Data supplement for Brikell et al., Genetic, Clinical, and Sociodemographic Factors Associated With Stimulant Treatment Outcomes in ADHD. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.20121686)

CONTENTS

Supplementary note 1. Polygenic risk score derivation

Polygenic risk scores (PRS) were trained using both internal (to iPSYCH2012) and external SNPs weights (from external GWAS summary statistics). We derived externally trained PRS for ADHD, ASD, depression, bipolar disorder and schizophrenia using the LDPred software,[1] specifying an infinitesimal model, as this provided the highest prediction accuracy (pseudo-R^2) for each target disorder. SNP weights were obtained from publically available external GWAS summary statistics (Table S1), selecting European ancestry discovery GWAS excluding the iPSYCH2012 sample. The LDPred PRS were derived for a set of genotyped SNPs (filtered for MAF>1% and missing values <10%) overlapping between the iPSCYH2012 sample and the external GWAS summary statistics and restricted to HapMap3 (v1.2).

To leverage having access to genotype data on a large number of individuals with ADHD, ASD and depression in iPSYCH2012, we also derived another set of internally trained PRSs for ADHD, ASD and depression in an unrelated, European ancestry subset of the iPSYCH2012 sample. For details on the method see Albiñana et al (2021).[2] Briefly, the internally trained SNP weights were obtained using the BOLT-LMM software.[3] We performed a mixed model prediction for each disorder (i.e. best linear unbiased prediction [BLUP]) in which genotyped SNPs in the iPSYCH sample (filtered for MAF>1% and missing values <10%) were included as random effects. Betas (i.e. prediction effects sizes) from this model take into account LD between nearby SNPs to correctly weigh their contribution to the phenotypic variance (see supplementary material of Loh et al, 2015).[3] To avoid overfitting, we used 10-fold cross-validation, training the model using 9/10ths of the data and testing it in the remaining tenth. Cross-validation was done for subsample of iPSYCH, excluding individuals of non-European ancestry and relatives with $\hat{\pi}$ coefficient > 0.2 (using PLINK--rel-cutoff). The internally trained PRSs were defined as the weighted sum of the training set prediction betas on the test set genotypes. The models were adjusted for genotyping wave, sex, age, and the first 10 principal components (PCs). The final PRS used for ADHD, ASD and depression were a linear combination of the internally and externally trained PRS variables, where the regression coefficients were inferred using two-fold cross validation. Finally, all PRSs were standardized to the mean and standard deviation of the iPSYCH2012 control population.[4]

PRSs were derived at the secured national GenomeDK high-performance computing cluster in Denmark and then imported to Statistics Denmark secure servers for associations testing with stimulant-treatment outcomes.

Supplementary note 2. Definitions of clinical and socio-demographic

Clinical and socio-demographic factors	ICD-10 code	Definition
Age at first ADHD diagnosis	F90, F98.8	Age at first registered diagnosis after age 3 in the PCRR or NPR among individuals with ADHD selected into iPSYCH2012
Family psychiatric history	F00-F99	At least one discharge diagnosis for any psychiatric disorder in the DPCRR in mother and/or father, at or prior to birthdate of index child
Low maternal education	na	Highest attained education in birth year of index child, with compulsory education or less (usually 9 years) classified as low
Low paternal income	na	Fathers annual income in birth year of index child, split into quintiles derived from income in the iPSYCH2012 controls for each birth year, with income in lowest quintile classified as low
Autism spectrum disorder	F84.0,F84.1, F84.5, F84.8, F84.9	≥ 1 discharge diagnosis after age 1 in the DPCRR
Intellectual Disability	F70-F79	≥ 1 discharge diagnosis after age 1 in the DPCRR
Oppositional Defiant Disorder/Conduct Disorder	F91, F90.1	≥ 1 discharge diagnosis after age 3 in the DPCRR
Tic disorder	F95	≥ 1 discharge diagnosis after age 3 in the DPCRR
Obsessive compulsive disorder	F42	≥ 1 discharge diagnosis after age 3 in the DPCRR
Anxiety disorder	F40, F41, F93	≥ 1 discharge diagnosis after age 3 in the DPCRR
Depressive disorders	F32,F33	≥ 1 discharge diagnosis after age 10 in the DPCRR
Bipolar disorder	F30,F31	≥ 1 discharge diagnosis after age 10 in the DPCRR
Substance use disorder	F10-F19	≥ 1 discharge diagnosis after age 10 in the DPCRR

Information on sex, date of birth, migration, death, and parents' personal identification number were obtained via the Danish Civil Registration System, which includes demographic information on all individuals registered in Denmark since 1968.[5] Date of first ADHD diagnosis, psychiatric comorbidities, and parental psychiatric history were defined from the Danish Psychiatric Central Research Registers (DPCRR), which contains data on inpatient care from hospitals and psychiatry departments since 1969 and outpatient care since 1995.[6] For date of first ADHD diagnosis, we also used information from the Danish National Patient Register (NPR), which contains ICD-coded inpatient care from 1977 and outpatient care since 1995.[7] Information on paternal gross income and maternal highest completed education were obtained from Statistics Denmark's socioeconomic registers.[8] Using previously published definitions, we defined parental psychiatric history[9] at or prior to child's 1th birthday. Low paternal income was defined as having a gross income in the lowest quintile, based on income levels for all

fathers of the iPSYCH2021 (population-representative) controls, in the year of their child's 1th birthday. Low maternal education was defined as having compulsory education, usually nine years, as the highest level of completed education, in the year of their child's 1th birthday.[10]

