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Genetic, clinical and socio-demographic factors associated with stimulant-treatment outcomes in ADHD

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Abstract

Objective: Stimulant-drugs are effective for treating attention-deficit/hyperactivity disorder (ADHD), yet discontinuation and switch to non-stimulant ADHD-drugs is common. This study aimed to identify genetic, clinical and socio-demographic factors influencing stimulant-treatment initiation, discontinuation and switch to non-stimulants in individuals ADHD.

Methods: We obtained genetic and national-register data for 9,133 individuals with ADHD from the Danish iPSYCH2012 sample, and defined stimulant-treatment initiation, discontinuation and switch from prescriptions. For each stimulant-treatment outcome, we examined associations with polygenic risk scores (PRSs) for psychiatric disorders, clinical, and socio-demographic factors using survival analyses, and conducted genome-wide association studies (GWASs) and estimated SNP-heritabilities (h^2_{SNP}).

Results: 81% initiated stimulant-treatment. Within two years, 45% discontinued stimulants and 15% switched to non-stimulants. Bipolar-PRS (hazard ratio[HR]=1.05, 95%confidence interval[CI]=1.02-1.09) and schizophrenia-PRS (HR=1.07,95%CI=1.03-1.11) were associated with discontinuation. Depression, bipolar and schizophrenia PRSs were marginally associated with switch (HR_{range}=1.05-1.07) with CIs including one. No associations were observed for ADHD-PRS and autism-PRS. Individuals diagnosed with ADHD ≥13 years-of-age had higher rates of stimulant initiation, discontinuation, and switch (HR_{range}=1.27-2.01). Psychiatric comorbidities generally reduced rates of initiation (HR_{range}=0.84-0.88), and increased rates of discontinuation (HR_{range}=1.19-1.45) and switch (HR_{range}=1.40-2.08). Estimated h^2_{SNP} were not significantly different from zero. No GWAS-hits were identified for stimulant initiation or discontinuation. A locus on chromosome 16q23.3 reached genome-wide significance for switch ($p=4.7\times10^{-8}$).

Conclusion: Our findings suggest that individuals with ADHD with higher polygenic liability for mood/psychotic disorders, delayed ADHD diagnosis, and psychiatric comorbidities have higher risk for

stimulant-treatment discontinuation and switch to non-stimulants. Despite limited sample size, one possible GWAS-hit for switch was identified, illustrating the potential of utilizing prescription databases in pharmacogenomics.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopment disorder affecting 5-10% of children and 2.5-5% of adults.(1) Stimulant drugs, particularly methylphenidate, are first-line recommended treatment for ADHD and have proven effective in reducing ADHD core-symptoms in clinical trials and meta-analyses. Due to lower effects sizes, non-stimulants (e.g. atomoxetine) are second-line treatment and primarily prescribed to individuals with poor stimulant-treatment response or tolerance. (2–4) Despite the high efficacy of stimulants, many patients discontinue treatment or switch to a non-stimulant ADHD-drug, with poor treatment response and adverse effects reported as the most common reasons.(5–7) As stimulant-treatment has been associated with positive effects on important functional outcomes,(8) it is imperative to identify genetic, clinical and socio-demographic factors influencing stimulant-treatment initiation, discontinuation and switch to non-stimulants in ADHD.

Genetics likely contribute to stimulant-treatment response and risk of adverse effects, yet few genetic variants have been robustly linked to stimulant-treatment outcomes in ADHD. A meta-analysis of candidate-gene studies reported replicated associations of methylphenidate efficacy with variants in the ADRA2A, COMT, SLC6A2, SLC6A3 and DRD4 genes.(9) However, candidate-gene studies are known to be problematic, with many identified variants failing to replicate in genome-wide association studies (GWASs).(10, 11) Two small GWASs (N>200) have been conducted on methylphenidate response,(12, 13) without any genome-wide significant hits identified, likely due to the limited sample sizes. Utilizing genetic data linked to individual-level electronic health records (EHRs), including prescriptions, is a promising avenue to obtain larger, representative samples for pharmacogenomic research. However, treatment outcomes are rarely reported in EHRs and must be approximated from prescriptions.(14, 15) Numerous pharmacoepidemiological studies have used discontinuation and switch to non-stimulants, defined from prescriptions, as proxies of suboptimal treatment outcomes in ADHD. (16–23) Nevertheless, we are not aware of any studies investigating the genetic contributions to these

stimulant-treatment outcomes, either through GWAS, single nucleotide polymorphism heritability (h^2_{SNP}), or polygenic risk score (PRS) analyses.

PRSs, which capture the weighted sum of an individual's phenotype associated risk alleles, may be a useful component in predicting treatment outcomes.(14, 15) A recent study of 214 ADHD-cases found that higher ADHD-PRS was associated with symptom improvement following stimulant-treatment.(24) Moreover, ADHD is genetically correlated with other psychiatric disorders, including autism spectrum disorder (ASD), depression, bipolar disorder and schizophrenia.(11, 25) Thus, it can be hypothesized that higher PRS for these disorders in individuals with ADHD may also influence stimulant-treatment outcomes, e.g. through increased risk of adverse treatment effects. Nevertheless, given the low predictive ability of current psychiatric PRSs, identification of patients at high risk of suboptimal stimulant-treatment outcomes will likely depend on combining genetic, clinical and socio-demographic information.(14) Psychiatric comorbidities can affect stimulant-treatment outcomes in ADHD,(2, 3) e.g., comorbid ASD has been linked to more adverse treatment effects,(26) and substance misuse to lower stimulant-efficacy. (27) There are also concerns that stimulants may induce or exacerbate tics, compulsive behaviors, anxiety, depression or psychotic symptoms. (3, 28, 29) Hence, individuals with ADHD and these comorbidities may be less likely to receive stimulants and more likely to discontinue or switch treatment. Age, sex, parental psychiatric illness and socioeconomic status have all also been linked to ADHD-treatment initiation, discontinuation and switch, albeit with mixed findings.(5, 7, 23, 30–32)

