from a large Psychiatric Genomics Consortium ADHD GWAS (Demontis et al., 2019) and an external linkage disequilibrium reference panel (Ge, Chen, Ni, Feng, & Smoller, 2019). Per-individual risks were further calculated with plink 2.0 (Chang et al., 2015). The PRS_{ADHD} was standardized for the PheWAS analysis and categorized into deciles for subsequent analyses to test differences in high v. low/middle genetic liability groups. Prior to the main

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analysis, we tested the association between PRS_{ADHD} and ICD-10 ADHD diagnosis history. The variance explained by the PRS_{ADHD} was computed by subtracting the Nagelkerke pseudo R2 from the full (PRS, birth year, recruitment year, sex, and 10 genetic principal components (PCs)) and the reduced (birth year, recruitment year, sex, and 10 PCs) logistic regression models. Details about the genotyping and imputation procedures in the EstBB can be found in Supplementary information.

Statistical analysis

Main analysis

PheWAS was implemented to test for the associations between PRS_{ADHD} and 1515 ICD-10 diagnosis codes in the undiagnosed subsample where all individuals with a history of ADHD diagnosis (F90*) were removed ($N = 464$). Individuals with ADHD diagnosis were excluded because compared to the PRS_{ADHD} analysis sample, they were significantly younger and had likely received treatment or other support to manage their ADHD-related risks. Analyses were performed as described in our pre-registered protocol (Haan, Krebs, Võsa, & Lehto, 2021). Analyses were conducted using logistic regression and adjusted for sex (except in sex-stratified analyses), birth- and recruitment year to adjust for birth cohort effects and different EstBB recruitment strategies used across two decades, and 10 PCs to adjust for genetic ancestry (except in secondary analyses). Relatedness was handled by excluding related individuals separately in the PRS_{ADHD} and ADHD diagnosis analysis samples (PI-HAT > 0.2) which remained 111 261 individuals in the PRS_{ADHD} analysis sample and 111 601 individuals in the ADHD diagnosis sample. Additionally, for comparison we ran the main analyses in the full cohort without excluding related individuals ($N = 196\,935$). We corrected for multiple testing by applying Bonferroni correction (p-value threshold 3.3×10^{-5}). PheWAS and mediation analyses were run in R (version 3.6.0). PheWAS results were visualized using the PheWAS library https://github.com/PheWAS/PheWAS. Other analyses were performed using Stata v.17.

PRS_{ADHD} deciles

We further examined the associations that survived the multiple testing correction in the PheWAS by using PRS_{ADHD} deciles (ranging from 10th to 90th percentiles) to explore the difference in the odds of being diagnosed with a specific medical condition in high *v.* low (10th *v.* 1st PRS decile) and in high *v.* middle (10th *v.* 5th PRS decile) ADHD genetic liability groups. While the difference in the top and bottom genetic liability groups reflects the differences between the two extreme ends of ADHD genetic liability, the top *v.* middle comparison reflects the differences between the highest and the population average ADHD genetic liability groups. Additionally, we explored sex differences in the top and bottom PRS decile analysis.

Secondary analyses

Comparison of effects across PRS_{ADHD}, ADHD diagnosis, and questionnaire-based ADHD analyses

To shed light on the different patterns in medical condition risk in biobank participants with high ADHD genetic liability but without an ADHD diagnosis, EHR-based ADHD diagnosis and clinically relevant ADHD symptoms, we conducted two sets of additional logistic regression analyses only on these medical outcomes that passed the multiple testing correction in the PRS_{ADHD} PheWAS analysis. First, we used the EHR-based ADHD diagnosis as the predictor and second, we used the questionnaire-based high ADHD risk as the predictor.

Causal mediation analysis with depression diagnosis

Considering the well-established link between depression, ADHD and more severe somatic health conditions, we ran causal mediation analysis for the identified phenotypes and included lifetime depressive episode diagnosis as a mediator. Lifetime depressive episode diagnosis was defined based on the ICD-10 diagnosis codes F32* and F33*. Causal mediation analysis was run using the R package ´mediation´ and 1000 simulations was used for calculating estimates (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014). Causal mediation analysis provides estimates for the average causal mediation effect, average direct effect, and total effect. Here we were interested in quantifying the proportion of effects on the medical conditions that were mediated by depression.

Results

A descriptive overview of the study samples is shown in Table 1. The main analysis study sample (PRS_{ADHD}) size was 111 261 individuals, after exclusion of related individuals ($N = 85\,674$), ADHD cases ($N = 464$), and individuals with missing EHR records ($N = 2887$). In total 65% of the study sample was female and the mean birth year was 1970. In the ADHD diagnosis analysis sample, the sample size was 111 601, of which 464 were diagnosed ADHD cases (0.5%). In the questionnaire-based ADHD sample, 3556 participants screened positive for high risk for ADHD (8%). Cross-group comparisons indicate that although the female–male ratio was similar in all three samples, individuals in the ADHD diagnosis analysis sample were considerably younger (mean birth year 1990) compared to the two other study samples (mean birth year 1970 for PRS_{ADHD} analysis sample and 1979 for questionnaire-based ADHD analysis sample).