Supplementary note 3. Genome-wide association analyses and h^2_{SNP} estimation

We conducted a within-ADHD-case GWAS for each stimulant treatment outcome using the BOLT-LMM software,[3] which computes association statistics for any N imputed SNPs using a mixed model built on a subset of hard-called genotypes (typically a subset of directly genotyped SNPs). Due to restriction on Statistics Denmark secure servers, where GWAS was performed, we did not have access to directly genotyped SNPs. In line with BOLT-LMM recommendations, we therefore defined a subset of imputed high-confidence autosomal LD-pruned SNPs (PLINK--indep-pairwise pruning done in two rounds with parameters 50 5 0.8 and 50 5 0.6), filtered for INFOSCORE>0.8 and MAF>1% (N=729,747). This SNP subset was then included in the mixed model (using the BOLT-LMM command –modelSnps) when performing association testing across the total number of 6,361,597 imputed variants passing QC. For association test of Initiation vs. No initiation, we used linear regression in BOLT as the estimated (pseudo-)heritability was too low to run BOLT-LMM (i.e. LMM may not correct for confounding). However, as our ADHD case sample was strictly filtered for ancestry and relatedness, and given that we covariate and PC-corrected all LMM analyses, there should only be minor differences in association estimates between the BOLT-LMM and the standard linear regression. For details and analytic guidelines, see the BOLT-LMM user manual.[11]

We used FUMA (Functional Mapping and Annotation)[12] to follow-up GWAS results of switch vs. adherence. Due to data export restrictions on Statistics Denmark secure servers, this was done for 85,679 LD-clumped SNPs with $p \leq 0.1$ (derived using PLINK --clump p1=0.1, p2=0.5, 250KB). Genomic risk loci were defined in FUMA by assigning SNPs in LD $r^2 \geq 0.5$ of an independent significant SNPs ($p<10^{-5}$) to the same genomic risk locus and merging independent significant SNPs closer than 250 kb into one genomic risk locus. Independent significant SNPs ($p<10^{-5}$) in each locus with a $R^2>0.1$ were clumped to define lead SNPs. Results are presented in Table S8. A regional plot of the genome-wide significant rs58543609 locus on chromosome 16q23.3 was made using LocusZoom (https://my.locuszoom.org/) (Figures 4, main text). We used FUMA to identify nearby genes and variants associated with gene expression (eQTLs) for the rs58543609 locus. First, positional mapping of proximal genes of the loci was done using ANNOVAR. Second, we ran eQTL mapping, assigning the lead SNP to genes likely to affect expression of those genes up to 1 Mb (cis-eQTL), restricted to eQTL with false discovery fate (FDR) $<1\times10^{-3}$. Annotation results from FUMA are presented in Table S9. We used GWAS catalog (ebi.ac.uk/gwas/) to look up previously reported GWAS associations of SNPs within 250kb of the lead genomic loci (BPrange 16:82315555-82397332 +/- 250kb) as well as for candidate genes identified

through ANNOVAR and eQTL mapping. Previously reported associations of potential interest are discussed in the results section of the main text. Finally, we used the GWAS ATLAS resource (https://atlas.ctglab.nl) to run PheWAS for the leadSNP and proxy SNPs. Our leadSNP was found in 105 GWAS, and thus we considered associations with Bonferroni corrected *p*-value ≤$4.7x10^{-4}$ as putative.

We estimated h^2_{SNP} using BOLT-REML on a subset of LD-pruned SNPs (r^2>0.5) more strictly filtered for MAF(>2%) and relatedness (PLINK--rel-cutoff 0.05) as per BOLT-REML recommendations,[13] retaining 441 381 SNPs and 7216 individuals with ADHD. Analyses were adjusted for sex, birth-year, age at ADHD diagnosis, genotyping wave and the first 10 PCs. We report h^2_{SNP} estimates on the observed scale, as re-scaling estimates to the liability-scale requires the (true) population prevalence,[14] which is not well established for the studied stimulant-treatment outcomes, and because re-scaling might not be appropriate for conditional traits (i.e., stimulant-outcomes are conditional on ADHD diagnosis/being prescribed a stimulant drug). We however also present estimated h2SNP on the liability-scale in Supplemental table S7, relying on prevalence estimates from the current study.

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TABLE S1. External summary statistics used for polygenic risk score (PRS) derivation

Polygenic risk score	External discovery GWAS	N SNPs used for LDPred PRS	N SNPs used for BOLT-LMM PRS
ADHD	Cross-Disorder Working Group of the Psychiatric Genomics Consortia (2013). doi: 10.1016/S0140-6736(12)62129-1. N: 1947 trio cases and pseudocontrols, 840 cases and 688 controls	544758	166329
ASD	Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium File name: PGC.ASD.euro.all.25Mar2015.txt https://www.med.unc.edu/pgc/download-results/ N: 5305 cases and 5305 pseudocontrols	171529	544352
Depression	Howard, D. M. *et al.* (2019). doi:10.1038/s41593-018-0326-7 N: 246 363 cases and 561 190 controls	166906	539744
Bipolar disorder	Stahl, E. A. *et al.* (2019). doi:10.1038/s41588-019-0397-8 N: 20 352 cases and 31 358 controls	206997	na
Schizophrenia	Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). https://doi.org/10.1038/nature13595 N: 34 600 cases and 45 986 controls	217991	na

Abbreviation: ADHD, attention-deficit/hyperactivity disorder. ASD, autism spectrum disorder.