In this study, we first aimed to identify PRSs for psychiatric disorders, clinical, and socio-demographic factors associated with stimulant-treatment initiation, discontinuation, and switch to non-stimulants, defined from prescriptions. Second, we explored the feasibility of conducting GWASs and estimating h^2_{SNP} for these stimulant-treatment outcomes. To do so, we utilized genetic and Danish national register data in a large sample of individuals with ADHD from the iPSYCH2012 case-cohort. (33)

Methods

Study population

The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH2012) case-cohort was identified from all singletons born in Denmark May 1, 1981- December 31, 2005 (33). iPSYCH2012 consists of a random population-sample of 30,000 controls, and all individuals with a major psychiatric disorder diagnosed by December 31, 2012. This included 18,726 individuals with ADHD identified by a discharge diagnosis with International Classification of Disease (ICD)-10 code F90.0(34) in the Danish Psychiatric Central Research Register (DPCRR), which contains inpatient care since 1969 and outpatient since 1995.(35) iPSYCH2012 is linked to Danish national registers with data available until 31 December, 2016. We restricted analysis to individuals with ADHD diagnosed between 1 January, 2005-31 December, 2012, as ADHD prevalence and treatment has increased markedly since the early 2000's in Denmark,(36) and because atomoxetine, the main non-stimulant ADHD-drug, was first approved in Denmark in 2006. Genotypes in iPSYCH2012 were obtained for 78,050 samples, and 554,360 SNPs were genotyped in 23 waves on the Illumina PsychChip v1.0 array. The procedure is described elsewhere.(33) For imputation, principal components analyses, and quality control, see Schork et al (2019).(37) Briefly, imputed best-guess genotypes were filtered on info score >80%, minor allele frequency (MAF)>1%, Hardy–Weinberg equilibrium ($p>1\times10^{-6}$), association with genotyping wave ($p>5\times10^{-8}$) and imputation batch ($p>5\times10^{-8}$), leaving 6,361,597 autosomal SNPs. Analyses were restricted to unrelated individuals of European ancestry identified using smartPCA.(38) After phenotype and genotype exclusions, 9133 individuals with ADHD were retained for analyses. The study population selection is described in Supplementary Figure 1.

Stimulant-treatment outcomes

ADHD-drug prescriptions were identified from the Danish National Prescription Registry (DNPR), which includes all prescriptions redeemed at pharmacies since 1 January, 1995, classified according to Anatomical Therapeutic Chemical (ATC) codes.(39) We included all stimulant

(Methylphenidate[N06BA04], Dexamfetamine[N06BA02], Lisdexamfetamine[N06BA12]), and non-stimulant, ADHD-drugs (Atomoxetine[N06BA09], Guanfacine[C02AC02]) approved in Denmark. Prescriptions for Modafinil (N06BA07) and Bupropion (N06AX12) following treatment with a licensed ADHD-drug were also included, as these are sometimes used as off-label ADHD treatment.(40) ADHD-drug treatment before age three is not recommend, thus prescriptions before this age were excluded. (2, 3)

ADHD stimulant-treatment outcomes were stimulant initiation, discontinuation, and switch to non-stimulant treatment within a two-year observation window (Figure 1).

Initiation of stimulants was defined as the date of the first prescription for any stimulant ADHD-drug. Individuals were followed from the date of their first ADHD diagnosis until the date of initiation, censoring (due to death or emigration), or end of follow-up, (i.e. 730 days after first ADHD diagnosis), whichever came first. To allow for a delay between first treatment contact and diagnosis, individuals with a prescription within six months prior to first ADHD diagnosis were considered to have initiated at start of follow-up. Individuals who initiated with a non-stimulant were excluded from the main analyses (n=568, 5.6% of the eligible sample), but contrasted to stimulant-initiators in supplementary analyses.

Individuals with ADHD who initiated stimulant-treatment were followed from the date of their first stimulant prescription until **discontinuation** or **switch**, censoring, or end of follow-up (i.e. 730 days after first dispensed stimulant). **Discontinuation of stimulants** was defined as a gap between stimulant prescriptions of ≥ 180 days, in line with previous research.(19–21) Date of discontinuation was set to 30 days after the final dispensed prescription (i.e. the median length between stimulant prescriptions [IQR=17-51days]), to account for consumption of the final prescription. **Switch to non-stimulants** was defined as the date of the first prescription of a non-stimulant ADHD-drug. **Discontinuation** and **switch** were treated as non-mutually exclusive outcomes due to the challenge of determining the exact length of each prescription, and because individuals who discontinue may later switch to non-stimulants. For

the same reasons, we did not differentiate between switch and augmentation (i.e. co-prescribing of stimulant and non-stimulant ADHD-drugs). See Figure 1 for details.

Polygenic risk scores

We included PRSs for ADHD, as well as ASD, depression, bipolar disorder and schizophrenia, based on their reported genetic correlations with ADHD (11, 41) and availability of sufficiently powered GWASs. We derived externally-trained PRSs using LDPred (42), with SNP-weights obtained from external GWAS summary statistics excluding iPSYCH2012 (Supplementary Table 1). We also leveraged having individual-level SNP-data on a large number of ADHD, ASD, and depression cases in iPSYCH2012, by deriving another set of internally trained PRSs using SNP-weights obtained from a best linear unbiased prediction [BLUP] of SNPs in the iPSYCH2012 sample.(43) The final ADHD-, ASD-, and depression-PRS were constructed as a linear combination of the internally and externally trained PRSs. All PRSs were standardized to the mean and standard deviation (SD) in the iPSYCH2012 controls. For details, see Supplementary Note 1

Clinical and socio-demographic factors

Clinical and socio-demographic factors were obtained from Danish national registers and chosen based on treatment guidelines and previous literature.(3, 7) We included sex, age at first register-based ICD-diagnosis for any ADHD-subtype (i.e. F90.x, F98.8, to capture earliest observable diagnosis), maternal education and paternal income in birth-year of the index child, parental history of any psychiatric disorder, and comorbid register-based diagnosis of ASD, intellectual disability (ID), oppositional defiant/conduct disorder (ODD/CD), tics disorder, obsessive compulsive disorder (OCD), anxiety, depression, bipolar disorder, and substance use disorder. Comorbid schizophrenia was not included as there were too few cases. Data sources and definition are outlined in Supplementary Note 2.

