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Genome-wide association meta-analysis of childhood ADHD symptoms and diagnosis identifies new loci and potential effector genes

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We performed a genome-wide association meta-analysis (GWAMA) of 290,134 attention-deficit/hyperactivity disorder (ADHD) symptom measures of 70,953 unique individuals from multiple raters, ages and instruments ($ADHD_{SYMP}$). Next, we meta-analyzed the results with a study of ADHD diagnosis ($ADHD_{OVERALL}$). $ADHD_{SYMP}$ returned no genome-wide significant variants. We show that the combined $ADHD_{OVERALL}$ GWAMA identified 39 independent loci, of which 17 were new. Using a recently developed gene-mapping method, Fine-mapped Locus Assessment Model of Effector genes, we identified 22 potential ADHD effector genes implicating several new biological processes and pathways. Moderate negative genetic correlations ($r_g < -0.40$) were observed with multiple cognitive traits. In three cohorts, polygenic scores (PGSs) based on $ADHD_{OVERALL}$ outperformed PGSs based on ADHD symptoms and diagnosis alone. Our findings support the notion that clinical ADHD is at the extreme end of a continuous liability that is indexed by ADHD symptoms. We show that including ADHD symptom counts helps to identify new genes implicated in ADHD.

Attention-deficit/hyperactivity disorder (ADHD) is, for many individuals, a persistent neurodevelopmental disorder[1,2]. ADHD is characterized by the following three core symptoms: hyperactivity, impulsivity and inattention[3]. It affects around 5% of children and adolescents and 2.5% of adults worldwide[4]. ADHD may be associated with serious consequences for affected individuals, their families and society at large, with symptoms persisting across multiple settings, that is, at home, at school and elsewhere[5,6]. This disorder has a predominantly genetic etiology, involving both common and rare genetic variants[7]. The mean estimated heritability across 37 twin studies of ADHD was 74%[8–10].

In 2019, a genome-wide association meta-analysis (GWAMA) of clinical ADHD, hereafter referred to as $ADHD_{DIAG2019}$, which included data from 20,183 cases and 35,191 controls, identified the first 12 genome-wide significant loci associated with ADHD[11]. The study reported that 22% of the variance in ADHD could be explained by all measured single nucleotide polymorphisms (SNPs). They also performed meta-analyses with data from deCode, 23andMe and the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium[12]. Four independent loci reached the genome-wide significance threshold in all three meta-analyses. Interestingly, most independent significant loci, 15, were found in the meta-analysis with EAGLE, based on a quantitative assessment of attention problems, implying that this can boost the power to identify associated variants. In 2023, $ADHD_{DIAG2019}$ was updated, almost doubling the number of cases[13]. In this updated GWAMA, $ADHD_{DIAG}$, the definition of cases was broader, for example, by including individuals who used ADHD prescription medication. The study reported 27 independent significant loci and estimated that 14% of the variance in ADHD could be attributed to the included SNPs. The broader definition of ADHD diagnosis not only resulted in a larger sample and therefore more power to detect implicated genetic variants, but also increased the heterogeneity of the phenotype, which may explain the decrease in estimated SNP heritability[14].

There is an increasing recognition that ADHD symptom counts in nonclinical samples can tap into the same genetic construct as clinically

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Table 1 | Cohort descriptives

Cohort	n_{unique}	n_{GWASs}	n_{obs}	Instrument	Raters	Minimum age	Maximum age	Mean age
ABCD	1,154	5	4,471	18	M,S,T	5	13	8.46
ALSPAC	7,308	7	33,973	18	M,T	7	18	10.99
BREATHE	1,638	1	1,638	13	T	7	11	9.23
CATSS	7,094	9	33,052	1,7,8,17,18	F,M,S	8	19	13.66
CHDS	626	4	2,429	12,16,17	M,S	10	16	13.72
COGA	2,072	1	2,072	13	S	R	R	R
COPSAC	459	1	459	18	M	6	9	8.5
Dunedin	882	2	1,069	16	M	13	15	14.06
E-risk	1,859	1	1,859	14	S	18	18	18
FinnTwin	1,138	5	4,998	15	F,S,T	10	18	13.80
Gen-R	2,654	8	13,646	2,3,4,17	F,M,S,T	3	12	6.95
GINIplus/LISA	1,439	2	2,582	18	M,S	9	17	12.43
GSMS	730	3	1,605	9	M	9	17	13.12
IBG	1,052	4	2,519	3	M	7	18	12.83
INMA	541	1	541	13	T	3	7	5.06
INSchool	3,557	21	15,813	3,4,6,18	F,M,S,T	5	17	9.94
MCTFR	2,040	2	3,662	13	T	11	14	13.26
MoBa	8,200	4	22,703	3,20	M	1	8	3.93
MSUTR	1,280	3	3,517	3,4,6	M,S,T	6	9	7.83
MUSP	1,242	3	3,624	3,6	M,T	4	15	11.21
NFBC1986	3,433	1	3,433	6,19	S	16	16	16.01
NTR	6,228	16	52,615	3,4,5,6,11	F,M,S,T	2	17	8.49
QIMR	3,978	3	5,528	20	M,S	9	18	14.01
Raine study	1,484	4	5,407	3	M,S	5	15	9.63
TCHAD	647	5	4,268	3,6	M,S	8	17	13.48
TEDS	6,030	26	49,985	16	M,S,T	1	18	8.89
TRAILS	1,354	9	10,657	3,4,6	M,S,T	10	18	13.44
VTSABD	834	3	1,469	9	M	8	18	14.08
Total	70,953	154	290,138					

Instrument codes—1, ASEBA-ABCL; 2, ASEBA-BPM; 3, ASEBA-CBCL; 4, ASEBA-TRF; 5, ASEBA-YASR; 6, ASEBA-YSR; 7, ASRS; 8, A-TAC; 9, CAPA; 10. Conner's; 11, Devereux; 12, DISC; 13, DSM-IV; 14, DSM-V; 15, MPNI; 16, RBPC; 17, Rutter/Conners; 18, SDQ; 19, SWAN; 20, RS-DBD. For the full descriptives, see Supplementary Tables 2 and 8. M, mother report; F, father report; S, self-report; T, teacher report; R, retrospective.

diagnosed ADHD, supporting the notion that clinical ADHD is at the extreme end of a continuous measure of ADHD symptoms[15,16]. This hypothesis was initially suggested based on multivariate twin studies[17]. In support, the genetic correlation (r_g) between quantitative ADHD symptom counts[12] and $ADHD_{DIAG2019}$ (ref. 11) was estimated to be 0.97 (s.e. = 0.21, $P = 2.66 \times 10^{-6}$), suggesting that combining these measures is a viable strategy to increase statistical power in ADHD GWASs. This was further supported by the increased number of genome-wide significant loci in the meta-analysis of $ADHD_{DIAG2019}$ and EAGLE, as compared to $ADHD_{DIAG2019}$ alone, and to meta-analyses of $ADHD_{DIAG2019}$, deCode and 23andMe.