TABLE S2. Baseline descriptive of included individuals with ADHD (N total = 9133)

Characteristic	N (%)
Female sex	2610 (29%)
Birth year	
1981-1985	457 (5%)
1986-1990	1085 (12%)
1991-1995	1910 (21%)
1996-2000	2649 (29%)
2001-2005	3032 (33%)
Age at first ADHD diagnosis, years	
3-6	1283 (14%)
7-9	2396 (26%)
10-14	2316 (25%)
15-20	1610 (18%)
21-32	1528 (17%)
ADHD stimulant-treatment outcome (2yrs)	
Initiation	7427 (81%)
Discontinuation	3370 (45%)
Switch to non-stimulants	1137 (15%)

Note. Percentage reported for stimulant discontinuation and switch to non-stimulant reflect the proportion of individuals with the outcome among those who initiated stimulant treatment (N=7427). Numbers do not add to 100% as discontinuation and switch were defined as non-mutually exclusive.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

TABLE S3. Hazard ratios (HR) and 95% confidence intervals (CIs) expressing the associations of polygenic risk scores with stimulant-treatment discontinuation and switch to non-stimulants, in the main model and fully adjusted model

Polygenic risk score	Discontinuation		Switch	
	Main model HR (95%CI)	Fully Adjusted HR (95%CI)	Main model HR (95%CI)	Fully Adjusted HR (95%CI)
ADHD (per 1 SD)	0.99 (0.96-1.03)	0.99(0.95-1.02)	1.01(0.95-1.07)	1.01(0.95-1.07)
ASD (per 1 SD)	1.02(0.99-1.05)	1.01 (0.98-1.05)	1.00(0.94-1.06)	0.99(0.94-1.05)
Depression (per 1 SD)	1.00 (0.96-1.04)	0.99(0.96-1.03)	1.06(0.99-1.13)	1.05(0.98-1.12)
Bipolar disorder (per 1 SD)	1.05(1.02-1.09)	1.05(1.02-1.09)	1.05(0.99-1.12)	1.04(0.98-1.11)
Schizophrenia (per 1 SD)	1.07(1.03-1.11)	1.07(1.03-1.11)	1.07(1.00-1.13)	1.05(0.99-1.12)

Note. Hazard ratios from the main models (same results as presented in Table 1, shown here only for comparisons) were adjusted for sex, age at first ADHD diagnosis split in five age-categories [1-6, 7-9, 10-14, 15-19, and 20-32 years], birth year in five categories [1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005], genotyping wave and the first four principal components. Fully adjusted hazard ratios were, in addition to above covariates, further adjusted for all clinical and socio-demographic covariates evaluated in the study (e.g., family psychiatric history, low maternal education, low paternal income, autism spectrum disorders, intellectual disability, oppositional defiant disorder/conduct disorder, tic disorder, obsessive compulsive disorder, anxiety disorders, depressive disorders, bipolar disorder and substance use disorder). See supplementary note 2 for details on covariate definitions. **Abbreviations:** PRS, polygenic risk score. SD, standard deviation. ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder.

TABLE S4. Hazard ratios (HR) & 95% confidence intervals (CIs) expressing the associations of polygenic risk scores (PRS) with stimulant initiation, discontinuation and switch to non-stimulants across PRS-quintiles

	Initiation	Discontinuation	Switch
PRS quintile	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
ADHD 1st	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	1.03 (0.96-1.11)	0.97 (0.87-1.07)	1.12 (0.93-1.35)
3rd	1.02 (0.95-1.10)	0.99 (0.89-1.11)	1.13 (0.93-1.36)
4th	1.07 (0.99-1.15)	1.00 (0.90-1.12)	1.06 (0.87-1.27)
5th	1.05 (0.98-1.13)	0.95 (0.85-1.06)	1.09 (0.91-1.32)
ASD 1st	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	0.99 (0.92-1.07)	1.05 (0.94-1.16)	1.07 (0.89-1.29)
3rd	1.01 (0.94-1.08)	1.00 (0.90-1.11)	1.11 (0.92-1.33)
4th	0.97 (0.91-1.05)	1.10 (0.99-1.22)	1.14 (0.95-1.37)
5th	0.99 (0.92-1.06)	1.06 (0.95-1.18)	0.94 (0.77-1.13)
Depression 1st	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	1.04 (0.97-1.12)	1.02 (0.91-1.13)	1.17 (0.97-1.42)
3rd	1.04 (0.97-1.12)	0.99 (0.89-1.10)	1.19 (0.98-1.43)
4th	1.01 (0.94-1.09)	0.94 (0.84-1.05)	1.12 (0.92-1.35)
5th	1.00 (0.93-1.07)	1.02 (0.91-1.13)	**1.26 (1.05-1.52)**
Bipolar disorder 1st	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	1.02 (0.95-1.09)	1.03 (0.92-1.15)	**1.25 (1.03-1.51)**
3rd	0.97 (0.91-1.05)	1.06 (0.94-1.18)	1.05 (0.86-1.27)
4th	0.96 (0.89-1.03)	1.07 (0.96-1.19)	**1.21 (1.00-1.47)**
5th	0.98 (0.91-1.05)	**1.21 (1.09-1.35)**	**1.25 (1.04-1.51)**
Schizophrenia 1st	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	1.01 (0.94-1.08)	1.00 (0.89-1.12)	1.16 (0.96-1.41)
3rd	1.00 (0.93-1.07)	1.10 (0.98-1.23)	1.20 (0.99-1.45)
4th	1.03 (0.95-1.10)	**1.13 (1.01-1.27)**	**1.33 (1.10-1.61)**
5th	0.94 (0.87-1.01)	**1.24 (1.11-1.39)**	1.17 (0.96-1.42)

Note. 1st quintile was set to reference. All models were adjusted for sex, age at first ADHD diagnosis split in five age-categories [1-6, 7-9, 10-14, 15-19, and 20-32 years], birth year in five categories [1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005], genotyping wave and the first 4 principal components. Significant associations are highlighted in bold. **Abbreviations.** PRS, polygenic risk score. ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder.

