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Genome-wide meta-analysis of ADHD symptoms in the adult general population reveals distinct genetics of inattention and hyperactivity-impulsivity

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Abstract

We conducted genome-wide meta-analyses (N = 141,505; Estonian Biobank and Norwegian Mother, Father and Child Cohort Study) with polygenic score-based validation (N = 19,857; Dutch Lifelines cohort) of self-reported attention-deficit/hyperactivity disorder (ADHD) symptoms in adults from the general population. We identified eight genetic loci associated with either total symptoms, inattention or hyperactivity-impulsivity domains. Distinct genetic architectures underlying the two symptom domains were demonstrated by their moderate genetic correlation (r_g=0.35, 95% CI 0.26 to 0.43) and by contrasting genetic association patterns across other phenotypes and medical conditions. Hyperactivity-impulsivity showed stronger genetic links with ADHD diagnosis, negative r_g-s (-0.28 to -0.19) with educational traits, and more associations with diagnoses in electronic health records. Whereas inattention was weakly genetically associated with ADHD diagnosis, showed positive r_g-s (0.24 to 0.29) with educational phenotypes, and fewer links with clinical outcomes. This is the first genome-wide study to detect significant signals associated with adult ADHD symptoms and symptom dimensions.

Main

Attention-deficit/hyperactivity disorder (ADHD) is a common, highly heritable neurodevelopmental condition characterized by impairing symptoms of inattention and/or hyperactivity-impulsivity[1,2]. Although ADHD is typically diagnosed in childhood or adolescence, ADHD and related symptoms often persist into adulthood[3]. Of individuals diagnosed with ADHD early in life, approximately 65% continue to experience symptoms later in life[4]. Moreover, because ADHD often remains unrecognized and unmanaged in adulthood – particularly in women –, ADHD-related difficulties, including attention and executive problems or restlessness, may substantially impact daily functioning of a large proportion of adults without a formal ADHD diagnosis[5,6].

Although ADHD is diagnosed as a binary condition, existing evidence from population-based and genetic studies indicate that ADHD lies at the extreme end of continuously distributed symptoms[7–9]. Short screening instruments, such as the Adult ADHD Self-Report Scale (ASRS)[10], are widely used to identify adults at high risk for ADHD and refer them for further assessment. These instruments typically map the presence and severity of core symptoms of inattention (e.g., difficulty concentrating, trouble completing tasks) and hyperactivity-impulsivity (e.g., often fidgeting, trouble waiting ones turn). A symptom-level approach allows higher levels of granularity by evaluating the impairment specifically in inattention and hyperactivity-impulsivity domains. Therefore, ADHD symptom measures capture a range of traits with possible impact on daily functioning even when all diagnostic criteria are not met, making them valuable tools for investigating the phenotypic manifestation of ADHD features and dimension in adults.

Self-rated ADHD symptoms in adulthood exhibit moderate heritability, 30–40%, which is notably lower than the high heritability, 70–80%, of cross-informant and clinically diagnosed ADHD, estimated in twin studies[11,12]. The latest genome-wide association study (GWAS) on ADHD diagnosis identified 27

significant genetic loci[13], but GWASs focusing on adult ADHD symptom dimensions have, thus far, been underpowered to identify any genome-wide significant associations[14,15]. However, a recent GWAS combined diagnostic and symptom-level data in children, which helped to detect novel loci associated with ADHD[9]. Our understanding of the genetics underlying adult ADHD symptoms and their genetic relationships with ADHD diagnosed in childhood, and other mental health, behavioural, and somatic conditions remains limited. Furthermore, while sex differences in ADHD symptom presentation are well documented[16], sex-stratified analyses are required to shed light on the genetics of adult ADHD symptoms in males and females. Addressing these gaps is critical for clarifying the biological underpinnings of specific ADHD symptoms and symptom domains across the life course.

Study overview

In this study (see Fig. 1 for overview) we conducted GWAS meta-analyses of three aggregated continuous measures of self-reported ADHD symptoms based on ASRS responses: total symptom score, inattention domain, and hyperactivity-impulsivity domain. Analyses were performed on data from 141,505 adults in two large population-based cohorts: the Estonian Biobank (EstBB, n = 77,276) and the Norwegian Mother, Father and Child Cohort Study parent generation (MoBa, n = 64,229). Additionally, we conducted GWAS meta-analyses separately for females (n = 95,986) and males (n = 45,519) and as well as for each of the six ASRS items. Meta-analyses were followed by downstream analyses, including polygenic score-based validation in the Lifelines cohort (N = 19,857), to further characterise the genetic architecture of adult ADHD symptoms.

Results

Descriptive overview of EstBB and MoBa samples

The EstBB and MoBa samples were similar in terms of the sex distribution and mean birth year (Table 1). However, the variance in the birth year was smaller in MoBa as it consists of parents of children born in 2000 to 2009, while EstBB consists of volunteers from the entire adult Estonian population. While the two samples were overall comparable, we observed differences in the mean age at response to the questionnaire (46 years in EstBB vs 36 years in MoBa), proportion with a university degree (56% in EstBB vs 64% in MoBa) and ASRS-based high risk for ADHD (9% in EstBB vs 4% in MoBa) (Table 1).

Table 1
Characteristics of the study sample.

	EstBB			MoBa		
	Total	**Males**	**Females**	**Total**	**Males**	**Females**
N	77,276	22,388 (29%)	54,888 (71%)	64,229	23,131 (36%)	41,098 (64%)
Age at response, mean (s.d.)	46 (13)	46 (13)	46 (13)	36 (6)	41 (5)	33 (5)
Birth year, mean (s.d.)	1975 (13)	1975 (13)	1975 (13)	1975 (5)	1974 (5)	1975 (5)
University degree, n (%)	43,393 (56%)	10,933 (49%)	32,460 (59%)	41,068 (64%)	12,946 (56%)	28,122 (68%)
ADHD diagnosis*, n (%)	916 (1.2%)	283 (1.3%)	633 (1.2%)	1,019 (1.6%)	376 (1.6%)	643 (1.6%)
ASRS-based high ADHD risk**, n (%)	6,698 (9%)	1,766 (8%)	4,932 (9%)	2,491 (4%)	1,160 (5%)	1,331 (3%)
Total symptom score, mean (s.d.)	7.9 (4.0)	7.7 (3.9)	7.9 (4.0)	7.3 (3.4)	8.3 (3.2)	6.8 (3.4)
Inattention domain, mean (s.d.)	5.1 (3.0)	4.9 (2.9)	5.1 (3.0)	4.8 (2.5)	5.3 (2.3)	4.5 (2.5)
Hyperactivity-impulsivity domain, mean (s.d.)	2.8 (1.8)	2.8 (1.8)	2.8 (1.8)	2.5 (1.7)	3.0 (1.7)	2.2 (1.6)

Note *Registry data available in EstBB since year 2004, in MoBa since 2008; **Total symptom score ≥ 14. s.d. - standard deviation; ADHD - attention-deficit/hyperactivity disorder; ASRS - Adult ADHD Self-Report Scale Version 1.1.

Main GWASs of ADHD symptom scores

We identified five lead variants for total symptom score, seven for inattention domain and two for hyperactivity-impulsivity domain across eight loci on six chromosomes, and these variants were annotated to 10 prioritized genes (Fig. 2; Extended Data Table 1; Supplementary Fig. 1a-c). All the identified lead signals were non-coding, common variants (minor allele frequency (MAF) > 0.05) that were present in both datasets (EstBB and MoBa). Genetic signals showed consistency in the direction of effects across both cohorts (Supplementary Table 1). The total symptom score shared three associated genetic loci with the inattention domain, and one with the hyperactivity-impulsivity domain (Fig. 2). The inattention and hyperactivity-impulsivity domains shared none of the genome-wide significant loci; five of the seven were also domain-specific at the nominal level (Fig. 2; Extended Data Table 1; Supplementary Table 1). Seven identified lead signals were located in or nearby genes previously linked to ADHD, such as *FOXP2*[13], *CADM1*[17], *BAIAP2*[18], *ARNTL/BMAL1*[19] and *HTR1D*[20]. Furthermore, according to mouse

genetics databases, four of these genes have shown evidence of abnormal behaviour in mice models: e.g., *CADM1* knock-outs (Cadm1$^{tm1a(EUCOMM)Wtsi}$/Cadm1$^{tm1a(EUCOMM)Wtsi}$) exhibited more anxiety-related behaviour, less locomotor activity and abnormal tail movements, and *FOXP2* knock-outs (Foxp2^{tm1Bux}/Foxp2^{tm1Bux}) exhibited abnormal reflex, impaired righting response, decreased locomotor activity and vocalization.

Item-level GWASs of ADHD symptoms

We found associated genetic variants for three inattention items, most of which were also detected on the domain level (Extended Data Fig. 1a-d; Supplementary Fig. 1d-g). The strongest genetic signal was identified for items *"How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?"* and *"How often do you have difficulty getting things in order when you have to do a task that requires organization?"* (gene *H4C8*, located in chromosome 6; Extended Data Fig. 1a&b). The *H4C8* gene was also the strongest signal in the total symptom score and inattention domain analyses, suggesting that this signal is mostly driven by these two inattention items. Two signals were identified for the item *"When you have a task that requires a lot of thought, how often do you avoid or delay getting started?"* (genes *BTN3A2* and *CADM1*, located in chromosome 6 and 11; Extended Data Fig. 1d). No genome-wide significant signals were detected for individual hyperactivity-impulsivity items (Extended Data Fig. 1e&f; Supplementary Fig. 1h&i).