PheWAS of PRS_{ADHD}

First, we tested the association of the PRS_{ADHD} with ADHD diagnosis (OR 1.34, CI 1.22–1.47) and questionnaire-based ADHD (OR 1.06, CI 1.02–1.09). Results indicate that 1 S.D. increase in PRS_{ADHD} corresponds to 34% increase in the odds of ADHD diagnosis and 6% increase in the odds of higher risk for self-reported questionnaire-based ADHD. PRS_{ADHD} explained 0.6% variance in EHR-based ADHD diagnosis and 0.04% in questionnaire-based high-risk ADHD.

Our PheWAS showed evidence of association between PRS_{ADHD} and for 80 ICD-10 diagnoses after correction for multiple testing (Figure 1, Table 2, Table S3). Overall, the top five medical conditions with the strongest evidence for associations were chronic obstructive pulmonary disease (COPD) (OR 1.15, CI 1.11–1.18), obesity (OR 1.13, CI 1.11–1.15), type 2 diabetes (OR 1.11, CI 1.09–1.14), dorsalgia (OR 1.08, CI 1.07–1.10), and polyarthrosis (OR 1.09, CI 1.07–1.12).

Sex-stratified analyses showed that for females, the top five associated medical conditions were obesity (OR 1.14, CI 1.11–1.16), polyarthrosis (OR 1.10, CI 1.08–1.13), medical abortion (OR 1.10, CI 1.08–1.13), dorsalgia (OR 1.09, CI 1.07–1.09), and headache (OR 1.08, CI 1.06–1.10). For males, the top five associated medical conditions were COPD (OR 1.17, CI 1.12–1.23), mental and behavioral disorders due to alcohol use (OR 1.11,

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Table 1. Descriptive overview of study samples

	PRS_{ADHD} analysis sample	ADHD diagnosis analysis sample Cases/controls	Questionnaire-based ADHD analysis sample* Cases/controls
N	111 261	464 (0.4%)/111 137 (99.6%)	3556 (8%)/41 152 (92%)
Sex			
Men	38 652 (35%)	283 (61%)/38 616 (35%)	917 (26%)/12 293 (30%)
Women	72 609 (65%)	181 (39%)/72 521 (65%)	2639 (74%)/28 859 (70%)
Birth year (mean, S.D.)	1970 (16.5)	1990 (10.3)/1971 (16.5)	1979 (13.3)/1972 (14.1)
Number of ICD-10 diagnoses (mean)	41	48/41	46/39
Education**			
Primary	7045 (9%)	61 (29%)/7040 (9%)	198 (7.6%)/1252(4.2%)
Secondary	38 092 (50%)	109 (52%)/38 261 (50%)	1225 (45.4%)/16 629 (42.8%)
Higher	31 790 (41%)	41 (19%)/31 763 (41%)	1239 (47%)/17 507 (53%)
Missing	34 334	253/34 284	894/8426
Depression diagnosis	19 997 (26%)	98 (46%)***/19 970 (26%)	1205 (45%)/7718 (24%)
ADHD diagnosis	0	464	44

Note: *Positive screening; **based on the complete set subset ($N_{ADHD\ PRS}$ = 76 927; $N_{ADHD\ diag}$ = 211/77 064; $N_{ADHD\ ASRS}$ = 2662/35 388), education was categorized as primary (1–4 grades, 5–9 grades, or no education; secondary (10–12 grades and vocational education); higher (university and research degree); ***data available for 211 participants in the ADHD diagnosis analysis sample and for 2662 participants who screened positive for ADHD in the questionnaire-based ADHD analysis sample; PRS, polygenic risk score; SD, standard deviation.