TABLE S5. Hazard ratios (HR) and 95% confidence intervals (CI) expressing the associations of polygenic risk scores, clinical, and socio-demographic factors with stimulant-treatment discontinuation and switch to non-stimulants, stratified by age at first ADHD diagnosis

	Discontinuation		Switch	
	ADHD diagnosis <13yrs	**ADHD diagnosis >=13yrs**	**ADHD diagnosis <13yrs**	**ADHD diagnosis >=13yrs**
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Polygenic risk scores (PRS)				
ADHD (per 1 SD)	**0.94(0.89-0.99)**	1.03(0.99-1.08)	0.98(0.90-1.07)	1.04(0.96-1.12)
ASD (per 1 SD)	1.02(0.97-1.08)	1.02(0.98-1.06)	1.01(0.92-1.10)	1.00(0.92-1.08)
Depression (per 1 SD)	0.96(0.91-1.02)	1.02(0.98-1.07)	1.04(0.95-1.14)	1.07(0.98-1.16)
Bipolar disorder (per 1 SD)	1.07(1.01-1.13)	1.04(1.00-1.09)	1.07(0.98-1.17)	1.04(0.96-1.12)
Schizophrenia (per 1 SD)	1.06(1.00-1.12)	**1.08(1.03-1.12)**	1.07(0.98-1.17)	1.07(0.99-1.16)
Clinical and socio-demographic factors				
Female sex	1.14(1.00-1.30)	0.94(0.86-1.02)	1.02(0.82-1.26)	**1.26(1.07-1.47)**
Parental psychiatric history	1.03(0.87-1.23)	**1.22(1.04-1.44)**	1.23(0.96-1.59)	1.04(0.77-1.40)
Low education, mother	0.94(0.84-1.05)	**1.14(1.04-1.25)**	1.00(0.83-1.20)	0.88(0.75-1.03)
Low income, father	1.04(0.91-1.19)	**1.16(1.05-1.27)**	0.86(0.68-1.07)	1.07(0.90-1.28)
Autism spectrum disorder	**1.41(1.24-1.60)**	0.86(0.70-1.06)	1.16(0.94-1.44)	0.85(0.58-1.24)
Intellectual disability	1.11(0.88-1.40)	0.93(0.71-1.22)	0.99(0.69-1.42)	1.05(0.68-1.60)
Oppositional defiant /Conduct disorder	0.97(0.70-1.33)	1.19(0.97-1.46)	1.14(0.73-1.79)	**1.59(1.17-2.16)**
Tics disorder	**1.30(1.05-1.61)**	0.92(0.67-1.26)	**2.24(1.71-2.94)**	**1.65(1.04-2.61)**
Obsessive compulsive disorder	**1.70(1.20-2.40)**	1.13(0.89-1.43)	**1.83(1.07-3.12)**	1.09(0.72-1.64)
Anxiety disorder	**1.57(1.23-2.01)**	1.09(0.93-1.28)	**2.14(1.54-2.98)**	1.19(0.91-1.55)
Depressive disorder	**3.05(1.76-5.28)**	1.00(0.88-1.13)	**3.43(1.53-7.71)**	1.16(0.93-1.43)
Bipolar disorder	n/a	**1.47(1.05-2.04)**	n/a	1.08(0.60-1.97)
Substance use disorder	n/a	**1.27(1.12-1.44)**	n/a	**1.44(1.17-1.79)**

Note: Hazard ratios (HRs) and 95% confidence intervals (95%CIs) are shown for treatment discontinuation and switch, stratified by age at first ADHD diagnosis before or after 13 years-of-age. There were too few cases with comorbid bipolar disorder / substance use disorder among individuals with ADHD diagnosed before 13 years-of-age to estimate separate HRs in this group. All models were adjusted for sex, age at first ADHD diagnosis split in five age-categories [1-6, 7-9, 10-14, 15-19, and 20-32 years], and birth year in five categories [1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005]. PRS models are further adjusted for genotyping wave and the first 4 principal components. Significant associations are highlighted in bold. **Abbreviations.** na, not applicable. ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder.

TABLE S6. Odds Ratios (OR) and 95% confidence intervals (CI) expressing the association of polygenic risk scores, clinical, and socio-demographic factors with non-stimulant ADHD drug treatment initiation (N=568) vs. stimulant treatment initiation (N=7427; reference)

	Non-stimulant initiators (N=568)	Stimulant initiators (N=7427)	OR (95%CI)
Polygenic risk scores (PRS)	**mean (SD)**	**mean (SD)**	
ADHD (per 1 SD)	0.39 (1.08)	0.42 (0.99)	0.97 (0.89-1.06)
ASD (per 1 SD)	0.03 (0.98)	0.07 (1.00)	1.00 (0.91-1.09)
Depression (per 1 SD)	0.19 (0.95)	0.10 (0.94)	1.06(0.96-1.16)
Bipolar disorder (per 1 SD)	0.15 (1.03)	0.01 (1.01)	1.05(0.96-1.15)
Schizophrenia (per 1 SD)	0.16 (1.05)	0.02 (1.01)	0.99(0.91-1.09)
Clinical and socio-demographic factors	**N (%)**	**N (%)**	
Female sex	180 (31.7)	2167 (29.2)	**0.77**(**0.64-0.93**)
ADHD diagnosis ≥ 13 years	486 (85.6)	3305 (44.5)	**6.12**(**4.20-9.00**)
Parental psychiatric history	39 (6.9)	688 (9.3)	0.86(0.60-1.20)
Low education, mother	299 (53.7)	3101 (42.2)	1.13(0.94-1.35)
Low income, father	150 (26.7)	1717 (23.3)	0.99(0.81-1.21)
Autism spectrum disorder	58 (10.2)	897 (12.1)	**1.60**(**1.18-2.15**)
Intellectual disability	10 (1.8)	154 (2.1)	1.13(0.54-2.09)
Oppositional defiant /Conduct disorder	16 (2.8)	125 (1.7)	1.29(0.72-2.15)
Tics disorder	37 (6.5)	301 (4.1)	**3.07**(**2.07-4.45**)
Obsessive compulsive disorder	23 (4.0)	171 (2.3)	1.59(0.98-2.46)
Anxiety disorder	60 (10.6)	401 (5.4)	**1.47**(**1.08-1.97**)
Depressive disorder	86 (15.1)	484 (6.5)	1.24(0.95-1.60)
Bipolar disorder	10 (1.8)	42 (0.6)	1.50(0.70-2.90)
Substance use disorder	177 (31.2)	436 (5.9)	**3.56**(**2.84-4.44**)