SNP-based heritability and genetic correlations of ADHD symptoms

Next, we estimated SNP-based heritability (h^2_{SNP}) and genetic correlations (r_g) across the ADHD symptom phenotypes (three scores and six items). The observed-scale h^2_{SNP} estimates ranged between 4–9% across the nine phenotypes (Fig. 3a; Supplementary Table 2). The inattention domain showed the highest h^2_{SNP} (0.09, 95% confidence interval (CI) [0.08, 0.10]), followed by total symptom score (0.08, 95% CI [0.07, 0.09]). The hyperactivity-impulsivity domain (h^2_{SNP}=0.05, 95% CI [0.04, 0.06]) and items generally showed lower h^2_{SNP} than the inattention domain and items. Across all pairwise r_g-s between the nine ADHD symptom phenotypes, most were significant (Fig. 3b; Supplementary Table 3). The total symptom score showed strong positive r_g with both the inattention (0.93, 95% CI [0.91, 0.94]) and the hyperactivity-impulsivity domain (0.67, 95% CI [0.62, 0.72]). Whereas we observed a moderate positive r_g of 0.35 (95% CI [0.26, 0.43]) between the two domains. R_g-s with the item-level ADHD symptoms ranged from 0.14 (cross-domain) to 0.95 (within inattention domain).

To investigate the genetic heterogeneity of the ADHD symptoms in the two cohorts, we examined h^2_{SNP} and r_g-s of all the nine phenotypes in EstBB and MoBa separately. The h^2_{SNP} estimates were overall comparable, ranging from 0.04 to 0.09 in EstBB and from 0.05 to 0.09 in MoBa (Supplementary Table 4). R_g-s between EstBB and MoBa cohorts were generally strong, ranging from 0.51 to 0.97 (Supplementary

Table 4), confirming that the genetic signals underlying the adult self-reported ADHD symptoms in both cohorts were similar.

Sex-specific analyses of the main GWAS

We ran sex-stratified GWAS meta-analyses and explored the genetic correlations between males and females across the three ADHD symptom scores. The sample size in male-specific analysis (n = 45,519) was smaller than in female-specific analysis (n = 95,986). In female-specific analyses, we identified three loci associated with total symptom score and the inattention domain (Extended Data Fig. 2a&c; Supplementary Fig. 5a&c), which overlapped with the detected signals in the main GWAS analyses (genes *H4C8*, *FNBP4*, and *CADM1*, located on chromosomes 6 and 11). While no genome-wide significant loci were identified in males (Extended Data Fig. 2b, d&f; Supplementary Fig. 5b, d&f), the genetic correlations between males and females across total symptom score, inattention and hyperactivity-impulsivity domains were strong, ranging from 0.85 to 1.0 (Supplementary Table 2). The SNP-based heritability estimates for females and males were comparable to the combined analysis (Supplementary Table 2). This suggests that the genetic signals underlying adult self-reported ADHD symptoms in males and females were largely overlapping.

Tissue set enrichment analysis

To investigate the potential biological implication of the genetic signals from our main analyses and to follow up on the relatively lower r_g between the inattention and hyperactivity-impulsivity domain, we examined the enrichment in tissues. After correcting for multiple testing, 13 brain tissues were significantly enriched for the inattention domain (the strongest being 'Frontal Cortex BA9' ($p = 1.31x10^{-8}$), 'Anterior Cingulate Cortex BA24' ($p = 5.3x10^{-8}$), and 'Frontal Cortex' ($p = 1.19x10^{-7}$)), while two brain regions were significantly enriched for the hyperactivity-impulsivity domain ('Spinal cord cervical c-1' (p = 0.0002) and 'Substantia Nigra' (p = 0.0007)) (Extended Data Fig. 3b&c; Supplementary Tables 5–6). For the total symptom score, 10 brain tissues were significantly enriched after correcting for multiple testing, the strongest including 'Frontal Cortex BA9' ($p = 3.18x10^{-5}$), 'Hypothalamus' ($p=5x10^{-5}$) and 'Hippocampus' ($p = 9.6x10^{-5}$) (Extended Data Fig. 3a; Supplementary Table 7).

Polygenic score-based validation in Lifelines

We used polygenic scores (PGS) to test whether the identified genetic signals are associated with ADHD symptoms in an independent adult sample. We computed PGSs for the three symptom scores (i.e., total symptom, inattention and hyperactivity-impulsivity domains) in the Lifelines cohort (N = 19,857) and then conducted PGS prediction models of corresponding ADHD symptom phenotypes (Supplementary Tables 8–9). The results showed that all three PGSs were significantly associated with their corresponding phenotypes in the Lifelines sample (PGS_{TOTAL}: β = 0.09, 95% CI [0.08, 0.10]; PGS_{INA}: β =

0.09, 95% CI [0.07, 0.10]; $PGS_{HYP/IMP}$: β = 0.07, 95% CI [0.06, 0.09]) (Fig. 4; Supplementary Table 10). Variance explained (R^2) by each PGS on their respective phenotype ranged from 0.5 to 0.8%.

Genetic correlations with other phenotypes

To map the association patterns with a broad range of mental health, neurodevelopmental, cognitive, socioeconomic, personality, behavioural and somatic outcomes, we estimated r_g-s between the nine meta-analysed ADHD symptom phenotypes, and 55 other traits. Because the total symptom score showed a strong r_g with the inattention domain, the association patterns of these two scores were highly similar. Thus, we focus on the comparison of the two symptom domains here, highlighting both the differences and similarities in their r_g profiles (Fig. 5; Supplementary Tables 11–12). R_g-s of the total symptom score can be found in the Supplementary Table 13, and the item-level analyses in the Supplementary Table 14.

After Bonferroni correction (0.05/55), both symptom domains showed a similar number of significant r_g-s with other traits: 32 for inattention and 33 for hyperactivity-impulsivity domain (Fig. 5; Supplementary Tables 11–12). The hyperactivity-impulsivity domain showed stronger r_g-s with every ADHD diagnosis phenotype included in the analysis: persistent ADHD (0.59, 95% CI [0.35, 0.83]), lifetime ADHD (0.45, 95% CI [0.37, 0.53]), late-diagnosed ADHD (0.43, 95% CI [0.34, 0.53]), and childhood ADHD (0.37, 95% CI [0.27, 0.46]) (Fig. 5; Supplementary Table 12). The inattention domain was significantly genetically correlated to only lifetime ADHD diagnosis (r_g=0.16, 95% CI [0.09, 0.23]) (Fig. 5; Supplementary Table 11) from all ADHD diagnosis phenotypes.

The strongest r_g for inattention domain was detected with subjective well-being (-0.48, 95% CI [-0.59, -0.37]), and for hyperactivity-impulsivity with neuroticism (0.50, 95% CI [0.44, 0.57]), but in general both domains showed similar patterns of association for the two phenotypes. While many r_g-s were similar in their direction and magnitude for the two symptom domains across the outcomes, especially the psychiatric and behavioural categories (e.g., depressive symptoms: r_g=0.41, 95% CI [0.31, 0.50] for inattention, and r_g=0.47, 95% CI [0.36, 0.58] for hyperactivity-impulsivity), some phenotypes were significantly associated with only one of the domains. For example, autism only with inattention domain (r_g=0.39, 95% CI [0.30, 0.49]), and cannabis use disorder and risk taking only with hyperactivity-impulsivity domain (r_g=0.33, 95% CI [0.22, 0.44] and r_g=0.25, 95% CI [0.16, 0.33], respectively). Some associations, especially in the cognitive and socioeconomic category, showed an opposite directional effect between the two symptom domains. Specifically, hyperactivity-impulsivity domain had negative, but inattention domain positive r_g-s with childhood and adulthood IQ, cognitive performance, educational attainment, occupational status, household income and sedentary behaviour at work (Fig. 5; Supplementary Tables 11–12).

Polygenic overlap analysis

We applied the bivariate causal mixture modelling (MiXeR)[21] to determine the polygenic overlap between inattention and hyperactivity-impulsivity domains, and between selected phenotypes based on the genetic correlation analysis. MiXeR considers variants regardless of effect directions and estimates the proportion with concordant effects. We included the following phenotypes that showed strong positive or opposite r_g-s with the symptom domains: lifetime ADHD diagnosis[13], depressive symptoms[22] and educational attainment[23]. First, we used univariate models to estimate the number of trait-influencing genetic variants accounting for 90% of the SNP-based heritability of each phenotype. Depressive symptoms did not pass the criteria in the univariate analysis to be used and reliably interpreted in the bivariate model, and we excluded it from pairwise analysis. We identified approximately 11.8K (s.d.=867) common variants causally influencing inattention domain and 10.7K (s.d = 1.8K) common variants influencing hyperactivity-impulsivity domain. Inattention and hyperactivity-impulsivity domains shared 10.0K (s.d.=1.2K) variants and the fraction of concordant effect directions within these was about 61% (Supplementary Fig. 6; Supplementary Table 15). For lifetime ADHD diagnosis, we detected 5.9K (s.d.=1.3K; 57% concordant) shared variants with inattention and 4.5K (s.d.=0.7K; 91% concordant) with hyperactivity-impulsivity. The number of shared causal variants with educational attainment was 11.1K (s.d.=1.1K; 61% concordant) for inattention, and 10.4K (s.d.=1.6K; 38% concordant) for hyperactivity-impulsivity (Supplementary Fig. 6; Supplementary Table 15).

Phenome-wide association study in the EstBB subsample

Next, we used the phenome-wide association study (PheWAS) approach across electronic health record (EHR)-based ICD-10 codes over 17 years to examine the links between ADHD symptom scores and all medical conditions. We conducted the analyses between PGSs for the three symptom scores, and diagnostic history in the EstBB subset of individuals, who were not in the discovery GWAS (N = 125,148; Supplementary Table 16).