Statistical analyses

Associations with PRSs, clinical and socio-demographic factors

We used Cox Proportional Hazards models to estimate associations, expressed as hazard ratios with 95% confidence intervals (CIs), of PRSs, clinical and socio-demographic factors with each stimulant-treatment

outcome. 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 associations were further adjusted for genotyping wave and the first four principal components. Sex, age at first ADHD diagnosis, birth-year, as well as parental education, income and psychiatric history, were modelled as time-fixed covariates. Psychiatric comorbidities were modelled as time-varying covariates to capture psychiatric problems emerging after start of follow-up. PRSs were modelled both as continuous covariates, estimating hazard ratios by one SD increase, and as quintiles, estimating hazard ratios in each PRS-quintile compared to the lowest.

We performed three supplementary analyses. For discontinuation and switch, we first ran multivariate Cox models, including each PRS separately in a model with all clinical and socio-demographic factors, to evaluate the impact of covariate adjustment on PRS associations. Second, we ran analyses stratified by age at first ADHD diagnosis (before and after 13 years-of-age), to evaluate if associations differed in children and adolescent/adults. Finally, we ran logistic regression to evaluate PRSs, clinical, and socio-demographic differences between individuals with ADHD who initiated treatment with a non-stimulant (i.e. those excluded from the main analyses) versus stimulant-initiators.

Analyses were conducted in R v.3.6.0.

GWASs and h^2_{SNP}

We conducted within-case GWAS and estimated h^2_{SNP} for stimulant-treatment initiation, discontinuation and switch, defined by treatment status at the end of follow-up. Stimulant-initiators (N=7427) were compared to non-initiators (N=1706). Individuals with ADHD who discontinued (N=3370) or switched (N=1137) were compared to individuals who remained in stimulant-treatment (i.e. no discontinuation or switch, N=3854). GWASs were performed using BOLT-LMM(44), and h^2_{SNP} estimated using BOLT-REML(45). Analyses were adjusted for sex, birth-year, age at first ADHD diagnosis, genotyping wave and

the first 10 PCs. We used FUMA for functional mapping and annotation of GWAS results (46). For details, see Supplementary Note 3.

This study was approved by the Danish Scientific Ethics Committee, the Danish Health Data Authority, the Danish Data Protection Agency, and Danish Newborn Screening Biobank Steering Committee. The Danish Scientific Ethics Committee, in accordance with Danish legislation, has, for this study, waived the need for informed consent in biomedical research based on existing biobanks.(33)

Results

Among 9133 individuals with ADHD, 29% were females and median age at first ADHD diagnosis was 12 years-of-age (IQR=8-17). Baseline descriptives are presented in Supplementary Table 2. Within two years of ADHD diagnosis, 7427 (81%) had initiated stimulant-treatment. Among stimulant-initiators, 3370 (45%) had discontinued stimulants and 1137 (15%) switched to non-stimulants within two years of stimulant-initiation.

Associations with PRSs, clinical and socio-demographic factors

PRS associations expressed by SDs (Table 1) showed that ADHD- and ASD-PRS were not associated with any stimulant-treatment outcome. PRS for bipolar disorder (hazard ratio=1.05, 95%CI=1.02-1.09) and schizophrenia (hazard ratio=1.07, 95%CI=1.03-1.11) were associated with discontinuation. PRS for depression (hazard ratio=1.06, 95%CI=0.99-1.13), bipolar disorder (hazard ratio=1.05, 95%CI=0.99-1.12), and schizophrenia (hazard ratio=1.07, 95%CI=1.00-1.13) were marginally, but not significantly associated, with CIs including or crossing one. PRS associations in the fully adjusted multivariate Cox models (Supplementary Table 3) were near identical to the main results.

PRS associations across quintiles (Figure 2, Supplementary Table 4) showed that individuals with ADHD in the highest PRS-quintile for bipolar disorder (hazard ratio=1.21, 95%CI=1.09-1.35) and schizophrenia (hazard ratio=1.24, 95%CI=1.11-1.39) had higher rates of discontinuation, compared to those in the lowest quintile. Further, those in the highest PRS-quintile for depression (hazard ratio=1.26, 95%CI=1.05-1.52) and bipolar disorder (hazard ratio=1.25, 95%CI=1.04-1.51) had higher rates of switch. For schizophrenia-PRS, rates were elevated across quintiles, but only significant at the 4^{th} quintile (hazard ratio=1.33, 95%CI=1.10-1.61). CIs for remaining estimates were near to or included one, and overlapped across quintiles.

Associations with clinical and socio-demographic factors are presented in Table 1 and Figure 3. Sex was not associated with initiation or discontinuation, however females had higher rates of switch (hazard

ratio=1.17, 95%CI=1.03-1.33). ADHD diagnosis ≥13 years-of-age was associated with higher rates of initiation (hazard ratio=1.27, 95%CI=1.17-1.38), discontinuation (hazard ratio=2.01, 95%CI 1.77-2.27), and switch (hazard ratio=1.91, 95%CI=1.53-2.39), compared to diagnosis <13 years-of-age. Low maternal education was associated with lower rates of initiation (hazard ratio=0.94, 95%CI=0.90-0.99) and low paternal income with higher rates of discontinuation (hazard ratio=1.11, 95%CI=1.03-1.20).