Here we combined information from 28 population-based cohorts in a GWAMA of continuous ADHD symptom scores, comprising a total of 70,953 participants (Table 1). The measures included repeated assessments (longitudinal data) by multiple raters (maternal, paternal, teachers and self-assessments) and instruments across ages (range = 2–18 years), for a total of 290,134 measures. We also included retrospective self-report data. The details in ref. 18 showed that using repeated measures greatly improved GWAS power over using a single aggregated outcome. We meta-analyzed all available data into a cross-rater/cross-age/cross-instrument GWAMA of ADHD symptoms ($ADHD_{SYMP}$), taking into consideration the dependency between multiple assessments within individuals[19]. Analyzing measures from multiple raters and ages may further increase the power of the analyses because of an increase in the validity of the ADHD symptom measures. Next, we estimated the genetic correlations (r_g) between $ADHD_{SYMP}$ and the meta-analysis of case-control samples[13], and meta-analyzed $ADHD_{SYMP}$ with $ADHD_{DIAG}$ ($ADHD_{OVERALL}$). Finally, we performed fine mapping and gene-based tests based on $ADHD_{SYMP}$ and $ADHD_{OVERALL}$, performed follow-up enrichment and pathway analyses, estimated genetic correlations between the GWAMA and a set of predefined outcomes from cognitive and externalizing behavior domains and assessed out-of-sample polygenic score (PGS) prediction in three cohorts.

Results

$ADHD_{SYMP}$ GWAMA

We first meta-analyzed the effect of each SNP across all available univariate GWASs of quantitative ADHD measures. Based on an effective sample size of 120,092, the estimated h^2_{SNP} of $ADHD_{SYMP}$ was 0.04 (s.e. = 0.01; $z = 8.12$). The mean χ^2 statistic was 1.09 with a linkage disequilibrium score regression (LDSC) intercept of 1.01 (s.e. = 0.01), indicating that there was no or very limited inflation in test statistics

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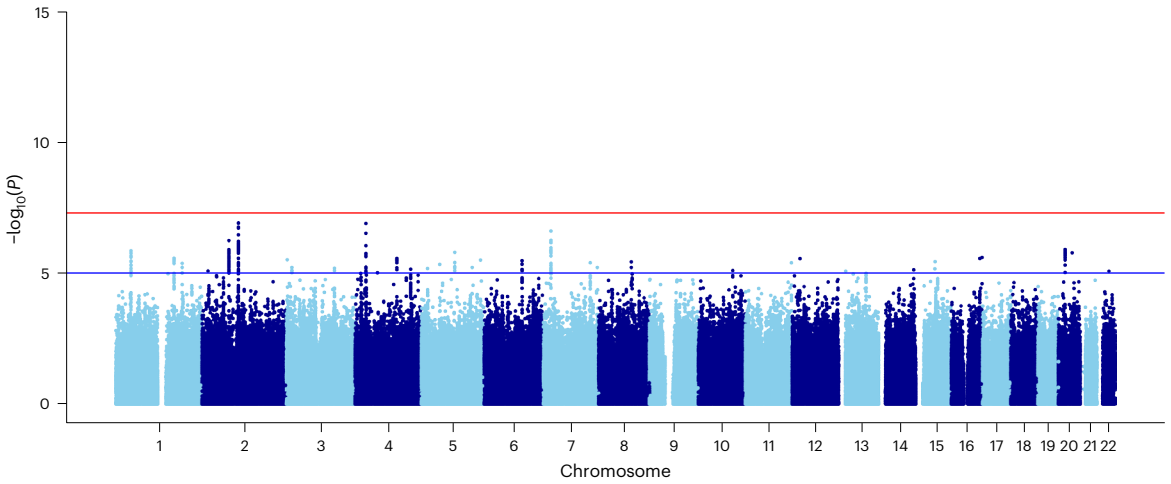

Fig. 1 | Manhattan plot of GWAMA of ADHD symptoms. The red line represents the genome-wide significance threshold ($P < 5 \times 10^{-8}$), adjusted for multiple comparisons of common variants across the entire genome. The blue line represents a more lenient threshold ($P < 1 \times 10^{-5}$).

due to confounding biases, such as population stratification. Rather, the GWAMA most likely captured the polygenic nature of childhood ADHD symptoms. The GWAMA of ADHD symptoms did not identify any genome-wide significant SNPs (Fig. 1 and Supplementary Table 11).

Stratified meta-analyses of ADHD symptoms

After meta-analyzing all univariate ADHD symptoms GWASs, we performed the following stratified meta-analyses: rater specific, age specific and instrument specific. For most stratified results, h^2z was <4. The genetic correlation between the two largest stratified GWAMAs, namely teacher-rated ADHD symptoms and mother-rated ADHD symptoms, was 0.72 (s.e. = 0.13), indicating that there are some rater differences in the effects of genetic variants, which likely depend on the different contexts in which teachers and parents observe the behavior[9]. Forest plots for the lead SNPs in all significant loci with the effect sizes from all stratified GWAMAs did not reveal any clear patterns, because the smaller sample sizes led to larger standard errors (Supplementary Data 1).

Meta-analysis with ADHD diagnosis GWAS

SNP heritability estimated with genomicSEM was 0.13 (s.e. = 0.01) for $ADHD_{DIAG}$. The estimated genetic correlation between $ADHD_{SYMP}$ and $ADHD_{DIAG}$ was 1.00 (s.e. = 0.06). The cross-trait intercept (CTI) was not substantially different from zero and was subsequently constrained to zero in the following meta-analysis.

Because the point estimate of the genetic correlation between $ADHD_{SYMP}$ and $ADHD_{DIAG}$ was not substantially different from 1, we constrained the genetic correlation at unity when pre-adjusting the weights and *z* scores for the meta-analysis of $ADHD_{SYMP}$ and $ADHD_{DIAG}$. A total of 6,571,852 SNPs were included in the meta-analysis. The SNP heritability of $ADHD_{OVERALL}$ was 0.11 (s.e. = 0.01), with a mean χ^2 statistic of 1.52. The LDSC-intercept and ratio were 1.02 (s.e. = 0.01) and 0.03 (s.e. = 0.02), respectively, indicating that approximately 3% of the signal might be due to confounding factors. Figure 2 shows a Manhattan plot of $ADHD_{OVERALL}$. A total of 2,039 SNPs reached genome-wide significance ($P < 5 \times 10^{-8}$), of which 644 were also reported in $ADHD_{DIAG}$ and 1,395 were new. The 2,039 SNPs corresponded to 43 independent lead SNPs in 39 independent significant loci, identified with FUMA (https://fuma.ctglab.nl)[20], CAVIARBF[21], FINEMAP[22] and PAINTOR[23] (for locus plots, see Supplementary Data 1 and 2). Of these 39 loci, 22 were also reported in $ADHD_{DIAG}$ and 17 were new. All 17 new loci were suggestive ($P < 1 \times 10^{-5}$) in $ADHD_{DIAG}$. This suggests that including $ADHD_{SYMP}$ led to an increase in power that pushed these 17 loci over the genome-wide significance threshold. There was some fluctuation in genetic effects among $ADHD_{SYMP}$ cohorts (Supplementary Data 2). Five independent significant loci in $ADHD_{DIAG}$ did not replicate in $ADHD_{OVERALL}$. Of these five loci, all lead SNPs were still suggestive in $ADHD_{OVERALL}$, two loci (on chromosomes 3 and 7) had opposite directions of effects, and three loci (on chromosomes 3, 4 and 8) had effects in the same direction (Supplementary Tables 12 and 13).