The PheWAS results of the two symptom domains differed in their number of significant associations after Bonferroni correction (0.05/1,698): 5 ICD-10 diagnostic codes were linked to PGS for inattention, but 37 ICD-10 codes to PGS for hyperactivity-impulsivity domain (Fig. 6; Supplementary Tables 17–18). The most significant association was with depressive episode for both the inattention (OR = 1.06, 95% CI [1.05, 1.08]) and hyperactivity-impulsivity (OR = 1.06, 95% CI [1.05, 1.08]) domains. For the inattention domain, we also observed significant associations with higher odds of personality disorders (OR = 1.15, 95% CI [1.09, 1.22]), recurrent depressive disorder (OR = 1.07, 95% CI [1.04, 1.09]), and dermatitis (OR = 1.06, 95% CI [1.04, 1.09]). We detected a negative association between the inattention PGS and hypertension (OR = 0.96, 95% CI [0.95, 0.98]). Mental and behavioural disorders were amongst the strongest associated health outcomes with the PGS for hyperactivity-impulsivity: e.g., anxiety disorders (OR = 1.07, 95% CI [1.05, 1.08]), and mental health disorders due to alcohol use (OR = 1.11, 95% CI [1.08, 1.14]). However, it showed more significant associations overall with somatic outcomes (e.g., dorsalgia: OR = 1.05, 95% CI [1.03, 1.06]), and injuries (e.g., physical assault: OR = 1.11, 95% CI [1.07, 1.14]) compared to the PGS for inattention. The results of the total symptom score are presented in Extended Data Fig. 4 and Supplementary Table 19.

Symptom domains and educational attainment

To follow up on the opposite association directions of the inattention and hyperactivity-impulsivity domains with educational phenotypes in the genetic correlation and polygenic overlap analyses, we ran additional analyses to further investigate the distinct links of the two symptom domains with educational attainment, using it as an available proxy phenotype for the cognitive and socioeconomic category.

First, the cohort- and sex-stratified r_g-s of the two domains with 55 other phenotypes separately in EstBB and MoBa, as well as in females and males, were consistent with the meta-analytic findings (Supplementary Table 20). R_g-s with educational attainment in stratified analyses were overall similar to those in the combined meta-analysed sample (r_g-s with inattention ranged from 0.18 to 0.31; r_g-s with hyperactivity-impulsivity from − 0.38 to -0.13). A comparable pattern was observed across other cognitive and socioeconomic traits (Supplementary Table 20).

Bidirectional two-sample Mendelian randomization (MR) on educational attainment[23] and the two domains using five analytical approaches showed the same pattern in both directions: negative causal associations for hyperactivity-impulsivity and positive associations for inattention symptoms (Fig. 7a; Supplementary Table 21).

Because the genetic correlation and MR approaches do not allow perspective on specific educational levels, we used phenotypic data in EstBB (n = 77,276) on three educational levels: basic, intermediate and advanced (i.e., university degree). Mean hyperactivity-impulsivity domain scores decreased with higher educational level ($p < 0.0001$ for all pairwise comparisons), whereas inattention showed a U-shaped pattern, with the lowest mean domain score in the intermediate group ($p < 0.01$ vs. both other groups) and similar scores in the basic and advanced groups ($p = 0.13$) (Fig. 7b; Supplementary Table 22a-c).

In an independent EstBB subset not included in the discovery GWAS and with educational data (N = 72,589), both PGSs for domains showed significant dose-response associations with educational level, again in opposite directions (Supplementary Table 23a&b). Each 1 SD increase in hyperactivity-impulsivity PGS was associated with 6% lower cumulative odds of higher educational level (OR = 0.94, 95% CI [0.92, 0.95]; R^2 = 0.12%), whereas each 1 SD increase in inattention PGS was associated with 5% higher odds (OR = 1.05, 95% CI [1.04, 1.07]; R^2 = 0.06%). Mean PGS values across educational levels mirrored this pattern (Fig. 7c; Supplementary Table 23c).

Discussion

By analysing data from over 141,000 adults across two population-based cohorts of European ancestry, we identified eight genetic loci associated with self-reported ADHD symptom scores. We found distinct genetic architectures of inattention and hyperactivity-impulsivity domains, as well as unique patterns of

associations across other phenotypes, and health profiles over 17 years of diagnostic history. The hyperactivity-impulsivity domain showed stronger genetic links with ADHD diagnosis, negative genetic correlations with cognitive and educational outcomes, and significant health impact in the medical records. The inattention domain was weakly genetically associated with ADHD diagnosis, showed positive genetic correlations with cognitive and educational traits, and had fewer links with clinical outcomes. Polygenic scores for the symptom scores predicted corresponding adult ADHD symptoms in an independent Lifelines sample, providing further support for the genetic signals while also highlighting the relatively small proportion of variance explained by these effects.

We detected five genetic loci for inattention and two for hyperactivity-impulsivity symptoms and most of these were non-overlapping between the two domains. The genetic correlation between the symptom domains was moderate at 0.35, and the SNP-based heritability was low for both domains but was relatively higher for inattention (9%) than for hyperactivity-impulsivity (5%). While the polygenic overlap analysis revealed that the domains shared most of their causal variants, approximately 61% showed concordant effects, further highlighting heterogeneity in the underlying genetics of the two domains. Additionally, tissue set enrichment analysis identified differing numbers of significant enrichments across the symptom domains, with inattention showing enrichment in 13 brain regions compared to two for hyperactivity-impulsivity. However, because the hyperactivity-impulsivity domain includes two items, compared to four in the inattention domain, these findings may reflect analytical power differences across domains. Notably, 11 additional brain regions showed increased tissue enrichment for hyperactivity-impulsivity at the nominal level but did not survive multiple-testing correction. Existing literature on adult self-rated ADHD symptoms is primarily based on twin and family designs, which tend to report higher heritability of the domains (33–42%)[24,25] and strong familial correlation between domains (r_F=0.94, s.e.=0.03)[26], compared with the SNP-based estimates we found. This is expected, as the GWAS-based approaches focus more narrowly on the additive effects of common SNPs, whereas twin and family designs capture broader heritable and familial influences. Nevertheless, our results are in line with the partially distinct genetic contributions of inattention and hyperactivity-impulsivity domains demonstrated in the twin studies[24,25,27].

Our sex-specific analysis showed strong genetic correlations between males and females, which aligns with previous studies, which have not identified statistically significant sex differences in the genetic risk associated with ADHD diagnosis[28,29]. This suggests that, although the literature indicates that ADHD symptom presentation differs between sexes – particularly the predominance of inattention symptoms in females[16] –, the underlying genetic basis may be similar. It implies that other factors (e.g., environmental, hormonal, neurobiological) could contribute to the phenotypic sex differences and their interactions rather than different genetic architecture *per se*.

Five out of the ten prioritized genes across eight loci have been previously linked to ADHD: *FOXP2*, *CADM1*, *BAIAP2*, *ARNTL/BMAL1*, and *HTR1D*. The *FOXP2* gene, associated only with the hyperactivity-impulsivity domain in this study, is involved in speech and language development[30]. It also shows the

most consistent links with ADHD diagnosis[13,31,32], and difficulties with self-regulation and inhibitory control[33], potentially contributing to the mechanistic pathway between ADHD and risk-taking behaviour and substance use[34,35]. Three genes identified in our study (*H4C8, KCNN2, FNBP4*) represent novel findings in the context of ADHD, however associations with related phenotypes have been previously reported. For example, the *H4C8* and *KCNN2* genes are linked to educational attainment[36,37] and *KCNN2* with autism[38]. The *FNBP4* gene has been linked with neuroticism[39] and alcohol consumption[40]. In our study, these three genes (*H4C8*, *KCNN2* and *FNBP4)* were associated with the inattention domain, not with hyperactivity-impulsivity, indicating their differential role in ADHD symptom domains in the general adult population. These results on diverse genetic associations emphasize the importance of investigating the genetic mechanisms of more specific ADHD features and dimensions than the medical diagnostic category, especially considering the heterogeneity of symptom representation in ADHD across demographic groups and the lifespan.

The genetic correlation and PGS-based PheWAS results revealed both shared and distinct genetic association patterns for the inattention and hyperactivity-impulsivity domains with other phenotypes and health outcomes. Both domains showed similar effect directions and magnitudes with affective phenotypes in the genetic correlation analysis, and depressive episode was the strongest association for both domains in the PheWAS analysis across all medical conditions investigated. These genetic links with affective phenotypes align with previous phenotypic evidence on increased emotional regulation difficulties in individuals with ADHD diagnosis[41,42] and with adult ADHD traits in the general population[43], further supporting the important role of the emotional dysregulation component in both ADHD symptom domains. However, we also detected significant differences across domains. First, the genetic associations between all ADHD diagnosis phenotypes (i.e., lifetime, childhood, persistent and late-diagnosed) and hyperactivity-impulsivity were stronger than with the inattention domain. This was also supported by the polygenic overlap analysis which revealed that the majority of shared causal variants to have concordant effects between hyperactivity-impulsivity domain and ADHD diagnosis (91%), while the proportion of concordant variants was much lower with inattention domain (57%). In the PheWAS analysis, PGSs for symptom scores were not significantly associated with ADHD diagnosis, which could be due to low statistical power from a small number of diagnosed cases among the independent subsample (ADHD prevalence 0.5%). The hyperactivity-impulsivity domain showed stronger genetic correlations with insomnia, substance use disorders and risk-taking behaviour, as well as a more pronounced impact on clinical outcomes in health records, particularly multiple injury-related diagnostic codes, including head and thorax injuries, bone fractures and assault. On the contrary, the inattention domain PGS showed very few associated medical conditions, despite the GWAS capturing more significant variants and detecting higher SNP-based heritability. Particularly, we found a negative genetic correlation with blood pressure and this effect direction was further confirmed by the PheWAS in an independent subsample where the PGS for inattention was negatively associated with hypertension diagnosis. The PheWAS results for hyperactivity-impulsivity show greater similarity to previously reported profiles of co-occurring medical conditions linked to ADHD diagnosis and polygenic scores[44–46] than those for the inattention domain. Our study further demonstrates that several associations with

somatic diseases – such as cardiometabolic, musculoskeletal and neurological – may be primarily driven by genetic signals of hyperactivity-impulsivity symptoms, but not inattention.