Comorbid OCD, anxiety, bipolar and substance use disorder were associated with lower rates of initiation (hazard ratio range=0.59-0.88). Further, ASD, anxiety, bipolar and substance use disorder were associated with higher rates of discontinuation (hazard ratio range=1.18-1.46), and ODD/CD, tics, anxiety and substance use disorder with higher rates of switch (hazard ratio range=1.41-2.08), compared to individuals with ADHD without these comorbidities. Estimates stratified by age at first ADHD diagnosis (Supplementary Figure 2, Table S5) showed that comorbid ASD was only associated with discontinuation in children (hazard ratios=1.41, 95%CI=1.24-1.60). Similarly, comorbid depression was associated with discontinuation (hazard ratio=3.05, 95%CI=1.76-5.28) and switch (hazard ratio=3.43, 95%CI=1.53-7.71) in children, but not in adolescents/adults. Associations of comorbid bipolar and substance use disorder with stimulant-treatment outcomes in the main analysis were driven by those diagnosed with ADHD during adolescence/adulthood, as there were too few comorbid cases (N<10) to estimate hazard ratios in children. CIs were overlapping for remaining age-stratified estimates.

Supplementary analyses (Table S6) showed that individuals with ADHD who initiated treatment with a non-stimulant drug (N=568) were more likely to be female (odds ratio=0.77, 95%CI=0.64-0.93 [male as reference]), diagnosed with ADHD ≥13 years-of-age (odds ratio=6.12, 95%CI=4.20-9.00), and have comorbid ASD, tics, anxiety or substance use disorder (odds ratio range=1.47-3.56), compared to stimulant-initiators.

GWAS and h^2_{SNP}

h^2_{SNP} on the observed-scale was estimated to 0.08 (SE=0.06) for initiation, 0.13 (SE=0.08) for discontinuation, and 0.09(SE=0.11) for switch. N and liability-scale converted estimates are provided in Supplementary Table 7. No genome-wide significant hits were detected for initiation and discontinuation ($p>5\times10^{-8}$) (Supplementary Figures 3-4). For switch, one locus on chromosome 16q23.3 ($p<4.7\times10^{-8}$, leadSNP rs58543609, CHR16:82376003 [GRCh37]) reached genome-wide significance (Figure 4). Using FUMA (46), AC024590.1 and RN7SKP190 were identified as the most proximal genes of the rs58543609 locus. Expression quantitative trait loci (eQTL) annotation identified one putatively associated gene, MPHOSPH6. A look-up in GWAS catalogue (47) identified no prior reports of the lead SNP, however a locus scan (CHR16:82315555-82397332) revealed suggestive associations in prior GWASs of cognitive performance, seasonal depression, face morphology and bone-mineral density. PheWAS implemented in GWASATLAS(48) revealed two putative associations with a measure of weekly alcohol intake and cerebellar volume. Associations for the 18 independent genomic loci reaching suggestive genome-wide significance ($p<10^{-5}$) and FUMA results are presented in Supplementary Table 8-9.

Discussion

This is, to our knowledge, to largest study thus far utilizing genetic and prescription data to investigate stimulant-treatment initiation, discontinuation and switch to non-stimulants in ADHD. We present novel findings suggesting that individuals with ADHD and higher polygenic liability for bipolar disorder, schizophrenia and possibly depression may be at increased risk of stimulant-treatment discontinuation and switch. We also identified several clinical factors contributing to stimulant-treatment outcomes, including delayed ADHD diagnosis and certain psychiatric comorbidities. We also present the first GWASs and h^2_{SNP} estimates of stimulant-treatment outcomes defined from prescription data, identifying one putative locus associated with switch to non-stimulants.

We found that majority (81%) of individuals with ADHD initiated stimulant-treatment, yet within two years, nearly half (45%) had discontinued treatment and 15% had switched to non-stimulants. Similar rates of discontinuation have previously been reported in Denmark, Sweden, the US, Korea, and Taiwan (19–23), highlighting that prescription databases provide relativity consistent estimates of ADHD treatment patterns, and that discontinuity is an important issue in the management of ADHD globally.

Individuals with ADHD in the higher PRS-quintiles for bipolar disorder and schizophrenia had 17-25% higher rates of discontinuation and switch, compared to the lowest PRS-quintiles. We also found that higher polygenic liability for depression may increase the rate of switch. These novels findings require replication, as some CIs included one, and the pattern of associations were not consistent with a dose-response relationship across all PRS-quintiles. Nevertheless, it can be hypothesized that elevated genetic liability for mood and psychotic disorders in individuals with ADHD may increase the risk of adverse effects of stimulant-treatment (e.g. mood destabilization/psychotic symptoms).(3, 29) In support of this, we also found that comorbid depression in children with ADHD, and comorbid bipolar disorder in adolescent/adults, were associated with higher rates of discontinuation. Another possibility is that prodromal mood/psychotic symptoms may, in some cases, be misdiagnosed as ADHD, potentially rendering stimulant-treatment inappropriate.(49) Nevertheless, given the high validity of ADHD

diagnoses in the Danish registers(50), and evidence of familial and genetic overlap between ADHD and mood/psychotic disorders, (11, 51) this is unlikely to fully explain our results. Regardless, these findings underscore the importance of screening for family history and symptoms of psychosis, (hypo-)mania, and depression prior to initiating stimulants. Importantly, our results also suggest that PRSs for bipolar, schizophrenia and depression may in the future complement such screening, assuming that their predictive validity can be substantially improved.(14) This is especially notable, as we found that PRS associations, although modest in effect size compared to psychiatric comorbidities, were largely unchanged after adjusting for comorbidities and socio-demographic factors. This suggests that higher PRS for mood/psychotic disorders in ADHD may act as an independent risk-factor for stimulant-treatment discontinuation and switch, which is measurable prior to the (potential) onset of such disorders and in patients with symptoms below the diagnostic threshold.