Note: ADHD patients who initiated treatment with a stimulant ADHD drug are set as reference (OR=1). ADHD patients who did not initiate any ADHD drug treatment within two years of first ADHD were are excluded from these analyses (N=1706). Significant associations are highlighted in bold. The first two columns present mean and standard deviation of PRSs, and N (%) exposed for clinical and socio-demographic factors. All models were adjusted for sex, age at first ADHD diagnosis split in five age-categories [1-6, 7-9, 10-14, 15-19, and 20-32 years], and birth year in five categories [1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005]. PRS models were further adjusted for genotyping wave and the first four principal components. Significant associations are highlighted in bold. **Abbreviations**: ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder. OR, odds ratio.

TABLE S7. Heritability estimates (h^2_{SNP}) from BOLT-REML for stimulant treatment outcomes on observed scale with standard errors (SE) and on the liability scale with estimated 95% confidence intervals (CI)

Phenotype	N cases	N controls	Sample prevalence	Assumed population prevalence	Observed-scale h^2_{SNP}	SE	Liability-scale h^2_{SNP} (95%CI
Initiation vs no initiation	5840	1376	0.81	0.70	0.07	0.06	0.17 (-0.11-0.45)
Discontinuation vs adherence	2647	3028	0.47	0.40	0.14	0.08	0.21 (-0.03-0.45)
Switch vs adherence	893	3028	0.23	0.10	0.06	0.11	0.09 (-0.24-0.41)

Note: Individuals with ADHD who initiated stimulant treatment were compared to those who did not (i.e. no prescription for any ADHD drugs within two years of first ADHD diagnosis). Individuals with ADHD who discontinued stimulant treatment or switched to non-stimulants were compared to those who adhered to stimulant treatment) (i.e. no gap longer than 180 days between stimulant prescriptions and no switch to non-stimulants) in the two years following initiation. Numbers for BOLT-REML are lower than those for BOLT_LMM GWAS due to stricter filtering for relatedness (PLINK--rel-cutoff 0.05). Assumed population prevalence are based on results from current study. Liability-scale conversion was conducted using the formula provided in Lee et al (2012).[15]

TABLE S8. Genome wide significant locus on chromosome 16 and independent loci reaching suggestive genome-wide significance ($p<10^{-5}$) from GWAS of switch to non-stimulant in individuals with ADHD

Index SNP	CHR	BP	p	beta	s.e.	A1	A0	FRQ	Nearest genes
rs58543609	**16**	**82376003**	**4,7E-08**	**0,132**	**0,024**	**C**	**G**	**0,030**	**AC024590.1, RN7SKP190**
rs9331341	6	157956467	1,7E-06	-0,064	0,013	T	C	0,110	ZDHHC14
rs148464215	6	12274147	2E-06	0,138	0,029	T	C	0,012	EDN1, SUMO2P12, RPL15P3, RP11-125M16.1, PHACTR1
rs13091227	3	134002855	2,1E-06	0,087	0,018	A	G	0,060	RYK, RP11-200A1.1
rs62285722	3	193168845	3,6E-06	0,076	0,016	A	G	0,091	ATP13A4
rs56118025	3	68587306	3,8E-06	0,119	0,026	G	A	0,029	FAM19A1
rs145099037	8	13293126	4E-06	-0,125	0,027	G	A	0,015	DLC1, RP11-145O15.3
rs13256016	8	71200159	4E-06	0,061	0,013	A	G	0,106	PRDM14, RP11-152C15.1, NCOA2, RP11-333A23.1
rs540968291	21	29773002	4,2E-06	0,109	0,024	T	A	0,026	AF131217.1
rs1519472	2	17769984	4,3E-06	0,084	0,018	T	A	0,054	PSMC1P10, RAD51AP2, VSNL1
rs12328194	2	211679188	4,8E-06	0,162	0,035	A	G	0,017	CPS1
rs1379767	12	41801294	6E-06	-0,045	0,010	G	A	0,207	PDZRN4, PDZRN4:RP11-413B19.2
rs2148515	13	49085415	8,8E-06	0,119	0,027	A	G	0,027	RB1, RB1:PPP1R26P1, RB1:LPAR6, RCBTB2, LINC01077, LINC00462
rs61430483	8	131615358	9,1E-06	-0,038	0,009	T	C	0,341	KB-1568E2.1
rs74393339	6	64762196	9,2E-06	0,084	0,019	T	C	0,041	EYS, EYS:RP11-349P19.1
rs143708125	6	71233312	9,4E-06	0,131	0,029	T	A	0,019	RP11-462G2.1, FAM135A, C6orf57, RP11-134K13.2
rs12195523	6	11597659	9,5E-06	0,041	0,009	G	C	0,217	TMEM170B, RP11-679B17.2
rs11680223	2	15380645	9,7E-06	0,049	0,011	T	G	0,166	NBAS

Note: Genome wide significant locus on chromosome 16 presented in bold together with independent loci reaching suggestive genome-wide significance ($p<10^{-5}$) in analysis of switch vs. adherence. CHR, chromosome; BP, chromosomal position; A1, effect allele; FRQ, allele frequency of A1; β, estimate of effect with respect to A1; s.e., standard error of β; p, association *p*-value of the index variant. 'Nearest genes' lists nearest genes of the region spanned by all SNPs with r2 ≥0.5 to the index variant as identified by ANNOVAR[16] implemented in FUMA.[12] Genes are encoded in symbol if available and otherwise by Ensembl ID.