Follow-up analyses

Fine mapping and gene-based tests. Follow-up analyses for $ADHD_{SYMP}$ did not reveal any implicated pathways or genes. For $ADHD_{OVERALL}$, gene mapping in FUMA mapped the 43 lead SNPs in 39 independent genomic risk loci to 204 associated genes (Supplementary Table 15), of which 45 were also reported in ref. 13. Second, gene-based tests were run in MAGMA[24], identifying 64 associated genes (Supplementary Table 16), of which 17 were previously reported in ref. 13. Third, we ran Fine-mapped Locus Assessment Model of Effector genes (FLAMES)[25], with the aim to get a better understanding of genes that are causally involved in ADHD. A total of 22 genes had FLAMES scores larger than 0.05 and were interpreted as potential effector genes, of which 14 were also tagged by the MAGMA gene-based test and 10 were previously reported in ref. 13. Four genes were not reported in ref. 13 but have previously been linked to ADHD, as listed in the GWAS Catalog (https://www.ebi.ac.uk/gwas/). Eight potential effector genes were not reported in ref. 13 or in any ADHD-specific studies listed in the GWAS Catalog—*EMCN*, *STK32C*, *PCDH17*, *TCF12*, *PEAK1*, *IGF1R*, *CTNNA2* and *ABCA12*. See Supplementary Table 17 for an overview of all potential effector genes, including Ensembl.org links, and refer to Supplementary Methods for the National Center for Biotechnology Information summaries for all of these genes.

Enrichment and tissue-specific expression. Gene-set analysis in MAGMA revealed no substantial enrichment in any MSigDB v2023 gene sets after correction for multiple testing. MAGMA expression analysis showed substantial enrichment of the GWAMA signal in gene sets differentially expressed in late infancy. Additionally, there was substantial enrichment in several brain tissue types, as well as in the pituitary gland (Supplementary Figs. 2 and 3).

Next, FUMA GENE2FUNC gene-set enrichment analyses of the 204 potential ADHD risk genes mapped by FUMA exhibited substantial enrichment in genes identified in GWAS of ADHD, cognition-related phenotypes and risk-taking behaviors. These 204 genes were not substantially enriched in any tissue types or in any of the Brainspan developmental stages of brain samples (http://www.brainspan.org), but were enriched in 29 gene sets that code for transcription factor targets. No synapse cellular component terms or biological processes

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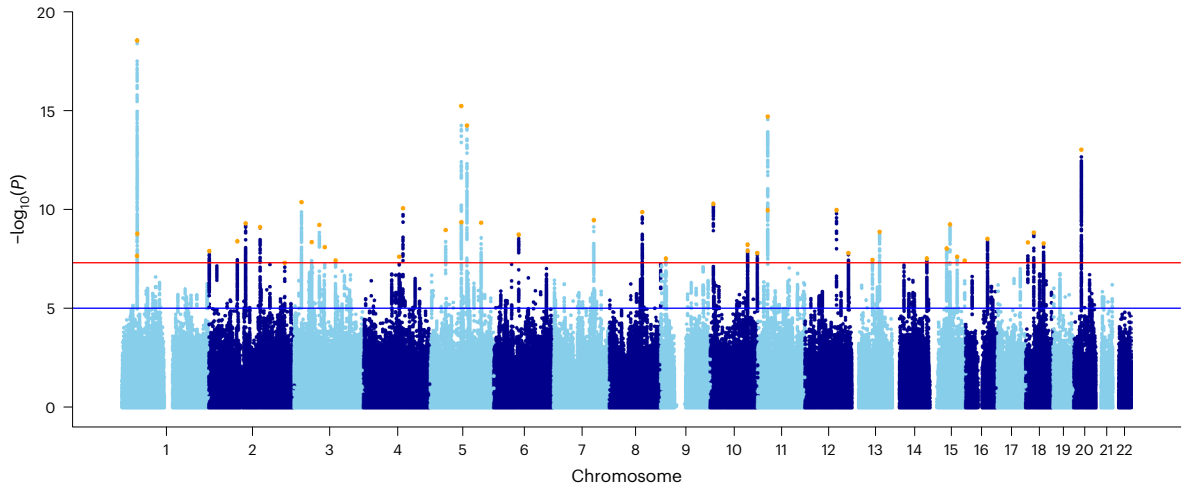

Fig. 2 | Manhattan plot of GWAMA of ADHD symptoms and ADHD diagnosis. Orange dots reflect lead SNPs. The red line represents the genome-wide significance threshold ($P < 5 \times 10^{-8}$), adjusted for multiple comparisons of common variants across the entire genome. The blue line represents a more lenient threshold ($P < 1 \times 10^{-5}$).

were enriched at 1% false discovery rate (testing terms with at least three matching input genes in SynGO; https://www.syngoportal.org). For a complete overview of all enrichment results and the included gene sets, see Supplementary Figs. 4–6 and Supplementary Methods.

We repeated the same analyses for the 22 potential effector genes identified by FLAMES. Again, findings were highly enriched for genes identified in GWAS of cognition-related phenotypes and risk-taking behaviors. The 22 genes were substantially overrepresented in gene sets that are differentially expressed in the frontal cortex, but not in the 'general tissue' type brain or in any of the Brainspan developmental stages. They were also enriched in 52 gene sets that code for transcription factor targets, 13 microRNA targets, 4 Gene Ontology (GO) biological processes, 1 canonical pathway and 8 cell-type signatures. No synapse cellular component terms or biological processes were enriched at 1% false discovery rate (testing terms with at least three matching input genes in SynGO). Nine genes were mapped to SynGO annotations, eight to cellular components and nine to biological processes. Gene enrichment was observed in integral components of the postsynaptic density membrane ($q = 1.46 \times 10^{-3}$), postsynaptic density ($q = 1.57 \times 10^{-3}$), postsynapse ($q = 5.67 \times 10^{-3}$) and synapse ($q = 7.22 \times 10^{-3}$), as well as in postsynaptic modulation of chemical synaptic transmission ($q = 3.28 \times 10^{-5}$), process in the synapse ($q = 3.97 \times 10^{-4}$) and synapse organization ($q = 1.62 \times 10^{-3}$) (where q is the false discovery rate-corrected P value). For a complete overview of all enrichment results and the included gene sets, see Supplementary Figs. 7–13, Supplementary Tables 18–19 and Supplementary Methods.