We found limited evidence for the contribution of ADHD- and ASD-PRS to stimulant-treatment-outcomes, possibly due to the lower power in the discovery GWASs of these disorders, or the challenge of using PRSs to predict secondary clinical characteristics in case-only samples.(52) Interestingly, a recent study(53) found no correlation between 23 genes identified as targets of ADHD drugs and ADHD-GWAS summary statistics. Instead, associations were observed for GWAS of alcohol consumption, schizophrenia, and depression with the DRD2, CYP2D6, and CHRM2 genes. This, together with our findings, suggests that effectiveness and/or tolerance of ADHD drugs may act through other genetic pathways than the ones underlying ADHD risk, and that genetic liability for psychiatric disorders emerging in adolescence/adulthood may be of importance for stimulant-treatment outcomes.(53)

Beyond bipolar disorder and depression (discussed above), several psychiatric comorbidities stood out as risk-factors for discontinuation and switch. Comorbid OCD and anxiety increased the risk of discontinuation and switch, and ASD increased risk of discontinuation, although only significantly so in children. Though evidence is low, these comorbidities have historically been suggested to increase the

risk of adverse effects of stimulant-treatment.(2, 3) Our data may either support the comorbidities' association with adverse effects, or merely confirm that this clinical perception is common. Among individuals with ADHD diagnosed in adolescence/adulthood, substance use disorder increased the risk of both discontinuation and switch, whilst comorbid ODD/CD was associated only with switch. The former may relate to evidence of lower stimulant-efficacy in ADHD with comorbid substance misuse and clinical concerns of misuse/diversion.(27) Finally, comorbid tics disorder increased the risk of switch to non-stimulants across ages, and of discontinuation in children, which could reflect that, although rare, stimulant-treatment may exacerbate or induce tics.(2, 3) Our findings emphasize the need for a broad and age-sensitive clinical assessment in ADHD prior to treatment-initiation, as well as close monitoring for psychiatric problems emerging during treatment, as comorbidities may negatively influence stimulant tolerance and efficacy. Older age at first ADHD diagnosis was also was also associated with elevated risk of discontinuation and switch, and treatment initiation with non-stimulants was more common in those diagnosed with ADHD after childhood. Similar findings have been reported in previous studies,(7, 16, 20, 23) emphasizing that adolescence and early adulthood are high-risk periods for ADHD treatment drop-out. Our results suggest that efforts are needed to improve treatment continuity in these age groups.

Finally, we evaluated the feasibility of using EHRs in ADHD pharmacogenomics. GWASs of stimulant initiation and discontinuation did not identify any genome-wide significant loci, and the common variant contribution estimated by h^2_{SNP} was not significantly different from zero for any stimulant-treatment outcomes. These null-findings are unsurprising given our limited sample size and the challenge of defining treatment outcomes that are proximal to the underlying biology.(54, 55) Nevertheless, it can be noted that despite large standard errors, our h^2_{SNP} point estimates are in line with heritabilities reported for other treatment-response traits in psychiatry (e.g., antidepressant treatment response (56)). Moreover, (potentially) low h^2_{SNP} does not imply that genetic factors are unimportant, as the power to detect genetic variants for a given phenotype depends both on its genomic architecture and GWAS

sample size.(57) We did identify one genome-wide significant locus associated with switch to non-stimulants on chromosome 16q23.3. The locus and most proximal gene (AC024590.1) have not been identified in prior GWASs, but the RN7SKP190 and cadherin-13 (CDH13) gene are located within 250kb of the locus, and have been associated with theoretically relevant traits, e.g., body-mass index, blood pressure and educational attainment.(47) However, the potential molecular consequences of the rs58543609 locus for switch require further investigation. Based on the modest h^2_{SNP} point-estimates and GWAS without any major gene effects, our results suggest that stimulant-treatment outcomes (as defined here) likely have a complex genetic architecture and that larger sample will be needed for gene discovery. Nevertheless, with the continuous integration of genetics in large EHRs databases globally, and rapid methods development for approximating treatment outcomes,(15) we believe our findings illustrate the potential of using prescription data in order to progress pharmacogenomics in ADHD.

Strengths and Limitations

Our study has several strengths, including the representativeness of the iPSYCH2012 sample and access to longitudinal register-data. There are also important limitations. First, pharmacoepidemiological studies rely on modelling treatment outcome proxies from prescriptions, and we do not know how well our proxies map onto actual drug consumption, nor the reasons for discontinuation/switch. Second, we were underpowered for GWASs and h^2_{SNP} estimation, limiting our ability to make firm conclusions regarding the common variant contribution to stimulant-treatment outcomes. Third, iPSYCH2012 only includes ADHD-cases with combined subtype (F90.0), meaning results may not apply in the broader ADHD-case group. Fourth, we did not have data on several factors shown to be important for ADHD treatment adherence (e.g. perceived stigma, patient/parents attitudes to treatment).(5, 7) Finally, the reliance on a highly homogenous Danish population sample may limit generalizability to more diverse populations.

Conclusion

We present evidence that individuals with ADHD who have a higher genetic liability for mood/psychotic disorders, are diagnosed after childhood, or affected by certain psychiatric comorbidities may be at increased risk of stimulant-treatment discontinuation and switch to non-stimulants. Our results also highlight that the majority of evaluated risk-factors, and in particular PRSs, only have modest effects on stimulant-treatment outcomes. Identifying individuals with ADHD at high risk of suboptimal treatment outcomes will thus likely depend on multifactorial prediction, including both genetic and clinical risk-factors. Our GWASs illustrate the potential of utilizing genomics linked to EHRs to identify genetic variants underlying stimulant-treatment outcomes in ADHD.

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Table 1. Hazard ratios (HR) and 95% confidence intervals (CI) expressing the association of polygenic risk scores, clinical, and socio-demographic factors with stimulant-treatment outcomes