TABLE S9. Functional mapping and annotation of GWAS results obtained from FUMA for switch vs. adherence

>>> See separate Excel table <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

FIGURE S1. Flow chart of study population selection from iPSYCH2012 ADHD cases

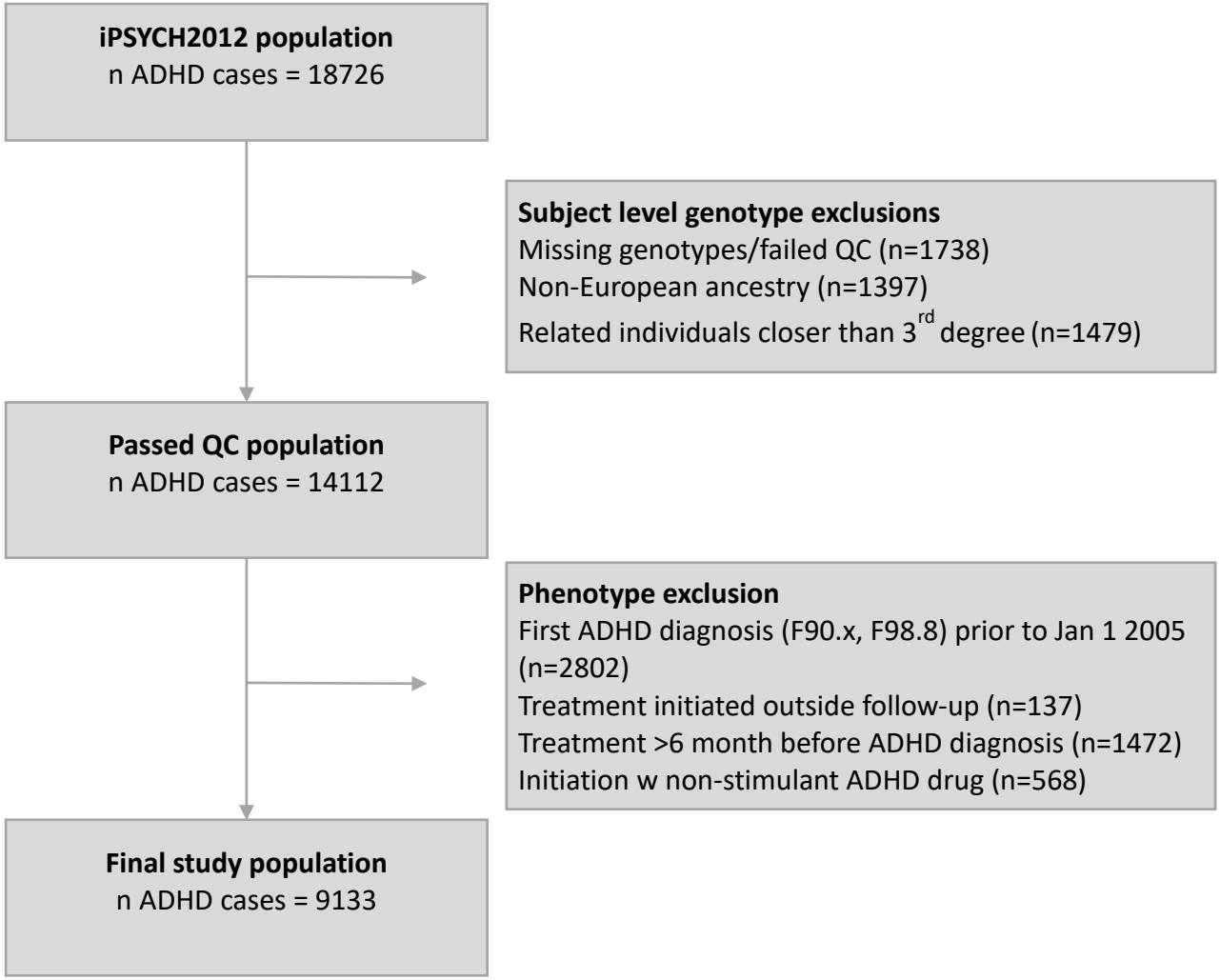
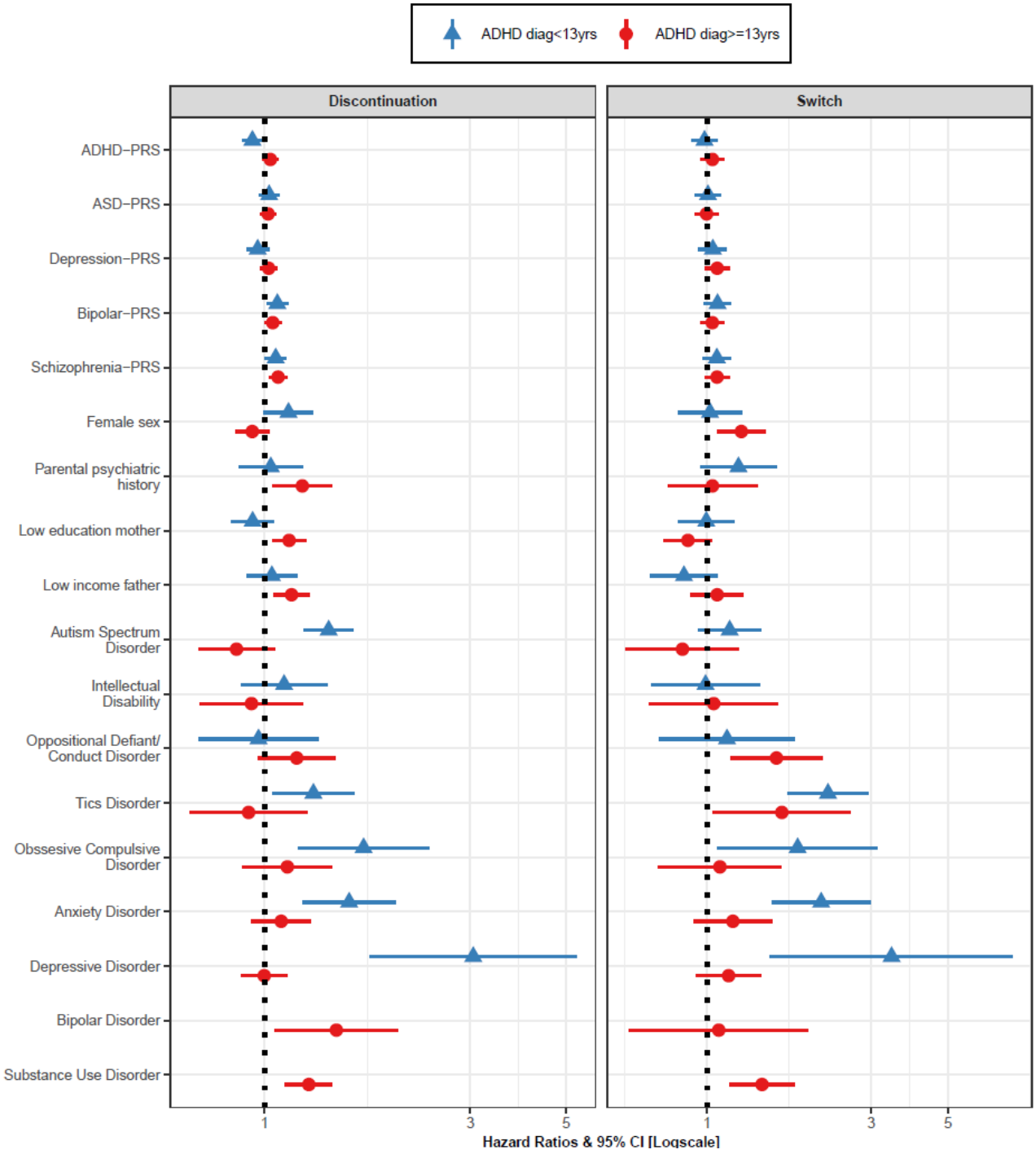
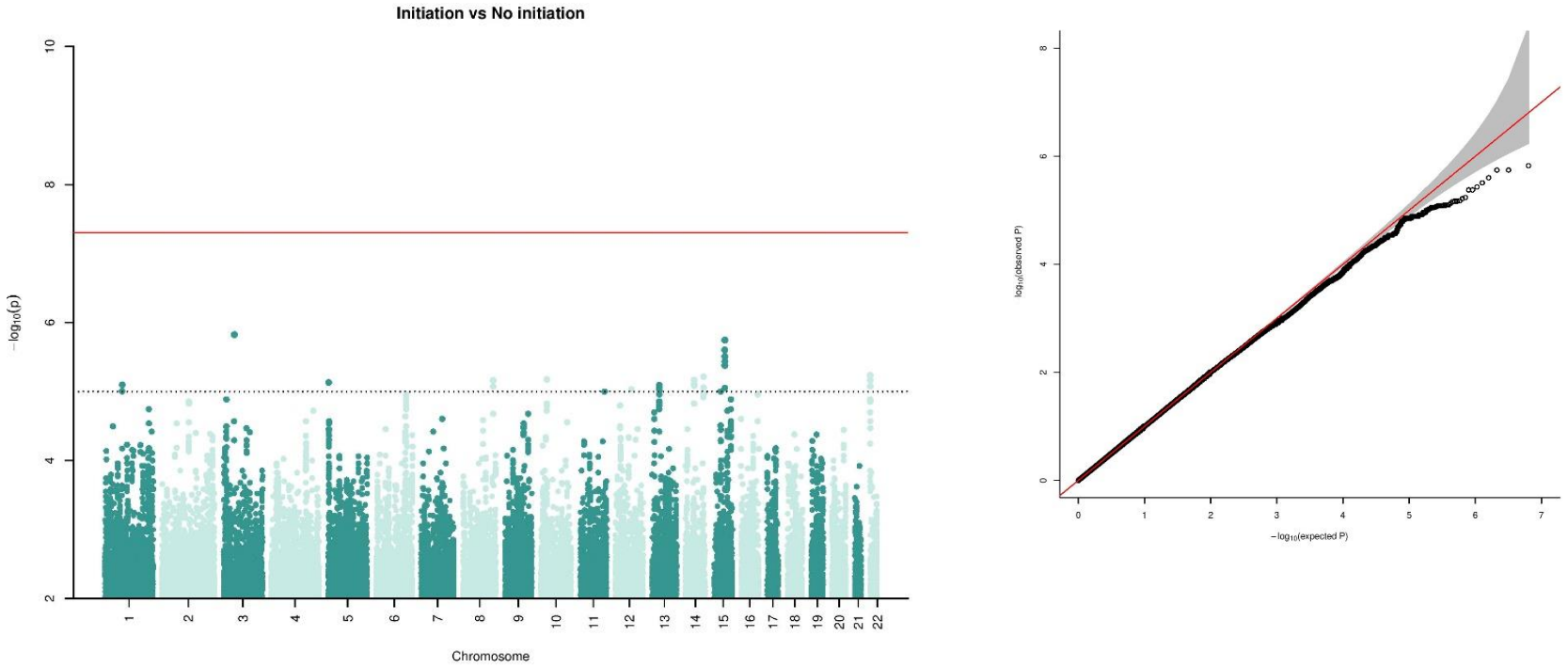