Interestingly, the two domains showed opposite genetic correlation directions with multiple cognitive and socioeconomic traits, such as IQ, cognitive performance, educational attainment and occupational status. The hyperactivity–impulsivity domain had negative associations, consistent with extensive evidence linking childhood ADHD to poorer long-term academic and employment-related outcomes[47–49]. In contrast, inattention showed positive genetic correlations with these traits, which was unexpected given that previous genetic studies have also reported negative associations between ADHD and cognitive and educational outcomes across both child- and adult-diagnosed samples[9,13,32,50]. Additionally, we observed a stronger positive genetic correlation between the inattention domain and autism compared to hyperactivity-impulsivity. This is notable considering findings that autism has also been positively genetically associated with educational attainment[38,51]. Our follow-up analyses with educational attainment revealed that hyperactivity-impulsivity symptoms showed negative associations at both the genetic and phenotypic levels. Inattention symptoms had positive genetic associations, whereas phenotypically, higher endorsement of inattention symptoms was observed in both basic and advanced education groups. Concentration difficulties, one of the core characteristics of the inattention domain, are among the most non-specific symptoms across all psychiatric diagnostic categories[52]. Also, attention and executive problems are strongly influenced by various external factors, such as poor sleep[53,54] and stress[55,56]. As a brief screening instrument aimed for detecting high risk individuals, the ASRS might also capture the non-specific attention problems which can be caused by factors other than ADHD. This is supported by recent meta-analyses which found that while self-reported ADHD screening instruments, including ASRS, are good at detecting ADHD cases from healthy controls, these tools are performing poorly in differentiating ADHD from other psychiatric disorders, such as depression, anxiety or substance use[57,58]. Thus, any associations with inattention require careful evaluation and interpretation to avoid potential misclassification between conditions. Additionally, individuals with university degree are more likely to have cognitively demanding occupations with higher workload and professional expectations. They may be more aware of and be more strongly affected by concentration and executive difficulties in their job roles, for example when meeting tight deadlines and completing challenging tasks. Therefore, the associations between adult self-reported ADHD symptoms and cognitive and educational outcomes may be more complex. Future studies should investigate the mechanisms linking higher academic and socioeconomic achievement with greater endorsement of inattention symptoms in adulthood, including potential mediation by co-occurring conditions, environmental demands, stress-related factors, and other external influences.

A major strength of this study is its large sample with adult ADHD symptom self-report data drawn from two population-based cohorts, with harmonized assessment using a validated instrument, thereby providing sufficient power to detect genome-wide significant signals. Although the genetic correlations between EstBB and MoBa across study phenotypes were strong, there may still be measurement heterogeneity due to differences in the age range of the two samples. To overcome this limitation, we

adjusted for birth year in the GWAS analyses and believe that the differences in age distribution did not significantly affect our findings. Additionally, the two ASRS items assessing hyperactivity-impulsivity primarily capture hyperactivity rather than impulsivity, which may not fully reflect all aspects of adult ADHD traits in the general population. Also, the 6-item ASRS instrument includes more inattention than hyperactivity-impulsivity symptoms, which biased the total symptom score results towards capturing more inattention-related signals. Future studies would benefit from using more comprehensive instruments to assess a broader spectrum of ADHD features in adulthood. In addition, the two cohorts included in this study were from European ancestry, had more females and individuals with advanced education, which affects the generalizability of our results to other ancestries and sociodemographic groups. As participation was higher among women and individuals with higher educational attainment, our cohorts differ from populations typically represented in ADHD research. Since this is the first study reporting significant genetic signals for adult ADHD symptoms, future studies should aim to diversify the study populations and further increase sample size to improve analytical power for gene discovery.

Conclusion

We present the first study to map the genetics of adult ADHD symptoms in the general population and demonstrate genetic heterogeneity between the inattention and hyperactivity-impulsivity domains using molecular genetic approaches. The results reveal distinct genetic architectures and different genetic association profiles across mental health, neurodevelopmental, behavioural, cognitive, socioeconomic and somatic phenotypes. Our findings indicate that self-reported hyperactivity-impulsivity symptoms in the general adult population reflect stronger genetic links and more similar patterns of co-occurring conditions with ADHD diagnosis compared to inattention symptoms. The results for the inattention domain may instead reflect broader, non-specific difficulties in concentration and executive functioning in the context of advanced education and environmental demands. These findings highlight the importance of dimensional symptom-level approaches in large scale genetic studies to improve understanding of the diverse mechanisms underlying specific mental and behavioural features across the life course.

Methods

GWAS discovery cohorts

All study participants were of European ancestry confirmed through principal component analysis (PCA) using genetic data.

EstBB

The Estonian Biobank (EstBB) is a large data-rich volunteer-based biobank covering approximately 20% of the adult population in Estonia (~ 212,000; 66% female; mean year of birth 1971)[59]. All EstBB

participants are genotyped, and the biobank is regularly linked to EHRs and national registries, such as the Estonian Health Insurance Fund database, cause of death register, and hospital records. Additional information on lifestyle, education, mental health and well-being was collected via questionnaires. Details about the recruitment of participants and overview of EstBB data can be found in Milani et al., 2025[59]. Description of genotyping, quality control and imputation procedures were performed as described previously in Ojalo et al., 2024[60]. The activities of the EstBB are regulated by the Human Genes Research Act, which was adopted in 2000 specifically for the operations of the EstBB. Individual level data analysis in the EstBB was carried out under ethical approvals [20.09.2023 1.1–12/3455 and 25.01.2024 1.1–12/212] from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs), using data according to release application [6–7/GI/28165] from the Estonian Biobank.

MoBa

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health[61,62]. Participants were recruited across Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort includes approximately 114,500 children, 95,200 mothers and 75,200 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth[63]. Genotype data is available for approximately 80% of the cohort. Details of MoBa genotyping and quality control are described in Corfield et al., 2024[64]. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (2016/1702).

Out-of-sample PGS analysis cohorts

To test the validation of PGS associations with adult ADHD symptoms in an independent sample, we used the Lifelines cohort, which is a large population-based multidisciplinary cohort and biobank[65,66]. Between 2006 and 2013, inhabitants of the northern part of the Netherlands and their families were invited to participate, contributing to a three-generation design. Baseline data were collected for 167,729 participants (58% female; mean age at response 41 years). Overview of the Lifelines sample (N = 19,857) is presented in the Supplementary Table 9.

PheWAS approach was used to investigate the health profiles associated with the genetic liability to the ADHD symptom scores in the EstBB subsample of individuals who were not in the discovery GWAS (N = 125,148; overview of the sample is outlined in the Supplementary Table 16).

For investigating PGS associations with educational attainment in an independent sample, we used the EstBB subset of individuals who were not in the discovery GWAS and had available data on educational level (N = 72,589). Educational attainment was defined by the educational level categories: basic, intermediate, advanced. Overview of the EstBB subsample is presented in the Supplementary Table 23a.

ADHD symptoms

ADHD symptoms were measured with the Adult ADHD Self-Report Scale Version 1.1 (ASRS) Screener[10]. In the six-item screening questionnaire respondents report the frequency of different DSM-IV Criterion A symptoms of adult ADHD, experienced during the last 6 months. The instrument items and their abbreviations in this study are as follows:

1. *How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?* (INA-1)
2. *How often do you have difficulty getting things in order when you have to do a task that requires organization?* (INA-2)
3. *How often do you have problems remembering appointments or obligations?* (INA-3)
4. *When you have a task that requires a lot of thought, how often do you avoid or delay getting started?* (INA-4)
5. *How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?* (HYP/IMP-1)
6. *How often do you feel overly active and compelled to do things, like you were driven by a motor?* (HYP/IMP-2)

All items were assessed on Likert scale ranging from 0–4: 0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = very often. The first four items capture inattention domain symptoms (INA-1, INA-2, INA-3, INA-4) and two last items capture hyperactivity-impulsivity domain symptoms (HYP/IMP-1, HYP/IMP-2). Based on these six items, three aggregated scores were computed: ADHD total symptom score (ADHD TOTAL SC; range 0–24), ADHD inattention domain score (ADHD INA SC; range 0–16) and ADHD hyperactivity-impulsivity domain score (ADHD HYP/IMP SC; range 0–8). In the EstBB sample, adjusted mean scores for inattention and hyperactivity-impulsivity domains were computed across educational levels by fitting linear models with the z-standardized domain score as the outcome, and including birth year and sex as covariates. Estimated marginal means for each educational level were obtained and post-hoc pairwise contrasts between educational levels were subsequently performed with Tukey's adjustment for multiple comparisons.

In EstBB, ADHD symptoms were reported as a part of a larger mental health online survey (MHoS) "Wellbeing and Mental Health" that was conducted in spring 2021[60]. The questionnaire was emailed to all living EstBB participants with available e-mail addresses (N = 184,622) of which 86,244 individuals returned the questionnaire. After excluding individuals older than 70 years due to the increased

likelihood of cognitive decline with related attention and executive function difficulties in older age groups[67,68], the total sample size was 77,276 individuals with genotype data. In MoBa, ADHD symptoms were assessed in mothers when children were at age 3 years (collected between 2002–2011). Fathers' questionnaire was sent out in 2015/2016 when children were at age 6 to 16 years. After excluding individuals older than 70 years, the total sample size was 64,229 individuals with genotype data.