Genetic correlations. We estimated genetic correlations between $ADHD_{OVERALL}$ and 49 preselected phenotypes. Results are summarized in Fig. 3 and Supplementary Table 19. Strong positive genetic correlations were observed between $ADHD_{OVERALL}$ and childhood aggressive behavior ($r_g = 1.13$, s.e. = 0.05) and antisocial behavior ($r_g = 0.97$, s.e. = 0.06). The correlation of 1.13 with childhood aggressive behavior reflects a high genetic correlation that is estimated to be greater than 1 due to sampling variation, as correlations estimated by LDSC in genomicSEM are not bounded between −1 and 1 (childhood aggression $h^2 z = 9.03$). Measures of smoking habits ($r_g = 0.46$–0.60, s.e. = 0.03) and number of children ($r_g = 0.38$, s.e. = 0.04) also showed moderate correlations, as did ratings of overall health ($r_g = -0.59$, s.e. = 0.03), educational attainment ($r_g = -0.55$, s.e. = 0.02) and childhood IQ ($r_g = -0.43$, s.e. = 0.06). In general, $ADHD_{OVERALL}$ showed weak-to-moderate genetic correlations with psychopathology, including major depressive disorder ($r_g = 0.57$, s.e. = 0.03) and autism spectrum disorder ($r_g = 0.39$, s.e. = 0.04). Weak negative genetic correlations were found between $ADHD_{OVERALL}$ and alcohol intake frequency ($r_g = -0.28$, s.e. = 0.03). Correlations with drinks per week ($r_g = 0.14$, s.e. = 0.03) and cannabis use ($r_g = 0.20$, s.e. = 0.03) were small and positive. Ref. 26 investigated the contrasting correlations for alcohol intake frequency and drinks per week. They found evidence to suggest that this discrepancy is the result of confounding socioeconomic status (SES) influences. $ADHD_{OVERALL}$ was weakly negatively genetically correlated with birth weight ($r_g = -0.10$, s.e. = 0.02), which confirms earlier findings of a causal relation between birth weight and ADHD[27]. $ADHD_{OVERALL}$ was positively correlated with childhood obesity ($r_g = 0.21$, s.e. = 0.05) and adult body mass index ($r_g = 0.30$, s.e. = 0.02). The genetic correlations estimated in $ADHD_{DIAG}$ and $ADHD_{OVERALL}$ were very similar. The general trends were the same: positive correlations with substance use, number of children and multiple psychopathologies. Negative correlations were found for cognitive traits, health outcomes and well being.

PGS analysis. We assessed the performance of PGSs based on $ADHD_{SYMP}$, $ADHD_{DIAG}$ and $ADHD_{OVERALL}$ by modeling their effect on an aggregated ADHD measure in three large cohorts (ALSPAC, MoBa and NTR). We meta-analyzed the results in these three cohorts, which indicated that $ADHD_{OVERALL}$ performed best ($\beta = 0.13$, s.e. = 0.04), followed by $ADHD_{DIAG}$ ($\beta = 0.11$, s.e. = 0.04) and $ADHD_{SYMP}$ ($\beta = 0.08$, s.e. = 0.03). Explained variance within each cohort was largest for the $ADHD_{OVERALL}$ PGS (0.3% in MoBa, 2.2% in ALSPAC and 3.1% in NTR), which was an increase compared to $ADHD_{DIAG}$ (0.2% in MoBa, 2% in ALSPAC and 2.5% in NTR). The PGS for $ADHD_{SYMP}$ explained 0.1% in MoBa, 1.1% in ALSPAC and 1.2% in NTR.

Discussion

We present a GWAMA of childhood $ADHD_{SYMP}$. A total of 28 cohorts with measures of ADHD symptom counts took part, contributing data from multiple raters and instruments across a wide range of ages. We meta-analyzed all continuous measures and combined these results with results from two GWAMAs of ADHD diagnosis ($ADHD_{DIAG}$)[11,13].

We did not identify genome-wide significant hits for ADHD symptoms, but estimated a genetic correlation with ADHD diagnosis ($r_g = 1.00$, s.e. = 0.06). This supports the notion that clinical ADHD is at the extreme end of a continuous genetic liability that is indexed by ADHD symptoms[15,16], as previously suggested based on multivariate twin studies[17]. The estimated h^2_{SNP} of $ADHD_{SYMP}$ was 0.04 (s.e. = 0.01), which may be considered low compared to the estimated h^2_{SNP} in refs. 11,13 (0.22 and 0.14, respectively). This may be due to the heterogeneous

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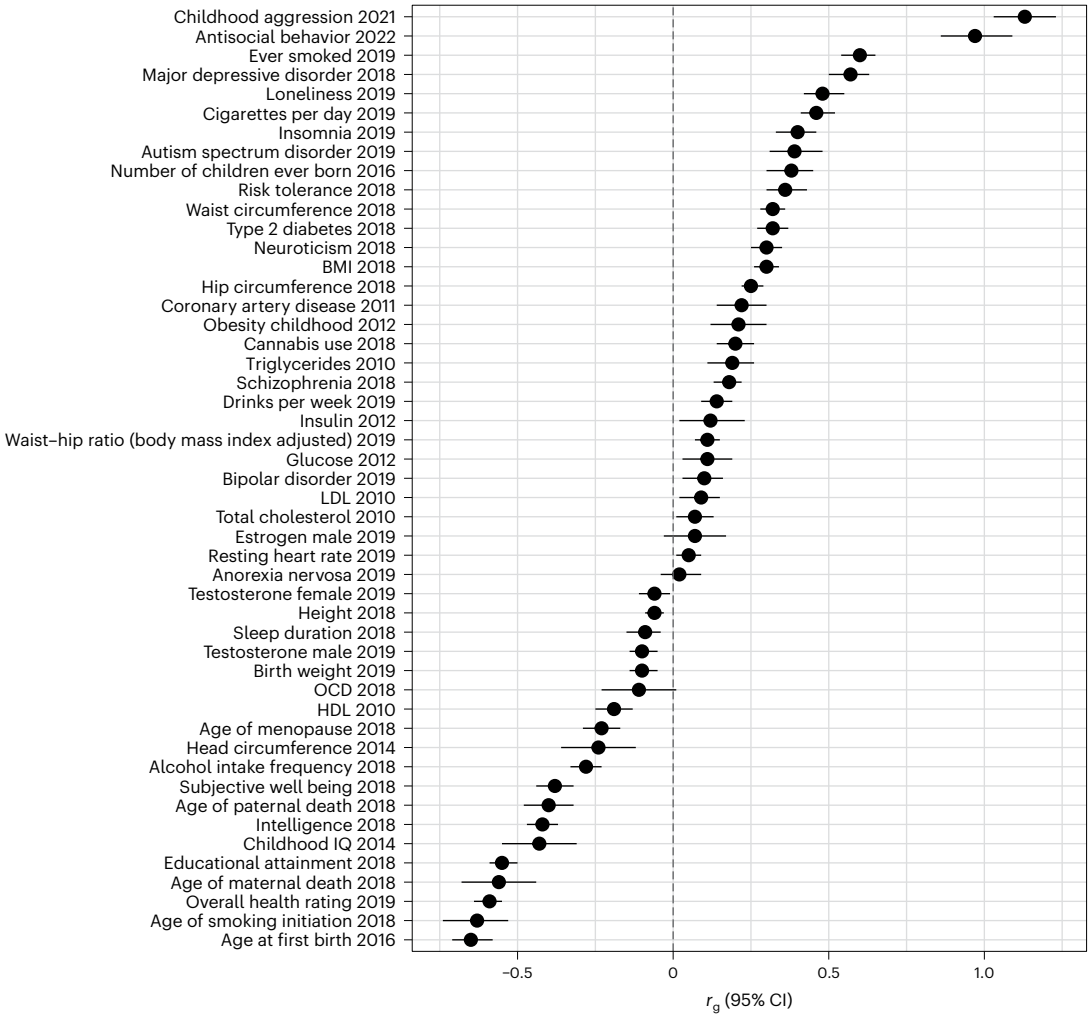

Fig. 3 | Genetic correlations with external phenotypes. Dots indicate genetic correlation estimates and bars indicate 95% confidence intervals. Study-specific information for each genetic correlation can be found in Supplementary Table 10. Genetic correlation estimates and s.e. are listed in Supplementary Table 20.

measurement error and bias in phenotyping by including symptom measures from different raters, and at different ages, which could subsequently suppress SNP heritability.