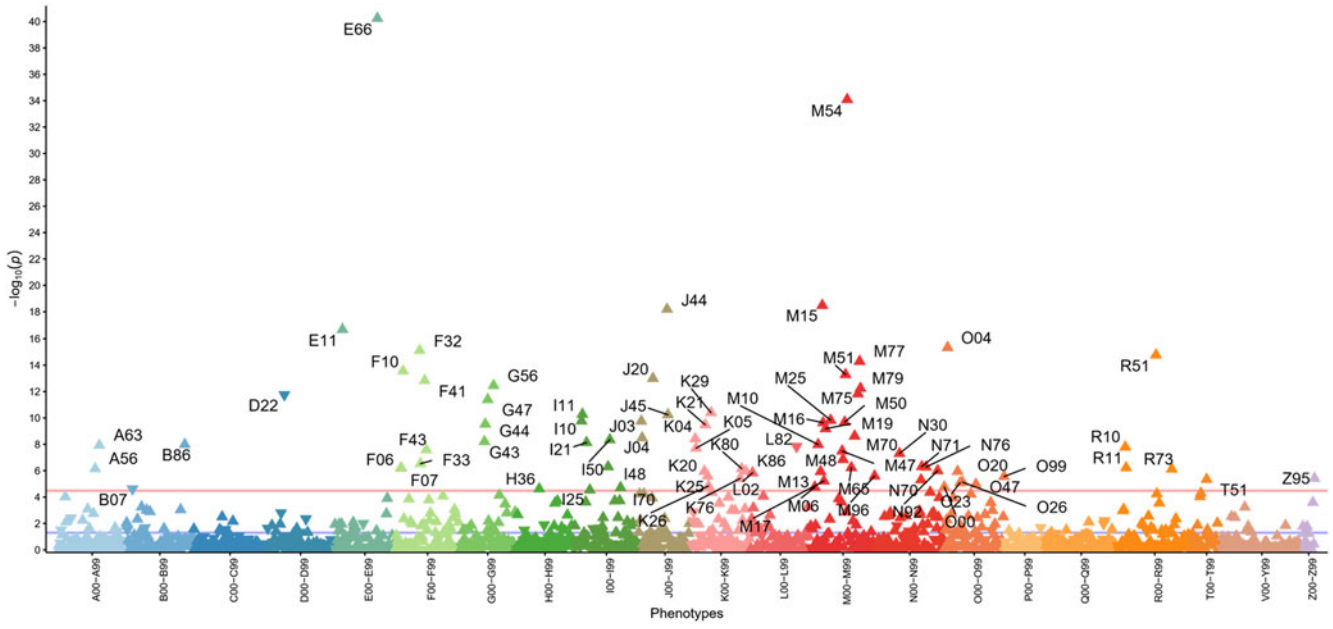

Figure 1. Associations between PRS_{ADHD} and ICD-10 codes after adjustment for multiple testing.
Note: The X axis indicates groups of ICD10 main codes colored respectively and Y axis $-\log_{10}$ of the *p* values. Each triangle in the plot represents one ICD-10 main code and the direction of the triangle represents direction of effect. Red line – Bonferroni-corrected significance level (3.3×10^{-5}). Phenotypes passed the Bonferroni correction from the lowest to highest *p*-values: E66, 'obesity'; M54, 'dorsalgia'; M15, 'polyarthrosis'; J44, 'chronic obstructive pulmonary diseases'; E11, 'non-insulin dependent diabetes'; O04, 'medical abortion'; F32, 'depressive episode'; R51, 'headache'; M77, 'other enthesopathies'; F10, 'mental and behavioral disorders due to use of alcohol'; M51, 'other intervertebral disc disorders'; J20, 'acute bronchitis'; F41, 'other anxiety disorders'; G56, 'mononeuropathies of upper limb'; M79, 'other soft tisuse disorders'; M75, 'shoulder lesion'; D22, 'melanocytic naevi'; G47, 'sleep disorders'; K29, 'gastritis and duodenitis'; I11, 'hypertensive heart disease'; J45, 'asthma'; M25, 'other joint disorders'; I10, 'primary hypertension'; J03, 'acute tonsillitis'; M50, 'cervical disc disorders'; M16, 'coxarthrosis'; G44, 'other headache syndromes'; K21, 'gastro-oesophageal reflux disease'; M19, 'other arthrosis'; M70, 'soft tissue disorders related to use, overuse and pressure'; J04, 'acute laryngitis and tracheitis'; K04, 'diseases of pulp and periapical tissues'; I50, 'heart failure'; G43, 'migraine'; I21, 'acute myocardial infarction'; B86, 'scabies'; M10, 'gout'; A63, 'other predominantly sexually transmitted diseases'; L82, 'seborrhoeic keratosis'; R10, 'abdonminal and pelvic pain'; K05, 'gingivitis and periodontal diseases'; F43, 'reaction to severe stress', M47, 'spondylosis'; N30, 'cystitis'; M48, 'other spondylopathies'; F33, 'recurrent depressive disorder'; N71, 'inflammatory disease of uterus'; I48, 'atrial inflammation of vagina and vulva'; M65, 'synovitis and tenosynovitis'; R11, 'nausea and vomiting'; F07, 'personality and behavioral disorders due to brain damage'; F06, 'other mental disorders due to brain damage'; A56, 'other sexually transmitted chlamydial diseases'; K80, 'cholelithiasis'; R73, 'elevated blood glucose level'; N92, 'excessive, frequent and irregulaar menstruation'; K86, 'other diseases of pancreas'; K20, 'oesophagitis'; O20, 'haemorrhage in early pregnancy'; M13, 'other arthritis'; L02, 'cutaneous abscess, furuncle and carbuncle'; M96, 'postprocedural musculoskeletal disorders'; K25, 'gastric ulcer'; O99, 'other maternal diseases'; Z95, 'presence of cardiac and vascular implants and grafts'; K76, 'other diseases of liver'; T51, 'toxic effect of alcohol'; N70, 'salpingitis and oophoritis'; M17, 'gonarthrosis'; O26, 'maternal care for other conditions related to pregnancy'; O23, 'infections of genitourinary tract in pregnancy'; O47, 'false labor'; K26, 'duodenal ulcer'; O00, 'ectopic pregnancy'; M06, 'other rheumatoid arthritis'; I70, 'atherosclerosis'; H36, 'retinal disorders in diseases classified elsewhere'; B07, 'viral warts'; I25, 'chronic ischaemic heart disease'.