Overview of the study samples is shown in Table 1. Distributions of the individual ADHD symptoms, total symptom, and domain scores in EstBB and MoBa separately are presented in Supplementary Fig. 7–9.

In Lifelines, ADHD symptoms were measured with the Dutch version of the adult ADHD DSM-IV questionnaire (Adult ADHD Rating Scale-IV) which consists of eleven inattention and twelve hyperactivity-impulsivity items[69]. These items were aligned with those from the ASRS, and a total of seven items were used in the PGS prediction analyses (Supplementary Tables 8–9).

GWAS meta-analysis

We conducted GWASs for nine ASRS-based phenotypes separately in EstBB and MoBa: total symptom score, the inattention domain score, the hyperactivity-impulsivity domain score, and each of the six items separately. The analyses were conducted using the REGENIE software (version 2.2.4)[70], adjusted for the first ten genetic principal components (PCs), as well as for birth year and sex in both cohorts. In MoBa, GWASs were additionally adjusted for the genotyping batch. Additionally, except for the item-level GWAS, all models were run stratified by sex to investigate sex-specific effects.

Inverse variance weighted fixed-effects meta-analysis without genomic control was performed using GWAMA v2.2.2[71] for each phenotype. In each meta-analysis we excluded variants with MAF < 0.01, resulting in 8,239,829 variants included for downstream analysis. The genome-wide significance threshold was of p-value $<5x10^{-8}$. Figures were produced using the qqman package version 0.19.0[72].

Annotation of GWAS signals

The online platform FUMA (v1.5.2)[73] was utilised to annotate the GWAS signals. First, FUMA identifies lead SNPs (p-value $< 5\times10^{-8}$ and LD $r^2 < 0.1$, based on 1,000 Genomes European reference) and independent significant SNPs at each risk locus (p-value $< 5\times10^{-8}$ and LD $r^2 < 0.6$). A maximum distance of 500 kb between LD blocks was set to merge into a single genomic locus. Next, FUMA identifies potential candidate SNPs that are in LD with any of the identified independent significant SNPs and annotates them via linking with several databases (ANNOVAR[74], RegulomeDB[75], CADD scores[76], which gives information on their location and variant effect, functional impact, and potential regulatory effects.

Nominating plausible candidate genes

In order to move from genetic variants to plausible candidate genes, we used different evidence levels, such as a) considering the nearest gene to the association peak, b) genes containing coding variants in high LD ($r^2 > 0.6$) with the lead variants identified in the present analysis c) genes that have been previously reported across genetic studies for ADHD or in other relevant neurological and/or behavioural phenotypes, and finally, we used the Mouse Genome Informatics (http://www.informatics.jax.org) and the Mouse Phenotyping Consortium (https://www.mousephenotype.org/) databases to evaluate the effect of candidate genes in mutant mice spanning neurological and behavioural phenotypes.

SNP-based heritability and genetic correlations

We used linkage disequilibrium score regression (LDSC) software v1.0.1 to estimate pairwise genetic correlations and to calculate SNP-based heritability[77]. For our LD score analyses we used HapMap3 reference panel and pre-calculated European LD scores without HLA region and based on the 1,000 Genomes Project Phase 3 provided by LDSC. Genetic correlations were estimated: (a) between EstBB and MoBa for the nine ADHD symptom phenotypes, (b) between females and males for the three meta-analysed ADHD symptom scores, (c) across all nine meta-analysed ADHD symptom phenotypes, (d) between the nine meta-analysed ADHD symptom phenotypes versus 55 publicly available GWASs or meta-GWASs for various psychiatric, cognitive, socioeconomic, personality, lifestyle and somatic phenotypes, (e) for the inattention and hyperactivity-impulsivity domain scores between the 55 other traits separately in EstBB and MoBa, and (f) for the meta-analysed inattention and hyperactivity-impulsivity domain scores between other traits separately in females and males. Bonferroni correction was implemented to account for multiple testing: across the nine ADHD symptom phenotypes studied ($0.05/9 = 0.006$), and across the 55 other phenotypes used ($0.05/55 = 9.1x10^{-4}$). SNP-based heritability was calculated for the nine ADHD symptom phenotypes in the meta-analysed total sample and separately in EstBB and MoBa, and for meta-analysed total symptom and domain scores in females and males.

Gene set and Tissue expression analysis

Gene set enrichment analysis and tissue set enrichment analysis were performed using MAGMA v1.08 implemented in FUMA v1.5.2. Gene sets were obtained from Msigcbv7.0 for ‘Curated gene sets’ and gene ontology ‘(GO) terms’. A total of 15,485 gene terms were tested, and Bonferroni correction was applied to account for multiple testing across 15,485 tests ($0.05/15,485 = 3x10^{-6}$) and none of the gene sets included in our gene set analyses showed to be significantly associated to the GWAS signals identified for any of the phenotypes. The tissue set enrichment analysis included 53 tissue types from GTEXv8 and Bonferroni correction was implemented to account for multiple testing across 53 tests ($0.05/53 = 9.4x10^{-4}$).

Causal shared and unique variants and polygenicity

MiXeR[21] was utilised to analyze the inattention and hyperactivity-impulsivity domains individually, and with selected phenotypes, i.e., lifetime ADHD diagnosis[13], depressive symptoms[22], educational attainment[23]. The objectives were to determine (1) the number of common variants affecting each trait, and (2) the genetic overlap between traits. MiXeR was employed with default settings in a two-step approach. Initially, the univariate model was applied to each trait to estimate the number of common variants with a nonzero genetic additive effect on the phenotype. This model provided estimates of 'polygenicity' (the proportion of non-null variants) and 'discoverability' (the variance in effect sizes of non-null SNPs). Subsequently, the variance estimates from the univariate analysis were used in a bivariate model to compare the two symptom domain scores with each other and with lifetime ADHD diagnosis and educational attainment. This produced estimates of SNPs with specific effects on either trait and SNPs with nonzero effects on both traits. For quality check, only models that generated a positive AIC value compared to a baseline infinitesimal model were selected.

Polygenic score predictions

For the PGS analyses, the PRS-CS-auto algorithm was first used to apply a Bayesian regression framework to infer the posterior effect sizes of SNPs by using summary results from the meta-analysed GWASs of total symptom, inattention, and hyperactivity-impulsivity domain scores and an external linkage disequilibrium reference panel[78]. Variant quality control thresholds for imputed genotypes included MAF > 0.01, imputation INFO score > 0.8, and the removal of ambiguous SNPs. Per-individual polygenic scores were further calculated with PLINK 2.0[79], with the number of variants included in the PGS scoring step in EstBB totaling 1,088,038 SNPs for total symptom, inattention, and hyperactivity-impulsivity domain scores. The PGSs were z-standardized prior to regression analyses.

In the Lifelines cohort, linear regression analyses were adjusted for birth year, sex and first ten PCs. In the EstBB subset, ordinal logistic regression analyses were adjusted for birth year, sex and first ten PCs, and the proportional odds assumption was assessed using the Brant test, which was met for both PGS models ($p > 0.05$). Adjusted mean values for the inattention and hyperactivity-impulsivity domain PGSs were then computed across educational levels in the EstBB subset by fitting linear models with the PGS as the outcome, including birth year, sex and first ten PCs as covariates, and obtaining estimated marginal means for each educational level.

The variance explained by each PGS in the regression analyses was computed by subtracting the R^2 (linear models) or the Nagelkerke pseudo R^2 (logistic models) from the full (PGS, birth year, sex and 10 PCs) and the reduced (birth year, sex and 10 PCs) models.

Phenome-wide association analyses in the EstBB

For PheWAS analysis, all ICD-10-based health conditions were used from the linked EHR data covering 17 years (2004–2020). ICD-10 main codes with < 10 cases were excluded leaving in total 1,698 ICD-10 phenotypes from all disease categories. Birth year, sex and first ten PCs were added as covariates to the logistic regression models. The Bonferroni adjusted p-value across 1,698 tests ($0.05/1,698 = 2.9x10^{-5}$) was used as a significance threshold to correct for multiple testing.

Mendelian randomization

Bidirectional two-sample Mendelian randomization (MR) was used to assess the potential causal relationship between the inattention and hyperactivity-impulsivity domains and educational attainment[23]. SNPs were selected as instruments based on a relaxed genome-wide significance threshold of p-value ≤ 5×10^{-7} and MAF > 0.01. SNPs were further clumped using the PLINK clumping method with a window of 10,000 kb and an r^2 threshold of 0.001 in the European population. The instruments used in the analysis were 15 for inattention, 6 for hyperactivity-impulsivity and 477 for educational attainment. Primary and sensitivity analyses were conducted as implemented in the TwoSampleMR R-package version 0.6.8[80] and MR-PRESSO R-package version 1.0[81]. Multiple MR methods were applied with different assumptions regarding pleiotropy to minimize the risk of bias in our estimates. Instrument strength was assessed using the mean F statistic and outcome r^2. To evaluate pleiotropy, the MR-Egger intercept was included for directional pleiotropy and the MR-PRESSO global and distortion tests for horizontal pleiotropy and its impact on estimates. Heterogeneity was examined using Cochran's Q for IVW MR and Rucker's Q for Egger MR.

Declarations

Data availability

Due to national and EU data protection regulations, the individual-level genotypic and phenotypic data from EstBB are available on request, following data access guidelines, including approval from the Research Ethics Committee of the Estonian Research Council: https://genomics.ut.ee/en/content/estonian-biobank#dataaccess.

Data from MoBa is managed by the Norwegian Institute of Public Health. Access requires approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with GDPR, and data owner approval. Participant consent does not allow individual-level data storage in repositories or journals. Researchers seeking access for replication must apply via www.helsedata.no.