FIGURE S2. Hazard ratios (HR) & 95% confidence intervals (CIs) of stimulant discontinuation and switch stratified by age at first ADHD diagnosis



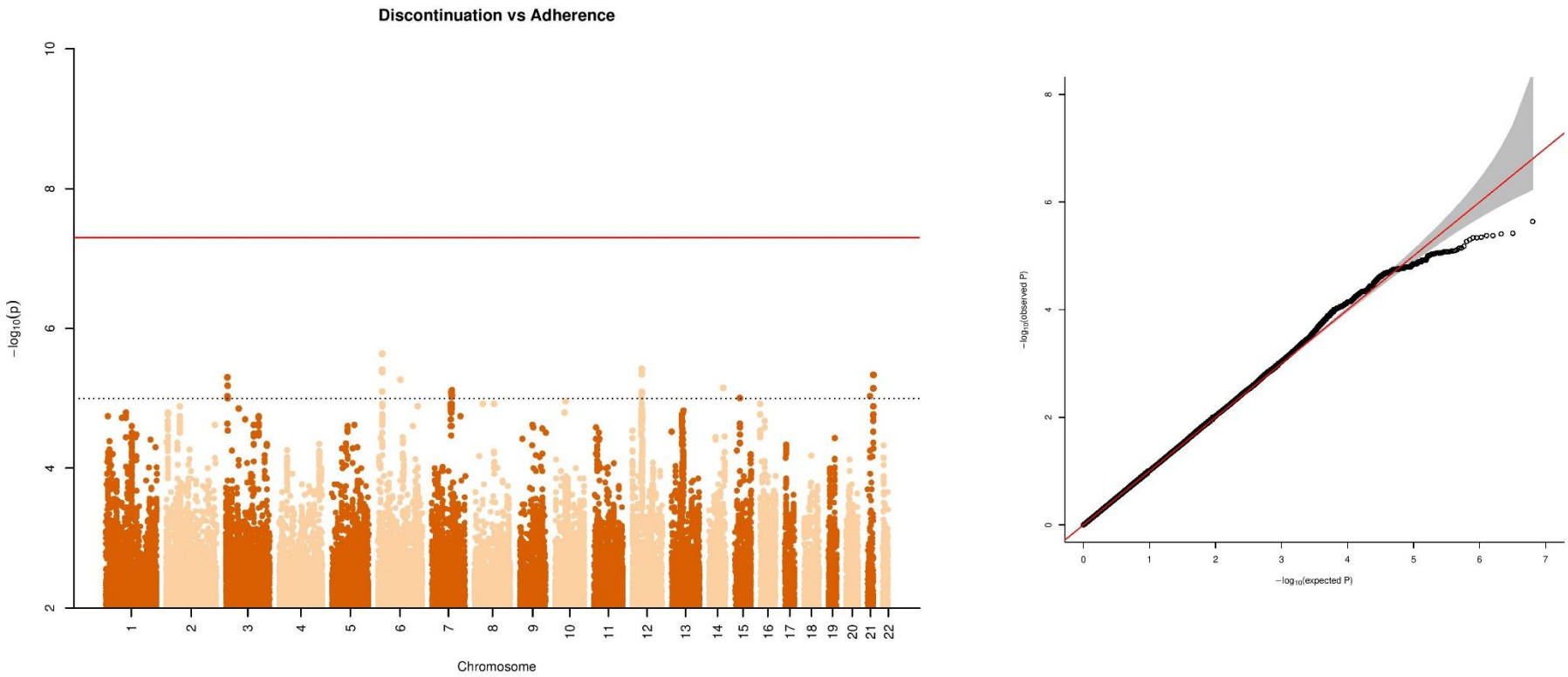
Note: Hazard ratios (HRs) and 95% confidence intervals (95%CIs) are shown for treatment discontinuation and switch, stratified by age at first ADHD diagnosis (before or after 13 years-of-age). There were too few cases with comorbid bipolar or substance use disorder among individuals with ADHD diagnosed <13 years-of-age to estimate separate hazard ratios in this group.

FIGURE S3. Manhattan and quantile-quantile plot of the association *p*-values for stimulant initiation from GWAS in individuals with ADHD



Note: Individuals with ADHD who initiated stimulant treatment (n=7427) were compared to those who did not (n=1706) (i.e. no prescription for any ADHD drugs within two years of first ADHD diagnosis). In the Manhattan plot, the -log^{10} of the *p*-value for each of SNPs is plotted against the genomic position. In the QQ-plot of 6,361,597 imputed SNPs, the black dots represent observed P-values and the red lines represent expected P-values under the null distribution.

FIGURE S4. Manhattan and quantile-quantile plot of the association *p*-values of stimulant discontinuation from GWAS in individuals with ADHD



Note: Individuals with ADHD who discontinued stimulant treatment (n=3370) were compared to those who adhered to stimulant treatment (n=3854) (i.e. no gap longer than 180 days between stimulant prescriptions and no switch to non-stimulants) in the two years following initiation. In the Manhattan plot, the -log10 of the P-value for each of SNPs is plotted against the genomic position. In the QQ-plot of 6,361,597 imputed SNPs, the black dots represent observed P-values and the red lines represent expected P-values under the null distribution.