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Table 2. Associations between PRS_{ADHD} and ICD-10 codes after adjustment for multiple testing

ICD code	*n*	OR	Lower CI	Upper CI	*p*-Value	ICD code name
A56	4804	1.078	1.047	1.111	6.98E−07	Other sexually transmitted chlamydial diseases
A63	14 384	1.055	1.036	1.075	1.17E−08	Other sexually transmitted diseases
B07	11 535	0.958	0.939	0.977	2.37E−05	Viral warts
B86	3132	1.111	1.072	1.152	1.02E−08	Scabies
D22	24 852	0.950	0.935	0.963	1.73E−12	Melanocytic naevi
E11	8102	1.111	1.085	1.139	1.98E−17	Non-insulin-dependent diabetes mellitus
E66	15 121	1.128	1.108	1.148	5.73E−41	Obesity
F06	2766	1.104	1.062	1.148	6.55E−07	Mental disorders due to brain damage and dysfunction
F07	981	1.176	1.103	1.253	6.22E−07	Behavioral disorders due to brain damage
F10	4,43	1.127	1.093	1.162	2.79E−14	Mental and behavioral disorders due to use of alcohol
F32	25 438	1.061	1.046	1.076	7.85E−16	Depressive episode
F33	8957	1.059	1.036	1.083	2.91E−07	Recurrent depressive disorder
F41	20 656	1.060	1.044	1.076	1.47E−13	Other anxiety disorders
F43	10 294	1.060	1.039	1.082	2.57E−08	Reaction to severe stress, and adjustment disorders
G43	10 666	1.063	1.041	1.085	6.10E−09	Migraine
G44	18 761	1.053	1.036	1.070	2.92E−10	Other headache syndromes
G47	17 571	1.061	1.044	1.079	4.04E−12	Sleep disorders
G56	12 102	1.075	1.054	1.096	3.52E−13	Mononeuropathies of upper limb
H36	2179	1.099	1.052	1.149	2.37E−05	Retinal disorders in diseases classified elsewhere
I10	32 483	1.050	1.034	1.066	1.70E−10	Essential (primary) hypertension
I11	24 146	1.063	1.044	1.082	5.27E−11	Hypertensive heart disease
I21	2244	1.141	1.091	1.194	7.32E−09	Acute myocardial infarction
I25	8465	1.059	1.031	1.087	2.88E−05	Chronic ischaemic heart disease
I48	6123	1.077	1.046	1.109	5.03E−07	Atrial fibrillation and flutter
I50	8996	1.083	1.054	1.112	4.49E−09	Heart failure
I70	3885	1.082	1.043	1.121	1.92E−05	Atherosclerosis
J03	34 073	1.045	1.031	1.059	1.75E−10	Acute tonsillitis
J04	34 461	1.040	1.027	1.054	3.22E−09	Acute laryngitis and tracheitis
J20	48 302	1.047	1.035	1.060	1.00E−13	Acute bronchitis
J44	4776	1.148	1.114	1.183	6.35E−17	Other chronic obstructive pulmonary disease
J45	12 409	1.065	1.045	1.086	5.68E−11	Asthma
K04	23 343	1.046	1.030	1.062	3.78E−09	Diseases of pulp and periapical tissues
K05	15 312	1.051	1.033	1.070	1.96E−08	Gingivitis and periodontal diseases
K20	2282	1.110	1.065	1.158	1.10E−06	Oesophagitis
K21	25 682	1.047	1.032	1.062	3.30E−10	Gastro-oesophageal reflux disease
K25	5377	1.070	1.041	1.101	2.56E−06	Gastric ulcer
K26	7097	1.056	1.031	1.083	1.42E−05	Duodenal ulcer
K29	29 638	1.048	1.034	1.063	4.02E−11	Gastritis and duodenitis
K76	4452	1.075	1.042	1.108	3.88E−06	Other diseases of liver
K80	11 366	1.053	1.032	1.075	6.99E−07	Cholelithiasis
K86	2517	1.107	1.062	1.153	1.09E−06	Other diseases of pancreas
L02	15 352	1.043	1.026	1.061	1.46E−06	Cutaneous abscess, furuncle, and carbuncle
L82	10 797	0.941	0.922	0.961	1.46E−08	Seborrhoeic keratosis

(*Continued*)