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Conflict of interest

Henrik Larsson reports receiving grants from TAKEDA; personal fees from and serving as a speaker for Medice, Takeda Pharmaceuticals and Neuraxpharm Sweden AB; advisory board for TAKEDA and

Neuraxpharm Sweden AB; all outside the submitted work. Henrik Larsson is editor-in-chief of JCPP Advances.

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Figures

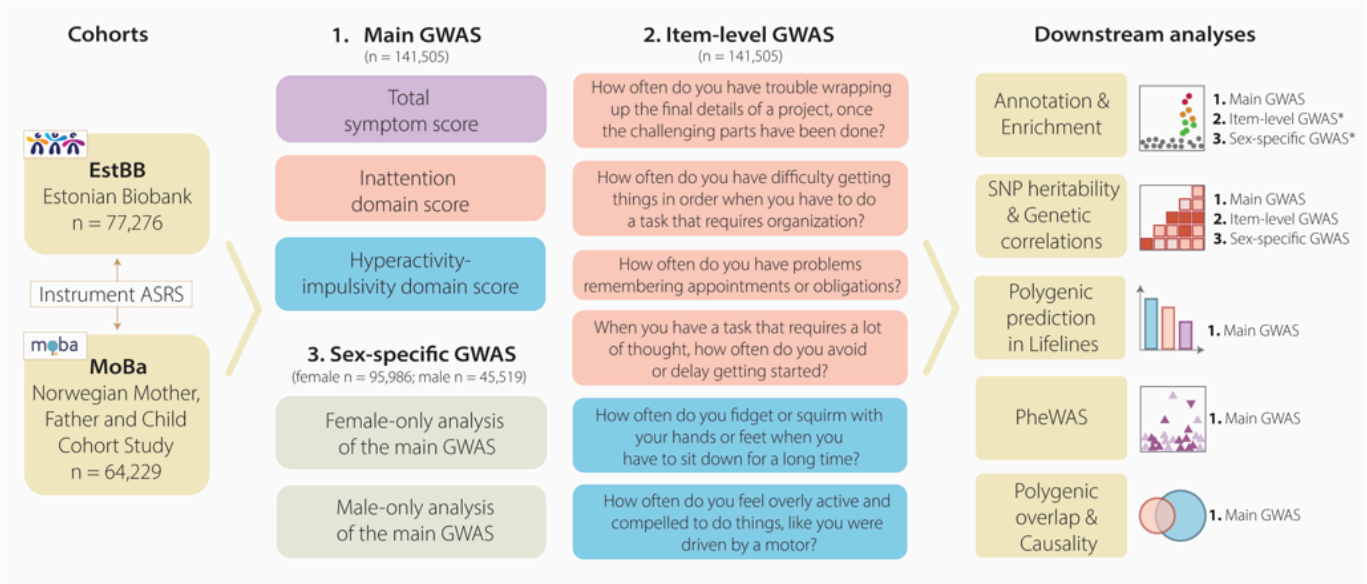


Figure 1

Study overview: Genome-wide meta-analysis of self-reported ADHD symptoms in adults.

Note: *Only annotations. GWAS - genome-wide association study; ASRS - Adult ADHD Self-Report Scale Version 1.1; PheWAS - phenome-wide association study.

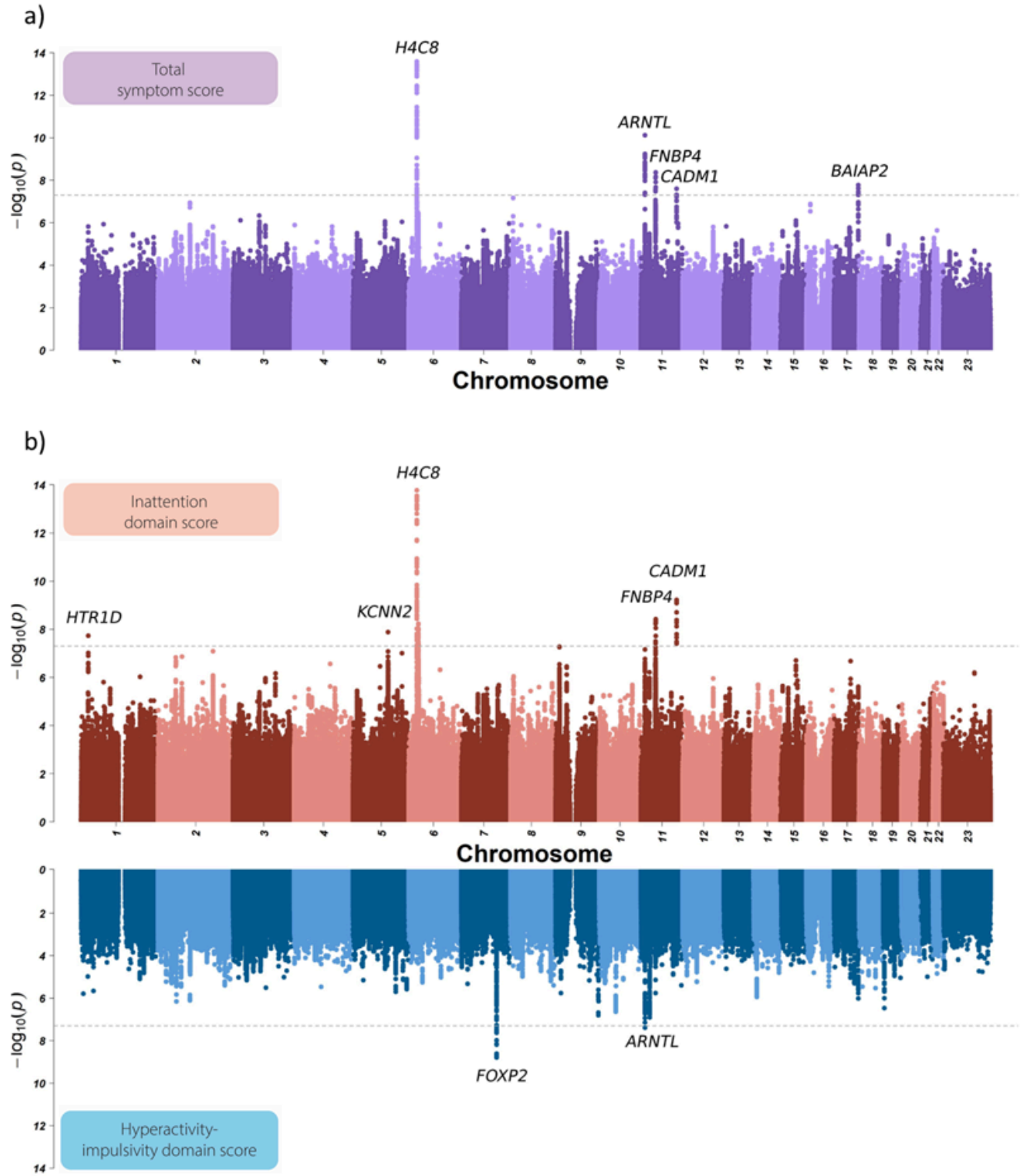


Figure 2

GWAS meta-analysis Manhattan plot of adult ADHD total symptom score and Miami plot of inattention and hyperactivity-impulsivity domains.

Note: Panel a) Total symptom score genome-wide associations across 23 chromosomes; Panel b) inattention domain (red) and hyperactivity-impulsivity domain (blue) genome-wide associations across

23 chromosomes. The horizontal dashed line indicates genome-wide significance ($p=5x10^{-8}$).

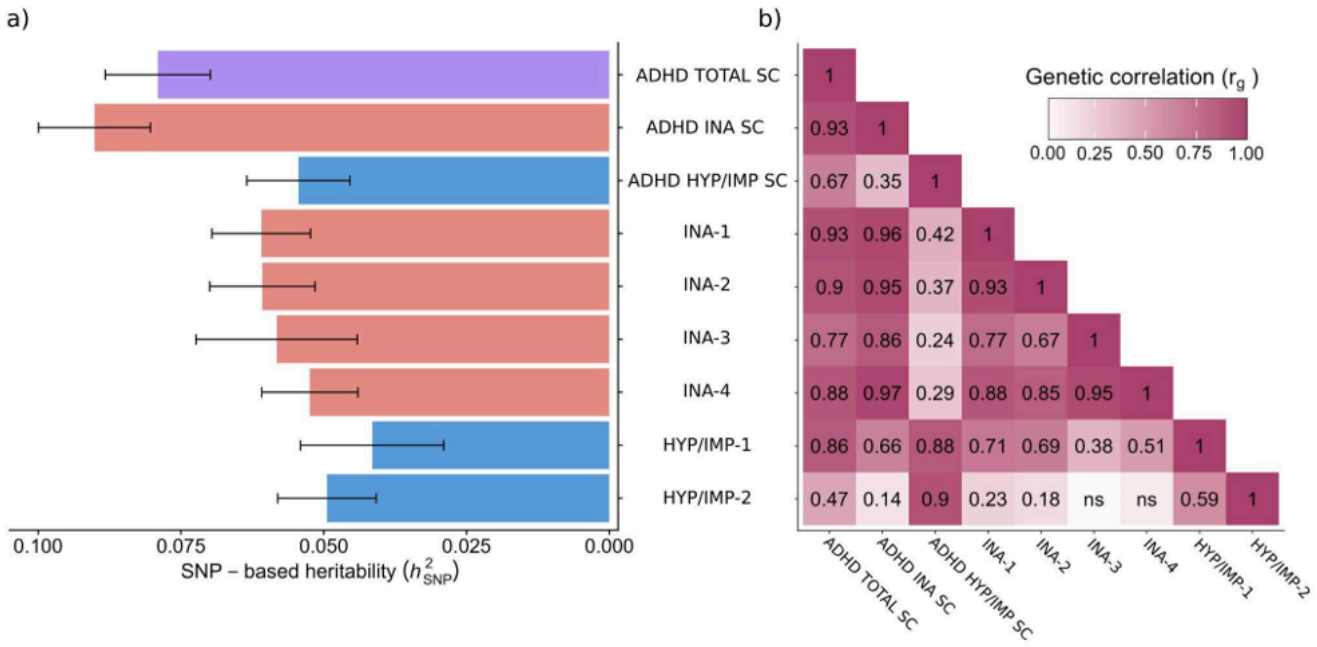


Figure 3

SNP-based heritability and genetic correlations of the adult ADHD symptom phenotypes.