By meta-analyzing GWASs of ADHD symptoms and ADHD diagnosis, we found 2,039 genome-wide significant variants in 39 independent loci, of which 17 were new. The studies discussed in refs. 11,13 identified 12 and 27 independent loci in 2019 and 2023, respectively. This shows that combining ADHD symptom counts with diagnosis can be effective in identifying implicated genetic variants for ADHD. This is of value because ADHD symptom measures have been widely collected. The estimated genomicSEM h^2_{SNP} of $ADHD_{OVERALL}$ was 0.11 (s.e. = 0.01) compared to 0.14 in $ADHD_{DIAG}$. Thus, by including $ADHD_{SYMP}$ in the $ADHD_{DIAG}$ results, h^2_{SNP} decreased slightly. We believe this is due to the heterogeneous measurement error and bias in the $ADHD_{SYMP}$ phenotyping[14]. The same can be observed when looking at the differences in h^2_{SNP} between $ADHD_{DIAG}$ from 2019 ($h^2_{SNP} = 0.22$), which was strict in its definition of ADHD cases, and $ADHD_{DIAG}$ from 2023 ($h^2_{SNP} = 0.14$), which was slightly more lenient in its definition of ADHD cases.

MAGMA analyses identified 64 potential ADHD risk genes, which were substantially enriched in genes previously identified in GWASs of cognitive phenotypes and risk-taking behaviors. The total GWAS signal was substantially differentially expressed in several brain-specific tissue types, general brain tissue types and the pituitary gland, as well as in late infancy Brainspan brain samples (www.brainspan.org). FUMA mapped significant loci to 204 genes. Again, genes were enriched in gene sets reported by previous GWASs of cognitive behavior, risk-seeking behavior, and brain development. FUMA enrichment analyses further revealed 29 transcription factor targets that may be of interest for ADHD.

To identify causal pathways from SNPs to ADHD, we ran FLAMES[25], which identifies likely effector genes. FLAMES reported 22 potential effector genes, of which 14 overlapped with the MAGMA genes, 12 were previously reported in ref. 13 and 8 were neither previously linked to ADHD nor reported in the GWAS Catalog. These 22 genes were substantially overrepresented in gene sets differentially expressed in the frontal cortex, enriched in 4 GO biological processes related to neural and physical development, 52 transcription factor targets, 13 microRNA targets, 8 different cell-type signatures, 4 synapse cellular components and 3 synaptic biological processes. In ref. 13, the set of potential ADHD risk genes was substantially enriched among genes upregulated during early embryonic brain development, but this result was not replicated in the current study. A common theme is that implicated genes are enriched in processes that are involved in neural development and functioning. The results provide several new avenues to investigate to gain more insights into the etiology of ADHD. The results may also provide useful information for the 22 potential effector genes compared to the 204 genes identified by FUMA positional mapping, expression quantitative trait locus mapping and chromatin interaction mapping. It is likely that this difference results from the difference in strategies used by both methods. FUMA maps every gene for which some functional

link is known to exist, whereas FLAMES weighs all these measurements and only prioritizes genes if they are clearly more likely causal genes than the other genes in the locus. Our findings indicate that FLAMES can help to identify functional pathways that may remain hidden with other approaches due to a reduction of noise from noncausal genes in the set of prioritized genes, which decreases the power to detect enrichment in functional gene sets.

Estimates of genetic correlations between $ADHD_{OVERALL}$ and other phenotypes showed substantial genetic correlations with all examined psychopathological traits except anorexia nervosa. Most striking were the genetic correlations of 1.13 with childhood aggressive behavior and 0.97 with antisocial behavior. Previous studies reported moderate-to-strong phenotypic correlations across sex-specific, rater-specific, age-specific and instrument-specific assessments between aggressive behavior and attention problems and hyperactivity[28]. When interpreting these strong genetic correlations, it is important to distinguish between biological pleiotropy and statistical pleiotropy[29]. In biological pleiotropy, the same genetic variants physically underlie both traits. In statistical pleiotropy, the genetic variants in one trait predict the effect of different genetic variants in another trait. It is likely that both types of pleiotropy contribute to the genetic correlation of around 1. We observed a negative genetic correlation between ADHD and alcohol intake frequency and a positive correlation between ADHD and number of drinks per week. The details in ref. 26 suggest that SES effects confound these different genetic correlations. We found a moderate genetic correlation with smoking behaviors, but a small correlation with cannabis use. We observed negative correlations with several cognitive traits, such as (childhood) IQ, verbal-numerical reasoning and educational attainment. Similar to a GWAS of childhood aggression[19], genetic correlations with multiple hormone levels were around zero. Finally, we found a small negative correlation with birth weight, but a weak positive correlation with childhood obesity and adult body mass index. These estimated genetic correlations were very similar to those estimated with $ADHD_{DIAG}$. The genetic correlations suggest wide pleiotropic effects of variants involved in ADHD. This is illustrative of the polygenetic nature of most behavioral, cognitive and mental health traits. It also indicates that genetic factors have a role in the comorbidity of psychopathological disorders.

To assess the performance of PGSs based on $ADHD_{SYMP}$, $ADHD_{DIAG}$ and $ADHD_{OVERALL}$, we modeled their effect on an aggregated ADHD measure in three cohorts (ALSPAC, MoBa and NTR). These results indicated that adding ADHD symptom counts increased the power of the PGS in the three cohorts. The differences were small, especially between $ADHD_{DIAG}$ and $ADHD_{OVERALL}$. In NTR data, the explained variance increased from 2.5% for the $ADHD_{DIAG}$ PGS to 3.1% for the $ADHD_{OVERALL}$ PGS. Therefore, we recommend using the $ADHD_{OVERALL}$ data to construct PGS in future work, especially when predicting ADHD symptoms.

Combining data collected using different instruments and by different raters helps to increase the sample size, and with that the statistical power of our analyses. This is illustrated by the increase in detected genetic variants associated with ADHD in $ADHD_{OVERALL}$. The main benefit of including multiple measures, ratings and instruments is that they are not dependent on a single context. However, we also observed that the genetic effects from $ADHD_{SYMP}$ were smaller compared to $ADHD_{DIAG}$, which may have suppressed SNP heritability. Our study raises the question of how to optimally make use of repeated measures and multiple raters and instruments. In general, GWAMAs could highly benefit from the increased power that could be acquired by including a wider range of measures.

Assessments of ADHD in individuals from non-European ancestry were rare in each of the included cohorts. Because of the low number of assessments, we excluded non-European individuals from our analyses. We know that results from European ancestry GWASs often also substantially predict differences in non-European ancestry groups, but effect sizes are diluted toward zero[30]. Regrettably, this means that knowledge generated by these types of studies risks benefiting individuals of European ancestry more than those from diverse backgrounds. To better understand the etiology of ADHD across individuals and backgrounds, it is important to continue ongoing efforts to increase the inclusivity of GWAS samples.