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Table 2. (*Continued.*)

ICD code	*n*	OR	Lower CI	Upper CI	*p*-Value	ICD code name
M06	5231	1.064	1.035	1.095	1.76E−05	Other rheumatoid arthritis
M10	5648	1.086	1.056	1.117	1.03E−08	Gout
M13	12 393	1.048	1.029	1.069	1.16E−06	Other arthritis
M15	15 398	1.094	1.073	1.116	3.30E−19	Polyarthrosis
M16	11 349	1.072	1.049	1.095	2.31E−10	Coxarthrosis [arthrosis of hip]
M17	20 209	1.040	1.023	1.058	6.06E−06	Gonarthrosis [arthrosis of knee]
M19	12 239	1.065	1.044	1.086	6.51E−10	Other arthrosis
M25	37 607	1.042	1.029	1.055	1.48E−10	Other joint disorders, not elsewhere classified
M47	11 483	1.061	1.039	1.083	3.23E−08	Spondylosis
M48	4395	1.088	1.054	1.123	1.42E−07	Other spondylopathies
M50	9756	1.072	1.049	1.096	2.08E−10	Cervical disc disorders
M51	19 210	1.064	1.047	1.082	5.15E−14	Other intervertebral disc disorders
M54	67 495	1.082	1.068	1.096	8.09E−35	Dorsalgia
M65	7097	1.064	1.039	1.091	5.86E−07	Synovitis and tenosynovitis
M70	14 454	1.056	1.037	1.074	2.39E−09	Soft tissue disorders related to use and pressure
M75	18 702	1.061	1.044	1.079	1.49E−12	Shoulder lesions
M77	19 470	1.066	1.049	1.083	5.15E−15	Other enthesopathies
M79	33 221	1.049	1.036	1.063	5.67E−13	Other soft tissue disorders, not elsewhere classified
M96	641	1.208	1.116	1.306	2.53E−06	Postprocedural musculoskeletal disorders
N30	35 670	1.039	1.025	1.054	4.98E−08	Cystitis
N70	5800	1.066	1.037	1.096	4.96E−06	Salpingitis and ophoritis
N71	3281	1.096	1.057	1.135	4.88E−07	Inflammatory disease of uterus, except cervix
N76	28 339	1.040	1.024	1.056	5.26E−07	Other inflammation of vagina and vulva
N92	18 806	1.043	1.026	1.061	9.93E−07	Excessive, frequent, and irregular menstruation
O00	1539	1.119	1.063	1.178	1.74E−05	Ectopic pregnancy
O04	8731	1.102	1.076	1.128	4.56E−16	Medical abortion
O20	6268	1.069	1.041	1.098	1.12E−06	Hemorrhage in early pregnancy
O23	5671	1.066	1.037	1.097	8.21E−06	Infections of genitourinary tract in pregnancy
O26	5444	1.068	1.038	1.099	7.36E−06	Maternal care for conditions related to pregnancy
O47	5395	1.067	1.037	1.098	1.06E−05	False labor
O99	11 384	1.052	1.030	1.075	2.76E−06	Maternal diseases complicating pregnancy, childbirth
R10	35 274	1.038	1.025	1.052	1.61E−08	Abdominal and pelvic pain
R11	4388	1.081	1.049	1.115	5.91E−07	Nausea and vomiting
R51	18 544	1.068	1.051	1.085	1.70E−15	Headache
R73	6301	1.068	1.041	1.097	7.47E−07	Elevated blood glucose level
T51	1066	1.154	1.085	1.226	4.53E−06	Toxic effect of alcohol
Z95	3722	1.088	1.050	1.128	3.80E−06	Presence of cardiac and vascular implants and grafts

Note: *n*, number of cases; CI, confidence interval.

CI 1.07–1.15), obesity (OR 1.11, CI 1.07–1.15), type 2 diabetes (OR 1.10, CI 1.06–1.14), and dorsalgia (OR 1.07, CI 1.04–1.09). Results are shown in online Supplementary Table S4 and Figures S1-S2.

The results in the full cohort (relatives not excluded) were largely similar, but additionally 52 associations passed correction for multiple testing potentially due to larger sample size and non-independence between observations (online Supplementary Table S5).