	Initiation			Discontinuation			Switch		
Polygenic risk scores (PRS)									
	HR	**LCI**	**UCI**	**HR**	**LCI**	**UCI**	**HR**	**LCI**	**UCI**
ADHD (per 1 SD)	1.02	0.99	1.04	0.99	0.96	1.03	1.01	0.95	1.07
ASD (per 1 SD)	0.99	0.97	1.02	1.02	0.99	1.05	1.00	0.94	1.06
Depression (per 1 SD)	0.99	0.97	1.02	1.00	0.96	1.04	1.06	0.99	1.13
Bipolar disorder (per 1 SD)	0.99	0.97	1.01	**1.05**	**1.02**	**1.09**	1.05	0.99	1.12
Schizophrenia (per 1 SD)	0.99	0.96	1.01	**1.07**	**1.03**	**1.11**	1.07	1.00	1.13
Clinical and socio-demographic factors									
	HR	**LCI**	**UCI**	**HR**	**LCI**	**UCI**	**HR**	**LCI**	**UCI**
Female sex	1.02	0.97	1.07	0.99	0.92	1.06	**1.17**	**1.03**	**1.33**
ADHD diagnosis ≥ 13 years	**1.27**	**1.17**	**1.38**	**2.01**	**1.77**	**2.27**	**1.91**	**1.53**	**2.39**
Parental psychiatric history	0.96	0.89	1.04	1.12	1.00	1.26	1.14	0.94	1.38
Low education, mother	**0.94**	**0.90**	**0.99**	1.05	0.98	1.13	0.92	0.82	1.04
Low income, father	0.97	0.92	1.02	**1.11**	**1.03**	**1.20**	0.97	0.85	1.12
Autism spectrum disorder	0.95	0.89	1.03	**1.19**	**1.07**	**1.33**	1.07	0.89	1.28
Intellectual disability	1.07	0.91	1.26	1.06	0.89	1.26	1.03	0.78	1.36
Oppositional defiant /Conduct disorder	1.17	0.97	1.39	1.13	0.95	1.35	**1.44**	**1.12**	**1.86**
Tics disorder	1.04	0.93	1.17	1.15	0.97	1.38	**2.08**	**1.65**	**2.63**
Obsessive compulsive disorder	**0.84**	**0.72**	**0.97**	1.22	1.00	1.48	1.27	0.92	1.76
Anxiety disorder	**0.83**	**0.75**	**0.92**	**1.18**	**1.04**	**1.35**	**1.44**	**1.17**	**1.77**
Depressive disorder	0.90	0.82	1.00	1.00	0.88	1.13	1.20	0.98	1.48
Bipolar disorder	**0.59**	**0.43**	**0.80**	**1.45**	**1.04**	**2.02**	1.08	0.60	1.97
Substance use disorder	**0.88**	**0.79**	**0.97**	**1.24**	**1.10**	**1.41**	**1.40**	**1.13**	**1.73**

Note: Significant associations are highlighted in bold. Sex, parental characteristics, and age at first ADHD diagnosis were modelled as time-fixed exposures, and psychiatric comorbidities were treated as time-varying exposures. All models were adjusted for sex, age at first ADHD diagnosis split in five categories [1-6, 7-9, 10-14, 15-19, and 20-32], 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.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder. ASD, autism spectrum disorder. SD, standard deviation. HR, hazard ratio. LCI, lower confidence interval. UCI, upper confidence interval.

Figure 1 Title. Flowchart depicting the two year observation period for initiation in 9133 eligible individuals with ADHD, and the two year observation period for discontinuation and switch in the 7247 individuals with ADHD who initiated stimulant treatment within two years of their first ADHD diagnosis.