In conclusion, the current study adds new insight into the genetic etiology of ADHD. By meta-analyzing GWAS results from symptom counts of ADHD in children with a diagnosis of ADHD, we identified new genome-wide significant loci and genes. The number of genome-wide significant genetic variants that are implicated in ADHD provides further insight into the polygenic etiology of ADHD. The 22 potential effector genes identified by FLAMES offer insights into several biological processes that may have a causal role in ADHD etiology, providing avenues for further research. The genetic correlations with other phenotypes further indicate the wide pleiotropic effects of genetic variants and the role that genetic variants has in the co-occurrence with mental health traits.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41588-025-02295-y.

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Methods

Ethics and inclusion statement

This study is the result of a large collaborative effort among multiple clinical and population-based cohorts. Researchers and principal investigators (PIs) representing the individual cohorts were involved in the design and execution of the study. Cohort-specific GWAS analyses were performed locally by local researchers. Local researchers and PIs were included as co-authors in consultation with the PIs of each included cohort. Data collections for the cohorts were approved by local ethics committees. Study approval was obtained from the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (NTR, 25 May 2007 and ACTION 2013/41 and 2014.252), an institutional review board (IRB) certified by the US Office of Human Research Protections (IRB−IRB00002991 under Federalwide Assurance (FWA00017598); IRB/institute codes).

Sample and cohorts

Childhood cohorts that collaborate within the 'Aggression in Children: Unraveling Gene–Environment Interplay to Inform Treatment and Intervention Strategies' (ACTION) consortium[19,28,31] and EAGLE consortium[32] took part in the meta-analysis of ADHD symptom counts ($ADHD_{SYMP}$). Cohorts assessed ADHD symptoms in children and adolescents aged 1.5 to 18 years and also included adult retrospective assessments. Each cohort followed a standardized operating protocol (available at https://www.action-euproject.eu/content/data-protocols and detailed in Supplementary Information). Cohorts could contribute one or several univariate GWASs. A separate analyses were performed for every unique combination of rater, instrument and age (so that each GWAS included a maximum of one measure for each individual), with a minimum of 450 observations per GWAS. Table 1 presents an overview of all included cohorts. Extended information on the cohorts can be found in Supplementary Table 8 and Supplementary Note. Assessments of individuals of non-European ancestry were limited for varying reasons, and analyses were restricted to individuals of European ancestry. In total, 28 cohorts contributed 154 GWASs, resulting in a total of 290,134 observations from 70,953 unique individuals (Supplementary Table 2).

Measurement of ADHD symptoms

ADHD symptoms in children and adolescents were rated by mothers, fathers, teachers and the individuals themselves. Additionally, two cohorts (QIMR and COGA) included retrospective assessments of (pre-)adolescent ADHD symptoms from self-report or maternal report. To maximize sample size, we included measurements of ADHD symptoms from multiple instruments. In total, 20 ADHD symptom assessment instruments were included in the meta-analysis (Supplementary Table 3). The most commonly used instruments were the Achenbach System of Empirically Based Assessment[33] and the Strengths and Difficulties Questionnaire[34].

Genotyping and quality control

Genotyping was performed within each cohort using common genotyping arrays (Supplementary Table 4), followed by cohort-specific quality control (QC) based on individual-based and variant-based call rate, Hardy–Weinberg equilibrium, excessive heterozygosity rates and minor allele frequency (Supplementary Table 5). A total of 78.6% of the cohorts imputed their genotypes to 1000 Genomes Project (1000G) phase 3 version 5, while the other cohorts used 1000G phase 1 version 3 as the reference set for the imputation (Supplementary Table 6). All genotypes were mapped to build 37 of the Human Genome Reference Consortium assembly (GRCh37).

GWAS model

Each cohort performed a univariate GWAS where ADHD symptoms were regressed on the SNP genotype, with age, sex and first five ancestry-based principal components as fixed effects, and, if necessary, cohort-specific covariates (Supplementary Table 7). Three cohorts (BREATHE, INMA and GINIplus/LISA) did not include PCs in their univariate GWAS. These were relatively small and homogeneous GWAS samples. Heterogeneity tests and forest plots indicated no clear outlying results for these three cohorts. The genetic correlation between the full GWAMA and one excluding these cohorts was almost one ($r_g = 0.99$, s.e. = 0.13), and both GWAMAs implicated the same genetic loci and lead SNPs. To correct for dependency between observations within univariate analyses, cohorts with related individuals applied a mixed linear model[35] or a sandwich correction of the standard errors[36].

GWASs were stratified by (1) rater, (2) instrument and (3) age, so that observations within a univariate GWAS were independent, with a minimum stratum sample size of 450 observations. In total, summary statistics for 154 univariate GWAS were uploaded. Descriptive statistics for each uploaded GWAS are shown in Supplementary Table 8. Each cohort also supplied information on the degree of sample overlap and phenotypic correlation between their univariate analyses. These statistics allowed us to account for dependency between observations within cohorts.

Pre-GWAMA QC

Summary statistics from each GWAS were subjected to QC using the EasyQC software package[37]. SNPs with a genotyping rate below 95% were removed. We applied variable QC filters on minor allele frequency and Hardy Weinberg equilibrium *P* value tailored to the sample size. Respective cutoffs of INFO > 0.6 and INFO >0.7 were applied to SNPs that were imputed using MACH and IMPUTE[38]. Reported allele frequencies were compared to the allele frequency in an imputation-matched reference population and variants with an absolute difference in allele frequency larger than 0.2 were removed. Supplementary Table 9 reports the number of SNPs before and after QC. We assessed heterogeneity by calculating the M statistic for each cohort and $ADHD_{DIAG}$. Results indicated that the contribution of the TEDS cohort was substantially weaker compared to the other cohorts. Plotting the M statistic against the average study effect size for the lead SNPs showed that it is unlikely that TEDS biased the results, which is also indicated by the forest plots for all lead SNPs (Supplementary Fig. 1 and Supplementary Data 1 and 2). Results also indicated that $ADHD_{DIAG}$ was substantially stronger in driving the lead SNP effects compared to the other cohorts. This is not unexpected, given that the ADHD diagnosis is a much narrower definition of ADHD than ADHD symptoms.

Meta-analysis of ADHD symptoms

The meta-analysis approach is equal to the method described in ref. 19. Due to sample overlap between multiple GWASs from the same cohort, the covariance between GWAS test statistics is a function of sample overlap and a truly shared genetic signal[39]. To correct for sample overlap during the meta-analysis, we applied a modified version of the multivariate meta-analysis approach mentioned in ref. 40, where we calculated the expected CTI[39] based on the observed sample overlap and phenotypic covariance, as reported by the cohorts. Finally, because the sum of the number of observations (n_{obs}) was an overestimate of the effective sample size (n_{eff}), we approximated the effective sample size as proposed in ref. 19 $-n_{eff} = \sqrt{\mathbf{n}^T}\,\mathrm{CTI}^{-1}\sqrt{\mathbf{n}}$. In this notation, $\mathbf{n}$ is a vector of sample sizes and CTI is the matrix of CTIs. SNPs with minor allele frequency <0.01, $n_{eff} < 15{,}000$, or observed in only one cohort were removed from further analyses. SNP heritability (h^2_{SNP}) was estimated by genomic Structural Equation Modeling in R[41].