PRS_{ADHD} deciles

The PRS_{ADHD} decile analysis of the 80 significantly associated medical conditions showed that individuals in the top PRS_{ADHD}

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decile had 70% higher risk for COPD (OR 1.70; CI 1.48–1.95); 59% higher risk for obesity (OR 1.59; CI 1.47–1.73), 51% higher risk for toxic effects of alcohol (OR 1.51; CI 1.16–1.97), 45% higher risk for type 2 diabetes (OR 1.45; CI 1.30–1.61), and 34% higher risk for polyarthrosis (OR 1.34, CI 1.23–1.47), compared to individuals in the lowest PRS_{ADHD} decile. The results using top *v.* middle PRS_{ADHD} decile were mostly in line with the results from top *v.* bottom PRS_{ADHD} decile analysis, but were non-significant for 23 medical conditions, e.g. other sexually transmitted diseases, heart failures, atherosclerosis, acute bronchitis, other arthritis, and pregnancy related conditions (Fig. 2; online Supplementary Tables S6-S7). The results comparing the high PRS_{ADHD} group separately in females and males are shown in Fig. 3 and online Supplementary Tables S8-S9. Eleven phenotypes were only available in females (such as pregnancy-related conditions). The majority of the associations between females and males were in the same direction. Of the phenotypes that were available in both genders, 15 associations were significant only in females (including, cystitis, cholelithiasis, gastro-oesophageal reflux disease (GORD), migraine, gastric ulcer, other arthrosis, other joint disorders, other spondylopathies, abdominal and pelvic pain, and other sexually transmitted disease (STD) diagnoses). In contrast, associations with personality and behavioral disorders due to brain damage/dysfunction, toxic effects of alcohol, and cardiac/vascular implants and grafts were only significantly associated in males.

Secondary analyses

Comparison of effects across PRS_{ADHD}, ADHD diagnosis, and questionnaire-based ADHD analyses

In the ADHD diagnosis analysis, 18 medical conditions had insufficient case numbers (<10 cases) to be included in these analyses (online Supplementary Table S10). We observed significant associations between ADHD diagnosis and 31 medical conditions, of which 6 medical conditions showed protective associations (e.g. other STDs, melanocytic nevus, excessive and irregular menstruation, medical abortion, and pregnancy-related conditions) (Fig. 3). Overall, 40% of the PRS_{ADHD} associations were also observed in the ADHD diagnosis analysis. We observed the strongest evidence for associations with psychiatric disorders, e.g. behavioral disorders due to brain disease (OR 6.42, CI 4.08–10.11), reaction to severe stress (OR 4.70, CI 3.83–5.76), recurrent depressive disorders (OR 3.97, CI 3.08–5.11), but also with asthma (OR 2.11, CI 1.64–2.70) and acute bronchitis (OR 1.72, CI 1.43–2.06).

In the questionnaire-based ADHD analysis, the direction of the effects was largely similar as in the PRS decile analysis and 78% of the PRS_{ADHD} associations were observed in the questionnaire-based ADHD analysis. We observed the strongest evidence for associations with recurrent depressive disorders (OR 3.78, CI 3.44–4.16), anxiety disorders (OR 2.31, CI 2.14–2.50), polyarthrosis (OR 1.94, CI 1.70–2.20), sleep disorders (OR 1.94, CI 1.77–2.13), and asthma (OR 1.64, CI 1.48–1.81). These results are shown in Fig. 4 and online Supplementary Tables S10-S11.

Causal mediation analysis

Our findings from causal mediation analysis showed that depression was a significant mediator for all 78 medical conditions (two depression diagnoses were excluded from the analysis), but the proportion of the effect between PRS_{ADHD} and medical conditions that was mediated by depression for majority of outcomes was generally small, ranging from 2 to 16%. Only for mental disorders, e.g. sleep disorders, anxiety disorders, reaction to severe stress, and mental disorders due to brain damage/dysfunction, the mediation effect accounted for more than 20% of the observed associations between PRS_{ADHD} and respective ICD-10 diagnosis (online Supplementary Table S12).

Discussion

In this study, we performed a PheWAS between PRS_{ADHD} and EHR-based diagnoses across all ICD-10 categories, using nationwide, population-representative clinical data with up to 17 years follow-up. This approach enabled the investigation of the associations between genetic liability to ADHD and medical conditions in a population without a history of ADHD diagnosis. Overall, our results indicate robust associations between ADHD genetic liability and 80 medical conditions, with obesity, dorsalgia, polyarthrosis, COPD, and type 2 diabetes among the top associated medical conditions.

These results are in line with previous findings on the associations between ADHD diagnosis and comorbid medical conditions (Du Rietz et al., 2021; Momen et al., 2020). Furthermore, similarly to our findings, other studies using PRS_{ADHD} (Kember et al., 2021; Leppert et al., 2020) also showed associations between $PRS_{ADHD,}$ mental and physical health problems, indicating a shared genetic background between ADHD and medical conditions. Another large-scale genetic study, based on UK Biobank data, found that genetic liability to multiple complex traits in adulthood, such as type 2 diabetes, obesity, peripheral artery disease, and polyarthritis, increases the risk for ADHD in childhood, which further shows the role of underlying genetic effects between physical health and ADHD across development (García-Marín et al., 2021a).