Note: Panel a) LDSC-based h^2_{SNP} estimates for ADHD symptom items and scores, error bars correspond to 95% confidence intervals. Panel b) LDSC estimates of pairwise r_g-s between ADHD symptom items and scores. Non-significant correlations are marked as 'ns'. ADHD TOTAL SC - Total symptom score; ADHD INA SC - inattention domain score; ADHD HYP/IMP SC - hyperactivity-impulsivity domain score; INA-1, INA-2, INA-3, INA-4 - inattention domain items and HYP/IMP-1, HYP/IMP-2 - hyperactivity-impulsivity domain items (see for item descriptions in the Note of Supplementary Table 2).

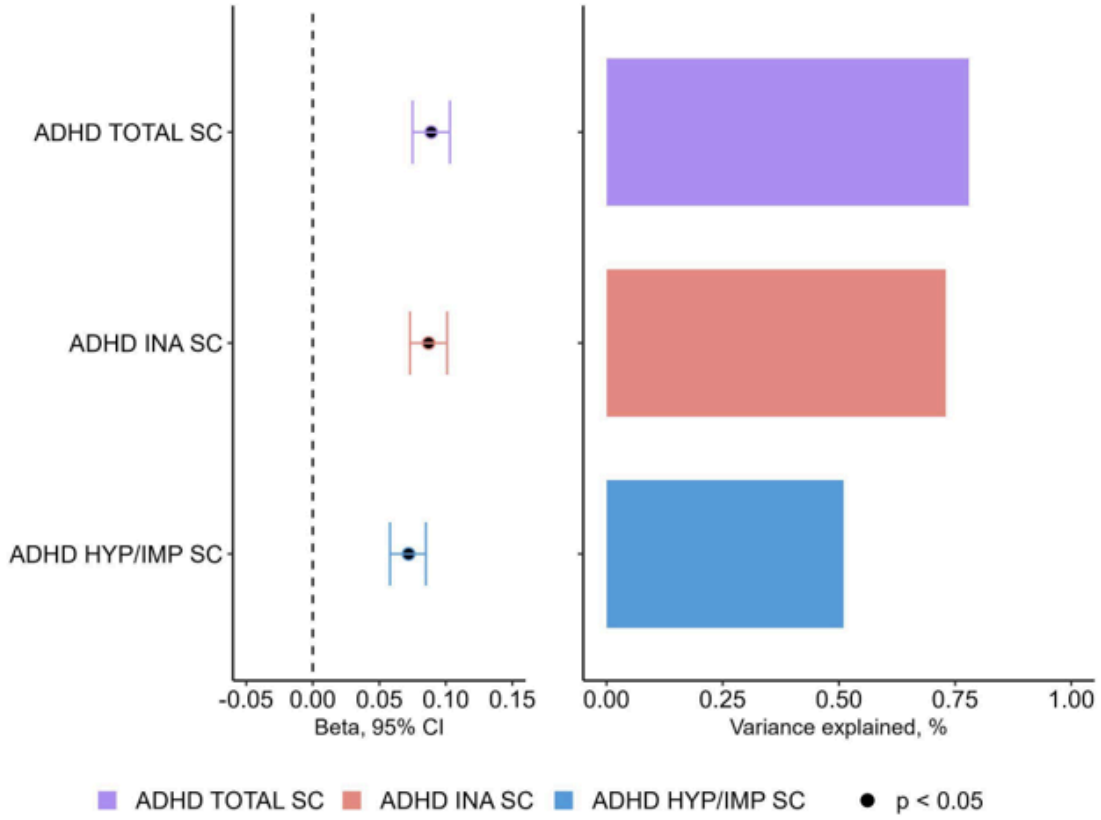


Figure 4

Polygenic score predictions of adult ADHD symptom scores in Lifelines (N=19,857).

Note: Polygenic score (PGS) analysis results for corresponding ADHD symptom score phenotypes in the Lifelines cohort, with the proportion of variance explained by each PGS; ADHD TOTAL SC - total symptom score; ADHD INA SC - inattention domain score; ADHD HYP/IMP SC - hyperactivity-impulsivity domain score; p - p-value; Beta - effect size; CI - confidence interval.

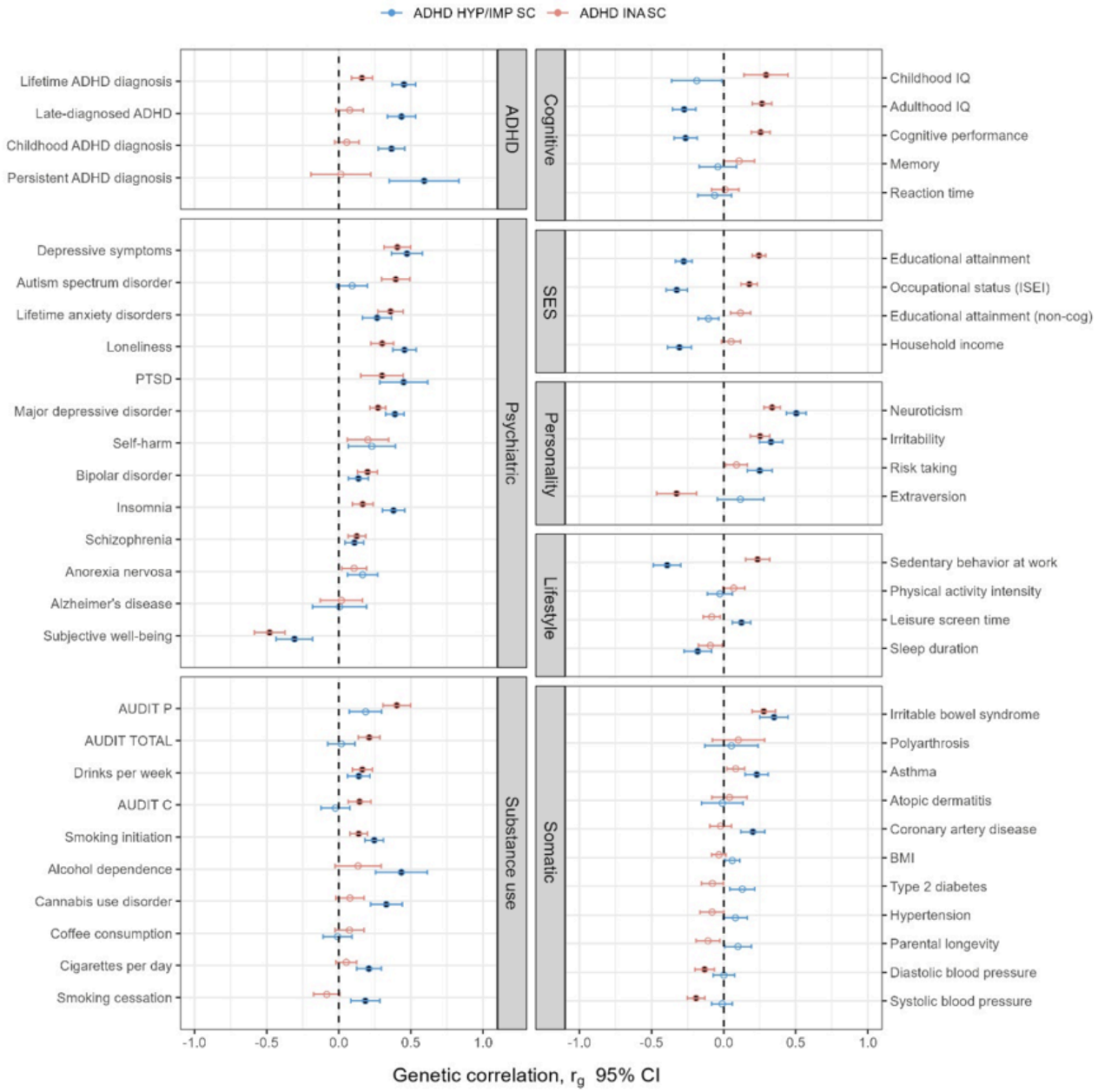


Figure 5

Genetic correlations of adult inattention and hyperactivity-impulsivity domains with 55 other phenotypes.

Note: LDSC-based pairwise r_g-s of inattention domain score (ADHD INA SC; red) and hyperactivity-impulsivity domain score (ADHD HYP/IMP SC; blue). Empty circles indicate associations not surviving the multiple-testing correction threshold ($p=9.1x10^{-4}$); results are sorted within categories by r_g-s for ADHD INA SC. ADHD - attention-deficit/hyperactivity disorder; AUDIT C - alcohol use disorder identification test - consumption; AUDIT P - alcohol use disorder identification test - problematic consequences, AUDIT TOTAL - total score on alcohol use disorder identification test; BMI - body mass index; IQ - intelligence quotient; ISEI - international socio-economic index of occupational status; PTSD -

post-traumatic stress disorder; SES - socio-economic status; non-cog - non-cognitive; CI - confidence interval.