Stratified meta-analyses of ADHD symptoms

After meta-analyzing all ADHD symptoms GWASs ($ADHD_{SYMP}$), we performed stratified meta-analyses—rater specific, age specific and instrument specific. For each stratified meta-analysis, we calculated genetic correlations (r_g) with other stratified meta-analysis results using LDSC in genomicSEM. To ensure sufficient power for the genetic correlations,

r_g was calculated across stratified assessments of ADHD if the z score for the corresponding GWAMA was 4 or higher.

Meta-analysis with case-control ADHD GWAS

In the next step, we meta-analyzed our $ADHD_{SYMP}$ GWAMA with a GWAS of ADHD diagnosis[13]. In $ADHD_{DIAG}$, cases are defined as clinically diagnosed with ADHD or prescribed medication specific to ADHD. $ADHD_{DIAG}$ included data from the Lundbeck Foundation Initiative for Integrative Psychiatric Research, the Psychiatric Genomics Consortium and deCode. Data were obtained for adults and children, resulting in a total of 38,691 cases and 186,843 controls.

For the meta-analysis, we first adjusted the test statistics and sample sizes for $ADHD_{SYMP}$ and $ADHD_{DIAG}$ as proposed in ref. 11. The lifetime population prevalence of ADHD was assumed to be 5%[4]. SNP heritability for $ADHD_{SYMP}$, and $ADHD_{DIAG}$, and r_g and CTI between $ADHD_{SYMP}$ and $ADHD_{DIAG}$ were estimated by genomicSEM in R[41]. We meta-analyzed the results from $ADHD_{SYMP}$ and $ADHD_{DIAG}$ based on the approach outlined in ref. 40. We specified the effective sample sizes for $ADHD_{DIAG}$ as suggested in ref. 19 – $n_{eff} = \frac{4}{\left(\frac{1}{n_{cases}} + \frac{1}{n_{controls}}\right)}$. SNP heritability was estimated using LDSC in genomicSEM[41]. There is no sample overlap between $ADHD_{SYMP}$ and $ADHD_{DIAG}$.

Follow-up analyses

Fine mapping and gene-based tests. To identify independent genome-wide significant loci and credible sets for each locus, we used FUMA[20], FINEMAP[22], PAINTOR[23] and CAVIARBF[21]. One causal variant was assumed per locus. In FINEMAP, PAINTOR and CAVIARBF, variants located within 1 Mb of index variants were included in the analyses. All SNPs within 95% of the total posterior probability of the variants were included in the credible sets if they were tagged in at least two of the three methods. In FUMA, linkage disequilibrium blocks of independent significant SNPs within 250 kb were merged into a single genomic locus. These loci were mapped to protein-coding genes if they were located within a maximum distance of 10 kb of an independent significant SNP, or if a variant was annotated to the gene based on expression quantitative trait locus data or chromatin interaction data from the human brain (see Supplementary Methods for the included datasets). These are the same settings as applied in ref. 13.

Next, gene-based tests were run in MAGMA[24]. MAGMA gene-based tests combine P values from multiple SNPs inside a gene to obtain a test statistic for each gene (z_{gene}), while accounting for incomplete linkage disequilibrium between SNPs. To this end, a list of 18,296 genes and their start-positions and end-positions, and preformatted genotypes, based on 1000G phase 3, were obtained from the MAGMA website (Supplementary Methods). We applied a Bonferroni correction for multiple testing at $\alpha = 0.05/18{,}296 = 2.733 \times 10^{-6}$.

It remains a challenge to identify which genes are causally involved in ADHD. FLAMES was recently developed with the goal of predicting the most likely effector genes from GWAS results[25]. FLAMES is a new framework that combines SNP-to-gene evidence and convergence-based evidence, outputting a single score per gene from fine-mapped GWAS loci. We performed statistical fine mapping using FINEMAP version 1.4.1 (ref. 22), and a linkage disequilibrium reference panel of 100,000 unrelated UK Biobank participants of European descent. Given that the GWAMA contains cohorts that do not belong to the UK Biobank, we restricted the maximum number of causal variants in a locus modeled by FINEMAP to 1, to avoid overfitting. As a result, each locus also leads to a maximum of one (most) likely effector gene per locus. We ran FLAMES (version 1.0.0) by inputting pathway naïve PoPS scores[42] for our GWAMA, the FUMA-defined loci and corresponding fine-mapped credible sets, resulting in a single FLAMES score per gene. Genes with FLAMES scores above 0.05 were interpreted as potential effector genes, as suggested by the FLAMES authors. For more information on FLAMES and the included functional annotations, see ref. 25. Functional annotation and enrichment analysis were done for a set of genes with FLAMES scores above 0.05.

Enrichment and pathway analyses. We performed MAGMA gene-set analyses in the full $ADHD_{OVERALL}$ results. Gene property analysis was performed to test relationships between tissue-specific gene expression profiles (see Supplementary Methods for an overview) and ADHD–gene associations. Next, genes mapped from credible sets by FUMA, and the set of potential effector genes identified with FLAMES were used in gene-set enrichment analyses. We ran hypergeometric tests using FUMA genes2func to assess if genes of interest are overrepresented in any of the predefined gene sets (see Supplementary Methods for all included gene sets). We used SynGO[43] v1.2 ('20231201') to test for enrichment in genes encoding for proteins involved in synaptic cellular components and biological pathways. The brain expressed background set was used, containing 18,035 unique genes.

Genetic correlations. We computed genetic correlations between $ADHD_{OVERALL}$ and 49 preselected traits, including cognition and externalizing behaviors, psychopathologies, anthropometric measures, metabolic, hormone and health outcomes (Supplementary Table 10). Phenotypes were selected based on established hypotheses or were at least nominally significantly ($P < 0.05$) genetically correlated with $ADHD_{DIAG2019}$ (ref. 11). Following ref. 43, we restricted genetic correlations to external phenotypes for which the z scores of the LDSC-based h^2_{SNP} are ≥4.

PGS analysis. We assessed the performance of PGSs based on $ADHD_{SYMP}$, $ADHD_{DIAG}$ and $ADHD_{OVERALL}$ by modeling their effect on an aggregated ADHD measure in three large cohorts (ALSPAC, MoBa and NTR). PGSs were constructed using PRScs (--n_burnin 10.000, --n_iter 25000), with summary statistics that excluded the target PGS cohort. We created an aggregated ADHD measure by combining the z scores of individual measures into a single standardized ADHD measure. We then performed regression analyses in R with ADHD as dependent variable, PGS as independent variable, and included sex, genotyping platform and ten genomic PCs as covariates. Because NTR includes data on family members, we controlled for dependency between observations by multilevel modeling in lme4 with a random intercept for families. Results from the three cohorts were meta-analyzed with the function metaplus in R. Explained variance was calculated separately in each cohort by comparing the explained variance of models with or without the PGSs.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Summary statistics for $ADHD_{SYMP}$ and $ADHD_{OVERALL}$ are available for download through GWAS Catalog (ebi.ac.uk/gwas/studies/GCST90568440 and ebi.ac.uk/gwas/studies/GCST90568441). $ADHD_{DIAG}$ summary statistics are available for download at the Psychiatric Genomics Consortium (PGC) website (https://www.med.unc.edu/pgc/download-results/). Raw data are available upon request through the individual participating cohorts. Individual cohort GWAS summary statistics are available upon request through the corresponding author. Datasets used for gene mapping and hypergeometric gene-set tests in FUMA are listed in Supplementary Methods.