Several of the observed associations between PRS_{ADHD} and medical conditions in non-diagnosed individuals are consistent with the few previous genetically informative studies on diagnosed ADHD and medical comorbidities, such as the nervous system (Du Rietz et al., 2021), respiratory (Du Rietz et al., 2021; García-Marín et al., 2021b), musculoskeletal (Du Rietz et al., 2021), and cardiometabolic diseases (Du Rietz et al., 2021; Garcia-Argibay et al., 2022). Several studies have demonstrated that some of the observed associations between medical conditions and ADHD diagnosis were mediated by lifestyle factors, such as tobacco use and alcohol misuse (Faraone et al., 2021; Garcia-Argibay et al., 2022), which may reflect the impulsive behavior characteristic to ADHD. Although we focused only on undiagnosed individuals in this study, the PRS_{ADHD} likely captures the genetic predisposition to ADHD-related traits, such as impulsivity and disorganization, which are strongly associated with risk behavior and unhealthy lifestyle (Solmi et al., 2021). Therefore, future studies should explore whether health-related behavior mediates the associations between ADHD genetic predisposition and medical conditions in different populations where detailed information on such behavior is available through questionnaires (lifestyle) or electronic health records (e.g. missing medical appointments and accident-related injuries). However, given the strong comorbidity between ADHD and depression, we utilized the diagnosis information to test mediation by depression diagnosis. As expected, we found that depression was a significant mediator for all observed medical conditions, but the effect from depression alone was rather small. Additionally, it is possible that adults with undiagnosed or subclinical ADHD may be more likely diagnosed with depression, either because of

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Figure 2. Comparison of associations between top vs bottom and top vs medium PRS_{ADHD} risk on ICD-10 codes after adjustment for multiple testing.
Note: PRS, 'polygenic risk score'; 95% CI, '95% confidence intervals'.

potentially expressed symptoms overlapping with depression (e.g. concentration problems, inattention) or being in an increased depression risk due to their unmanaged ADHD.

A recent Mendelian randomization study showed a bidirectional causal effect between ADHD and obesity-related traits (e.g. waist-hip-ratio (WHR) and BMI-adjusted WHR) and

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Figure 3. Comparison of associations between high PRS_{ADHD} risk and ICD-10 codes in females and males.
Note: PRS, 'polygenic risk score'; 95% CI, '95% confidence intervals'; ICD-10 codes less than 10 cases were excluded from analyses.

reported genetic overlap between BMI and ADHD (Karhunen et al., 2021). It has been also shown that obesity increases the risk for a chronic inflammatory state (Andersen, Murphy, & Fernandez, 2016), which can lead to several diseases, such as hypertension, type 2 diabetes, cardiovascular disease, and musculoskeletal diseases (Furman et al., 2019; Nikiphorou & Fragoulis,

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Figure 4. Comparison of associations between ADHD diagnosis and questionnaire-based ADHD on ICD-10 codes after adjustment for multiple testing.
Note: PRS, 'polygenic risk score'; 95% CI, '95% confidence intervals'; ICD-10 codes less than 10 cases were excluded from analyses.

2018). There is also some evidence that inflammation plays an important role in the etiology of ADHD (Dunn, Nigg, & Sullivan, 2019). It has been reported that individuals with ADHD had an increased inflammatory marker interleukin 6 (IL-6) which has been linked with an increased risk of diabetes (Donfrancesco et al., 2020; Wang et al., 2013). Similarly, the

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role of obesity and inflammation markers are well described in the etiology of cholelithiasis and GORD (El-Serag, 2008; Littlefield & Lenahan, 2019). Therefore, it is plausible that obesity can act as a mediator on the pathway between ADHD and several medical conditions. In fact, the study by Garcia-Argibay et al. found that BMI-mediated associations between PRS_{ADHD} and medical conditions like hypertension, type 2 diabetes, migraine, and sleep disorders (Garcia-Argibay et al., 2022).

The sex-stratified analysis generally showed similar associations in males and females. Several conditions that were statistically significant only in one gender (e.g. diseases of the musculoskeletal and digestive system, personality and behavioral disorders due to brain damage/dysfunction, toxic effects of alcohol, and cardiac/vascular implants and grafts), we observed similar effect sizes in both genders, potentially indicating insufficient case numbers in the sex-stratified analyses. However, we also observed some sex differences. The association with sexually transmitted chlamydial diseases was more strongly associated with females. The literature supports the link between ADHD and risky sexual behavior. Several studies have shown that ADHD is associated with higher risk of sexually transmitted diseases and more and younger age at first pregnancies (Hechtman et al., 2016; Hosain, Berenson, Tennen, Bauer, & Wu, 2012). The study by Leppert et al. (2020) also demonstrated the association between PRS_{ADHD} and younger age at first sexual intercourse in the UK Biobank. Although the prevalence of chlamydia is similar in females and males, the disease is more often asymptomatic in males. Considering that women are more frequently screened in a routine gynecological care, it is possible that the stronger association observed in females can be explained by higher likelihood of receiving a diagnosis (Dielissen, Teunissen, & Lagro-Janssen, 2013). Other associations observed more strongly in females were with cystitis, migraine, cholelithiasis, abdominal and pelvic pain, and GORD diagnoses. Cystitis, migraine, abdominal and pelvic pain, and cholelithiasis have been reported to be more common in women, which has been suggested to be explained by female hormones and inflammation processes (Allais et al., 2020; Curran, 2015; Littlefield & Lenahan, 2019; Patnaik et al., 2017). However, although GORD symptoms are equally prevalent in males and females (El-Serag, 2008), it has been suggested that estrogen may mediate the association in females (Nilsson, Johnsen, Ye, Hveem, & Lagergren, 2003).