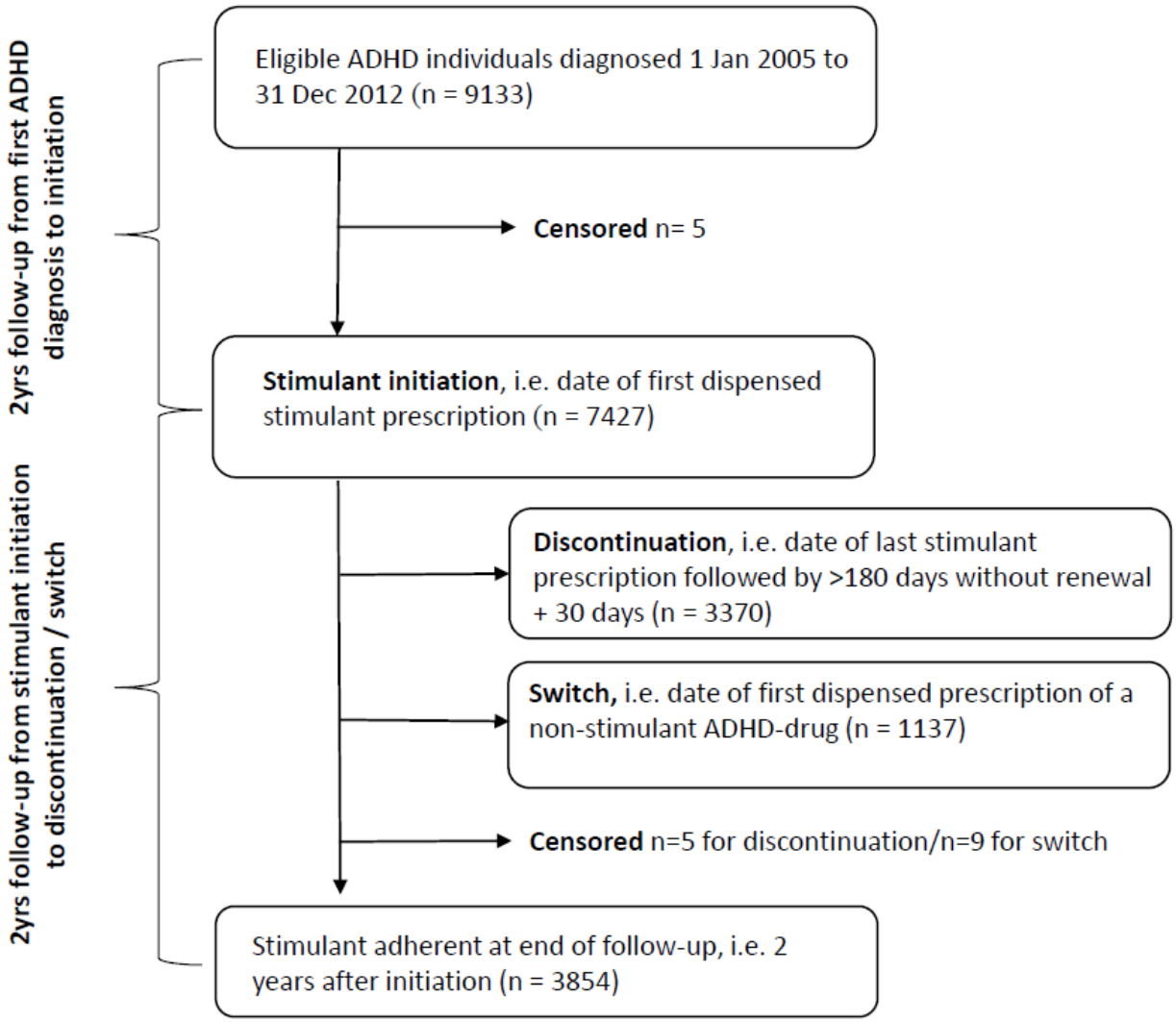

Figure 1 Note: Censoring due to death or emigration are reported separately for discontinuation and switch as these were modelled as separate, non-mutually exclusive outcomes. Individuals could switch to non-stimulants prior to discontinuation, to then go on to either co-medicate (augmentation) or fully discontinue

stimulants. Conversely, individuals could discontinue stimulants and then switch to non-stimulant ADHD-drug treatment. In total, 934 individuals had both a discontinuation (i.e., a gap between stimulant prescriptions > 180 days) and a switch (i.e. a prescription of a non-stimulant ADHD-drug) during follow-up. Among individuals who switched to non-stimulants, 203 (18%) augmented their stimulant treatment (i.e. “switch” without discontinuation during follow-up).

Figure 2 Title. Hazard ratios (HR) & 95% confidence intervals (CIs) of stimulant-treatment initiation, discontinuation and switch to non-stimulants across polygenic risk scores quintiles

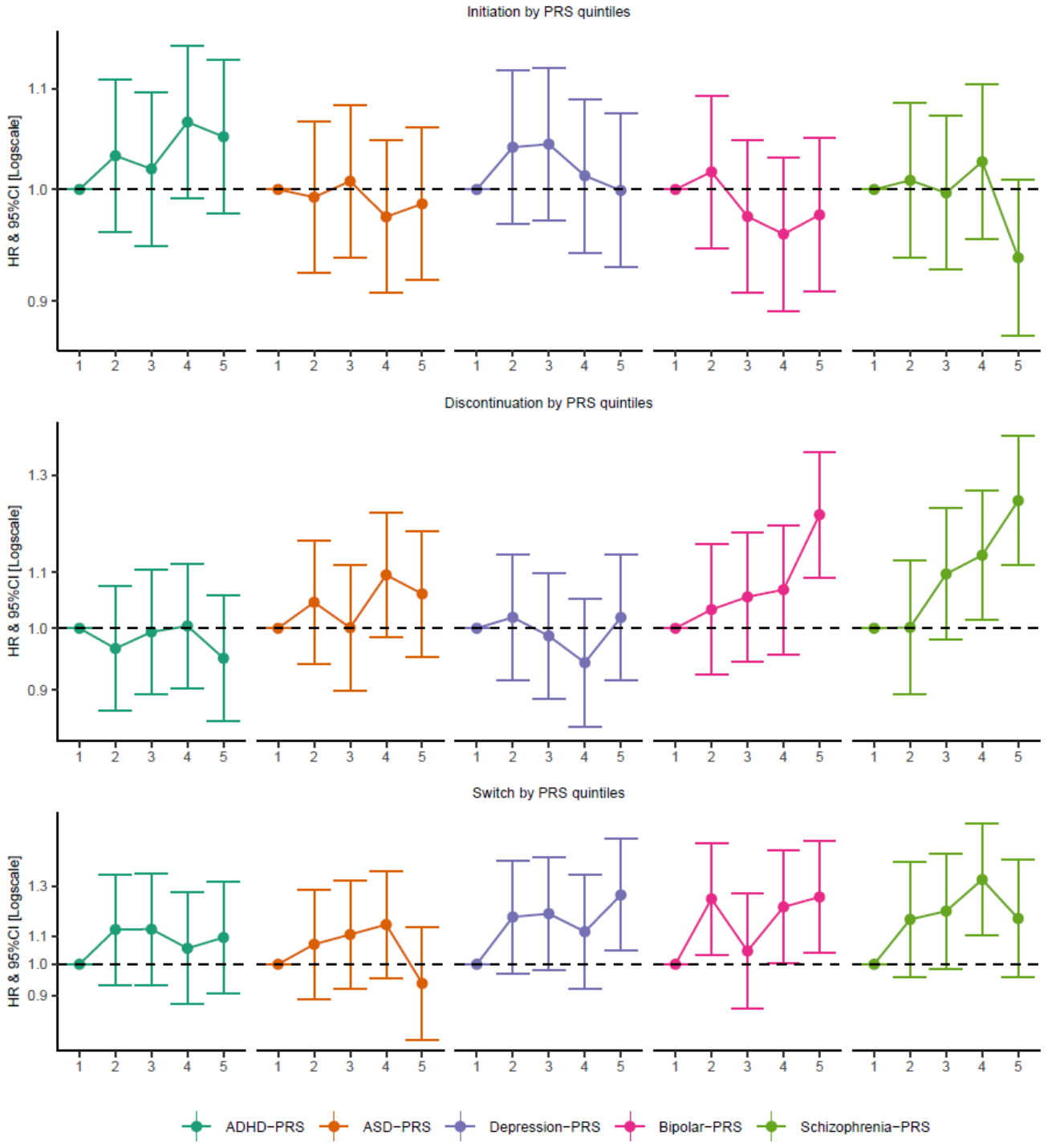

Figure 2 Note: 1st quintile was set to reference. All models were adjusted for sex, age at first ADHD diagnosis split in five age-categories [1-6, 7-9, 10-14, 15-19, and 20-32 years], birth-year in five categories [1981-1985, 1986-1990, 1991-1995, 1996-2000, and 2001-2005], genotyping wave and the first 4 principal components.

Figure 2 Abbreviations. ADHD, attention-deficit/hyperactivity disorder. ASD, autism spectrum disorder. PRS, polygenic risk score.