Code availability

The complete analysis plan is available for download at https://www.action-euproject.eu/sites/default/files/Action%20AGG%20AP%20SOP.pdf. The N-weighted GWAMA code is available via GitHub at https://github.com/baselmans/multivariate_GWAMA and via Zenodo at https://doi.org/10.5281/zenodo.15862079 (ref. 44. For a list of software and versions used, see Supplementary Methods.

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Author contributions

C.M.v.d.L. conducted the central analyses and wrote the manuscript. M. Schipper performed the FLAMES analyses. H.F.I., B.St.P., T.Z., R. Pool, E.M.L.K., I.B., M.S.A., J.C.-D., S.A., I.M.N., K.B., T.P., H.Z., S.G., F.A., C.A.W., G.S., V.K., D.E.A., R. Border, R.E.P., J.A.P., E.T., N.V.-T., T.K., E.V., A.K.H., S. Llop, M.-J.L.-E., C.J., D.M.D., T.S.A., A.A., K.R., Q.C., Y.L., J.M., R. Bosch, N.L., A.N., J.E., K.L.G., J.J.M., X.T., S.M., J.G.S., A.A.S., L.M.E., K.S., L.S., R.V., C.J., Q.L., J.P., J. Horwood and W.E.C. performed cohort-specific analyses. J.-J.H., R.C., S.J., M.S.A., J.C.-D., S.A., R. Bosch, N.L., S.A.B., C.C., J. Haavik, A.K.H., A.S., S. Llop, M.-J.L.-E., L.A., M.M., N.V.-T., E.A.E., K.K., M. Stallings and M.R. coordinated genotyping. B.St.P., S.A., J.S., H.L., S. Lundström, R.J.R., A.G.U., F.A.H., H.S., Ø.H., A.R., A.K.H., S. Llop, M.-J.L.-E., L.A., M.K., M.M., J.R.H., G.P.S.K., P.R.N., A. Mamun, J.M.N., S.B., C.H., C.A.R., M. Stallings, S.W., T.L.W., L.E., J.L.S., A. Miller, A.H., K.B., J.S., M. Standl, J. Heinrich, J.B., J. Horwood, R. Pool, H.H.M., W.E.C., C.M.M, N.W., M.-R.J., W.I., A.C., T.E.M., A.J.O.W., C.E.P., K.L.K., D.M.D., M.S.A., J.C.-D., S.A., R. Bosch, N.L., S.A.B., J.A.R.-Q., R.C., A.M.W., T.K., E.V., T.R.-K., N.G.M., S.E.M., T.V., J.K., H.T., C.A.H., A.J.O., M.C., P.L., R. Pool, M.B., M.G.N. and D.I.B. collected samples and conducted phenotyping. B.St.P., J.S., H.L., S. Lundström, S.A.B., R.J.R., A.G.U., J.R.H., G.P.S.K., P.R.N., J.M.N., S.B., C.H., J. Hewitt, M. Stallings, S.W., L.E., J.L.S., H.H.M., W.E.C., C.M.M., N.W., M.-R.J., W.I., A.C., T.E.M., A.J.O.W., C.E.P., KL.K., D.M.D., J.A.R.-Q., H.S., A.S., S. Llop, M.-J.L.-E., L.A., M.K., G.M.W., M.M., G.M.W., T.R.-K., N.G.M., S.E.M., T.V., J.K., H.T., G.D.S., C.A.T., A.J.O., M.C., M.R., P.L., R. Plomin, M.B., M.G.N. and D.I.B. led the study design and principal investigator oversight. All above mentioned authors and E.M.D. contributed to critical revisions of the manuscript and approved the final version for submission.

Competing interests

J.A.R.-Q. was on the speakers' bureau and/or acted as a consultant for Biogen, Idorsia, Casen-Recordati, Janssen-Cilag, Novartis, Takeda, Bial, Sincrolab, Neuraxpharm, BMS, Medice, Rubió, Uriach, Technofarma and Raffo in the last 3 years. He also received travel awards (air tickets and hotel) for taking part in psychiatric meetings from Idorsia, Janssen-Cilag, Rubió, Takeda, Bial and Medice. The Department of Psychiatry, chaired by him, received unrestricted educational and research support from the following companies in the last 3 years: Exeltis, Idorsia, Janssen-Cilag, Neuraxpharm, Oryzon, Roche, Probitas and Rubió. M.C. has received fees to give talks for TAKEDA and Laboratorios RUBIO. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41588-025-02295-y.

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Software and code

Policy information about availability of computer code

Data collection	NA
Data analysis	N-weighted GWAMA code: https://github.com/baselmans/multivariate_GWAMA R version 4.4.1 (2024-06-14) GenomicSEM version 0.0.5 FINEMAP version 1.4.1 CAVIARBF C++ version PAINTOR version 3 FLAMES version 1.0.0 FUMA version 1.6.2 MAGMA version 1.08 EasyQC version 23.8

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Data availability
Summary statistics for ADHDSYMP and ADHDOVERALL are available for download through GWAS catalog (https://www.ebi.ac.uk/gwas/). ADHDDIAG summary statistics are available for download at the PGC website (https://www.med.unc.edu/pgc/download-results/). Raw data are available upon request through the individual participating cohorts. Individual cohort GWAS summary statistics are available upon request through the corresponding author. Datasets used for gene mapping and hypergeometric gene-set tests in FUMA are listed in the Supplementary Notes.

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Reporting on sex and gender	Sex was included as covariate in the analyses. Sex was identified based on genetic information.
Reporting on race, ethnicity, or other socially relevant groupings	Results are based on a sample of participants from European descent. This was done based on availability of data.
Population characteristics	Respondents are children with measures of ADHD symptoms. For a complete overview, see Supplemental Table 8.
Recruitment	Recruitment was dependent on the cohort that provided the data. Information on the individual cohorts and their recruitment tactics is given in the Supplemental Text.
Ethics oversight	Study approval was obtained from the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam (NTR 25th of May 2007 and ACTION 2013/41 and 2014.252), an Institutional Review Board certified by the U.S. Office of Human Research Protections (IRB number IRB00002991 under Federal-wide Assurance-FWA00017598; IRB/institute codes).

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Study description	Genome wide association analysis of quantitative measures of ADHD.
Research sample	Children with ADHD measures from European descent and ADHD diagnosed cases and controls. See also Table 2, and Demontis et al. 2023.
Sampling strategy	Sampling strategies differed between cohorts. For a complete overview, please consult the Supplemental Notes
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Timing	Data collection differed between cohorts. For a complete overview, please consult the Supplemental Text.
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