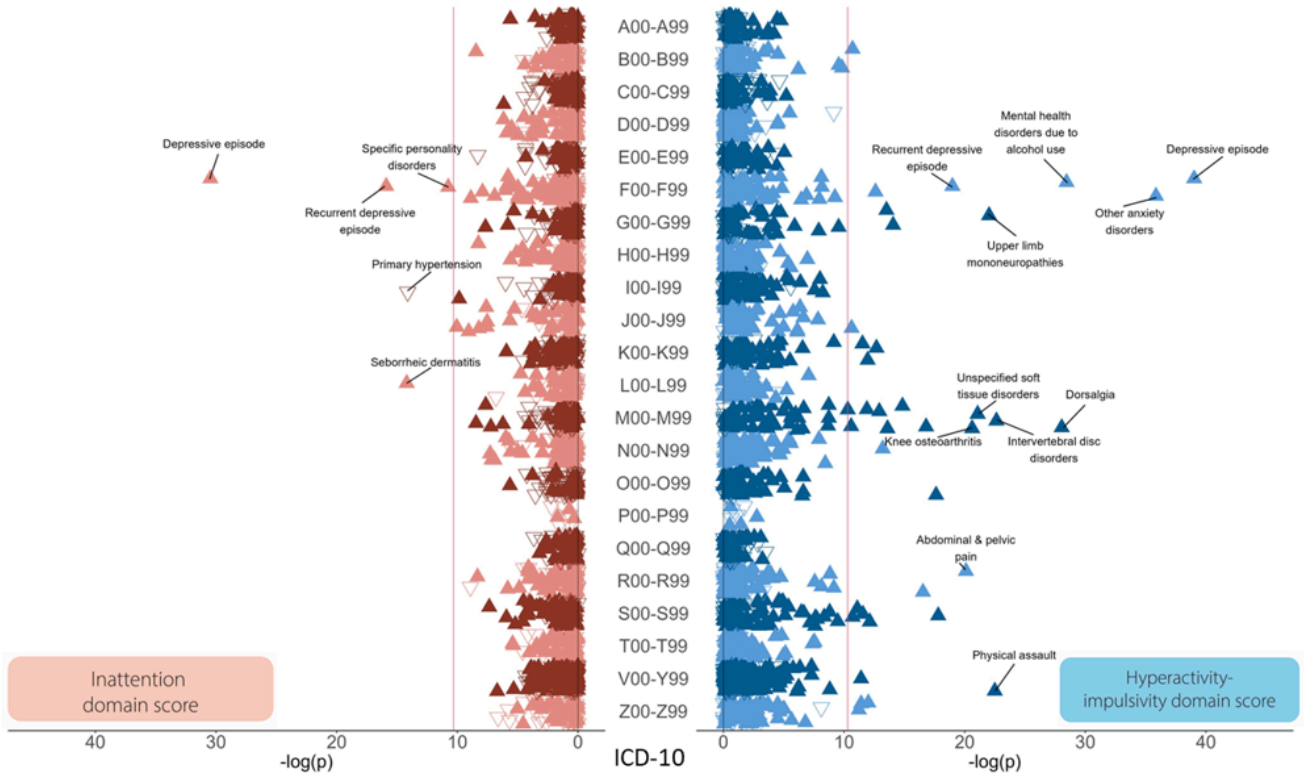


Figure 6

Phenome-wide associations of polygenic scores for adult inattention and hyperactivity-impulsivity domains with ICD-10 diagnostic history in the Estonian Biobank (N=125,148).

Note: Left (red) – inattention domain score results, all significant hits are labelled. Right (blue) – hyperactivity-impulsivity domain score results, top 11 significant hits are labelled. Upwards arrow indicates positive association; downwards empty arrow indicates negative association; red line represents significance threshold at $p=2.9x10^{-5}$; ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) categories: A00-B99 - Certain infectious and parasitic diseases, C00-D48 - Neoplasms, D50-D89 - Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, E00-E90 - Endocrine, nutritional and metabolic diseases, F00-F99 - Mental and behavioural disorders, G00-G99 - Diseases of the nervous system, H00-H59 - Diseases of the eye and adnexa, H60-H95 - Diseases of the ear and mastoid process, I00-I99 - Diseases of the circulatory system, J00-J99 - Diseases of the respiratory system, K00-K93 - Diseases of the digestive system, L00-L99 - Diseases of the skin and subcutaneous tissue, M00-M99 - Diseases of the musculoskeletal system and connective tissue, N00-N99 - Diseases of the genitourinary system, O00-O99 - Pregnancy, childbirth and the puerperium, P00-P96 - Certain conditions originating in the perinatal period, Q00-Q99 - Congenital malformations, deformations and chromosomal abnormalities,

R00-R99 - Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, S00-T98 - Injury, poisoning and certain other consequences of external causes, V01-Y98 - External causes of morbidity and mortality, Z00-Z99 - Factors influencing health status and contact with health services.

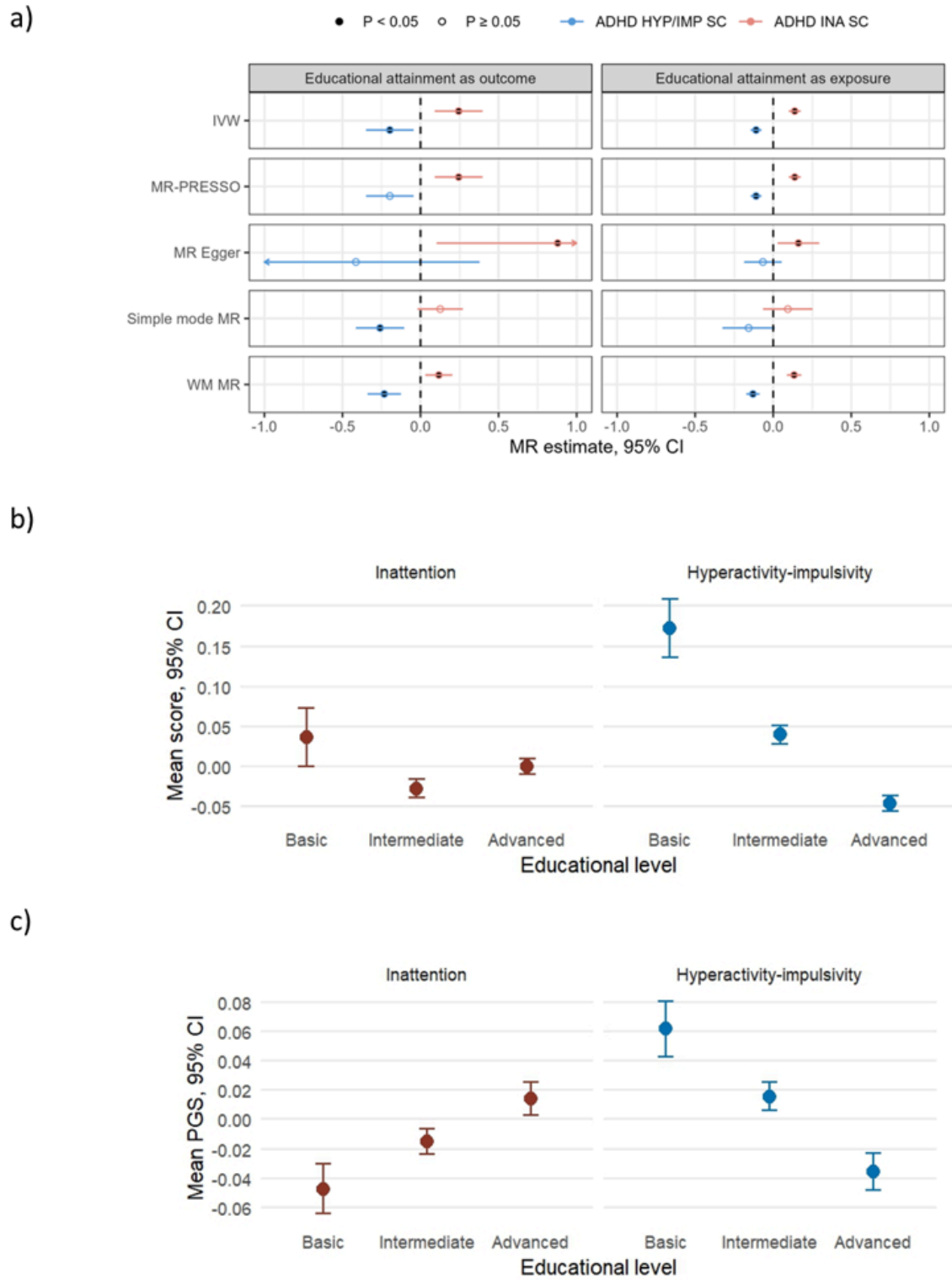


Figure 7

Genetic and phenotypic associations between symptom domains and educational attainment.

Note: Panel a) Mendelian randomization (MR) results in the meta-analysed GWAS sample (N=141,505) between educational attainment and inattention (ADHD INA SC; red) and hyperactivity-impulsivity (ADHD HYP/IMP SC; blue) domain scores. WM - Weighted median, IVW - Inverse variance weighted, MR-PRESSO - Mendelian Randomization Pleiotropy RESidual Sum and Outlier; P - p-value. For MR-PRESSO, 95% confidence intervals (CI) were approximated as β±1.96×s.d. for visualization purposes only, MR-PRESSO uses permutation-based inference and does not provide asymptotic standard errors. Panel b) Mean z-standardized domain scores adjusted by sex and birth year per educational level in the EstBB sample (n=77,276). Panel c) Mean z-standardized PGSs adjusted by sex, birth year, and 10 PCs per educational level in the out-of-sample EstBB subset (N=72,589).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTablesADHDSYMP.xlsx
- ExtendedDataFiguresandTablesADHDSYMP.docx
- SupplementaryFiguresADHDSYMP.docx