Although the majority of the associations observed in the PRS_{ADHD} analysis sample were in the same direction as in the ADHD diagnosis and questionnaire-based ADHD analysis samples, we observed opposite effects for some conditions in the ADHD diagnosis sample (such as conditions only expressed in females, e.g. pregnancy-related conditions). It is possible that the protective associations observed with these conditions could be affected by treatment effects, potentially reducing the likelihood of psychosocial or environmental risk factors (Fuller-Thomson & Lewis, 2015), and altering reproductive behavior (Østergaard, Dalsgaard, Faraone, Munk-Olsen, & Laursen, 2017; Skoglund et al., 2019). Additionally, it is possible that the diagnosed ADHD sample in EstBB is healthier, more educated, and practicing healthy lifestyle compared to the average ADHD patient.

Our results suggest that ADHD-related medical conditions are also present in individuals without ADHD diagnosis but who have high genetic liability for ADHD. Evidence suggests that ADHD in adults is likely underdiagnosed and undertreated across countries (Fayyad et al., 2017). For example, ADHD lifetime prevalence in EstBB is 0.5% and yearly prevalence of ADHD was 0.8% in 2015–2020 in Estonia overall. This further highlights the importance of improving screening and management of ADHD in adult populations, in order to reduce the risk of severe physical comorbidities and potentially shorter life expectancy in individuals with subclinical or currently undiagnosed ADHD. This is also supported by our findings of the ADHD screening questionnaire, which revealed that 8,7% of the participants have high ADHD risk. However, for broader applicability, future studies should replicate these findings in other cohorts with varying rates of ADHD prevalence among adults and investigate the impact of high ADHD risk on overall mortality and survival.

Strengths and limitations

The major strength of this study is inclusion of medical conditions across all ICD-10 diagnoses codes based on EHR with 17 years of follow-up, as well as combining genetic data with EHR and questionnaire data. EHR data is, as compared to self-reported data, not affected by recall bias and has better validity for many diagnoses as information is collected prospectively. Furthermore, we used data from a population-based biobank with a large sample size and high coverage of the whole population, thereby improving our statistical power to detect associations of even small effects.

However, this study also has some limitations. First, although EHR is a comprehensive data source, it only includes individuals with more severe symptoms and/or diseases who have received medical treatment. This may lead to misclassification bias, particularly in psychiatric categories, given the low EHR-based ADHD prevalence in EstBB. It is also possible that some individuals who received their ADHD diagnosis in childhood could have been left out of the study as EHR covers the period from 2004 to 2020. However, ADHD is often underdiagnosed in middle-age and older adults because ADHD in adulthood has been recognized fairly recently (Franke et al., 2018). Availability of data from 2004 can also affect our mediation analysis results as we cannot be certain that depression was not present prior to any of the medical conditions identified in the PRS_{ADHD} analysis. Second, population-based cohort studies may be affected by selection bias as healthier and better educated people are more likely to participate in health studies (Larsson, 2021). The 'healthy volunteer' selection bias has been previously described in the UK Biobank (Fry et al., 2017) and may also exist in the EstBB. Third, given the small number of ADHD cases in our sample, we could not test the effect of ADHD medications on the results. It is well-reported that ADHD drug treatment can help to reduce various negative health outcomes and decrease the risk of risky behavior (Faraone et al., 2021). It is possible that the protective and statistically non-significant associations observed with some phenotypes in the ADHD diagnosis analysis could be affected by treatment effects. However, it is also plausible that individuals with ADHD diagnosis in the EstBB differ substantially from the average individual with ADHD diagnosis due to selection bias. Fourth, since the ADHD diagnosis analytical sample had higher mean birth year, the observed findings may have been affected by underestimation of associations as some diseases typically emerge in older age.

Conclusion

Our study showed that genetic liability for ADHD is associated with increased risk for various medical conditions in individuals

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without ADHD diagnosis history. The results largely mirror the known associations between diagnosed ADHD and physical disease comorbidities of which many may be linked to adverse health behaviors This knowledge can have implications for prevention and health policy as better detection and timely management of ADHD symptoms may help to reduce the risks for poor health choices and adverse medical consequences across the life span. Although PheWAS design does not allow us to conclude which specific mechanisms underlying behind the observed associations, it provides insights for future studies to further investigate potential underlying pathways.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000606.

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All other authors report no competing interests, including authors from the Estonian Biobank Research Team.

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