Figure 3 Title. Hazard ratios (HR) & 95% confidence intervals (CIs) expressing the association of clinical and socio-demographic factors with stimulant initiation, discontinuation and switch to non-stimulants

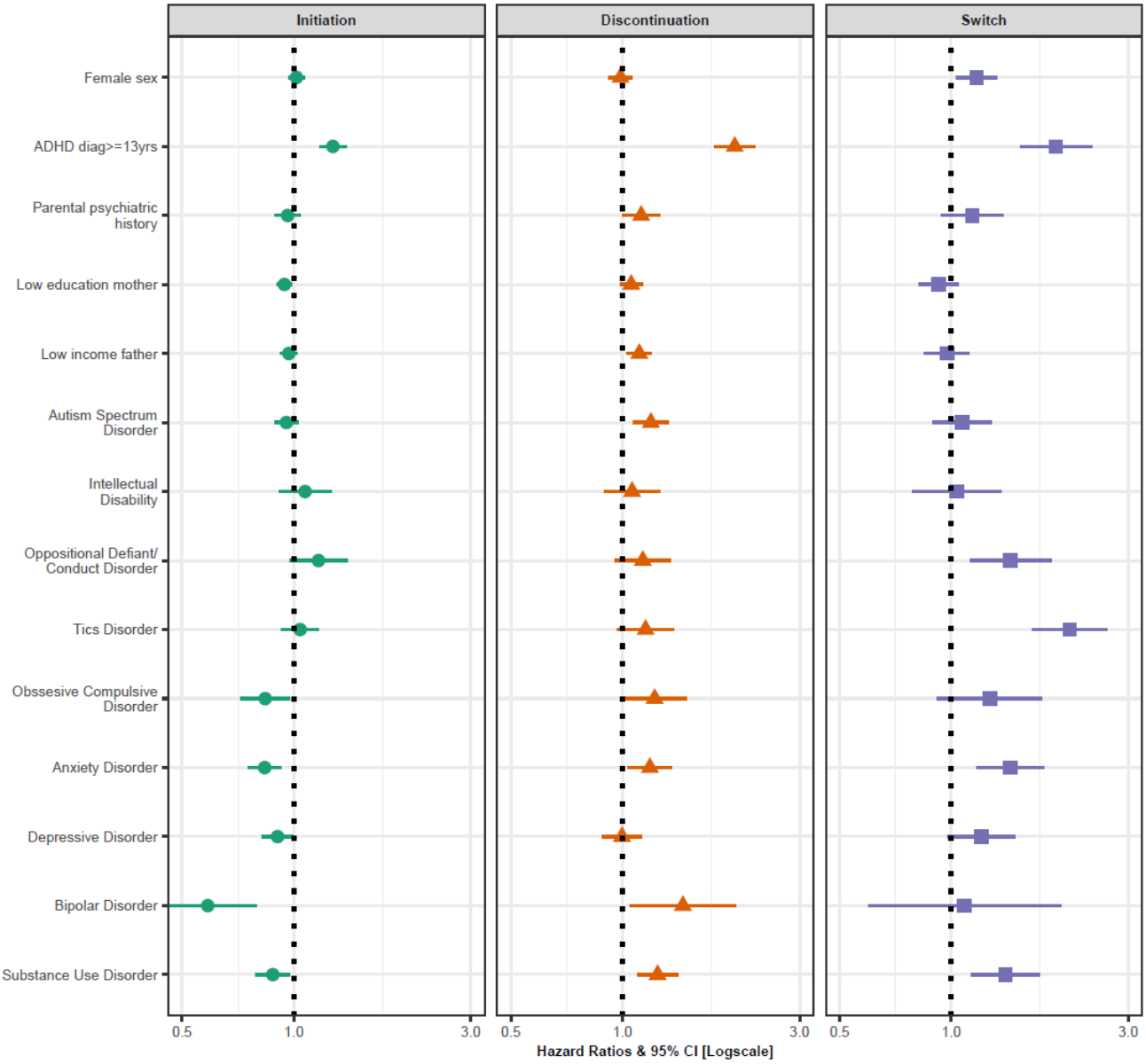

Figure 3 Note: Sex, age at first ADHD diagnosis, parental education, income and psychiatric history were treated as time-fixed exposures. Psychiatric comorbidities were treated as time-varying exposures. All

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].

Figure 4 Title. Manhattan plot (A) and quantile-quantile plot (B) of the association p-values, and (C) regional plot of top locus on chromosome 16q23.3, from GWAS of switch to non-stimulants in individuals with ADHD

Figure 4 Note: Individuals with ADHD who switched to non-stimulant treatment (n=1137) were compared to those who remained on stimulant-treatment (n=3854) (i.e. no discontinuation and no switch) in the two years following stimulant-treatment initiation. In the Manhattan plot (A), the $-\log^{10}(P)$ for each SNP is plotted against the genomic position. In the QQ-plot (B), the black dots represent observed p-values and the red lines represent expected p-values under the null distribution. In the regional association plot (C) around the lead SNPs rs58543609, chromosomal base-pair position are on the X-axis and significance of the association expressed as $-\log^{10}(P)$ on the Y-axis. Nearest genes are shown below plot.

Supplementary methods and materials

Genetic, clinical and socio-demographic factors associated with stimulant-treatment outcomes in ADHD

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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 cases ADHD, ASD and depression cases 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 (2020).[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: 5,305 cases and 5,305 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).https://doi.org/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 table supplementary note 2 for details on covariate definitions.

Abbreviations: PRS, polygenic risks cores. 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.

Abbreviations. PRS, polygenic risks cores. ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder. Significant associations are highlighted in bold.

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 (BD) / substance use disorder (SUD) 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. **Abbreviations.** na, not applicable.

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 (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. **Abbreviations**: ADHD, attention deficit hyperactivity disorder. ASD, autism spectrum disorder. OR, odds ratio. LCI, lower confidence interval. UCI, upper confidence interval.

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. Number for BOLT-REML are lower than those 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

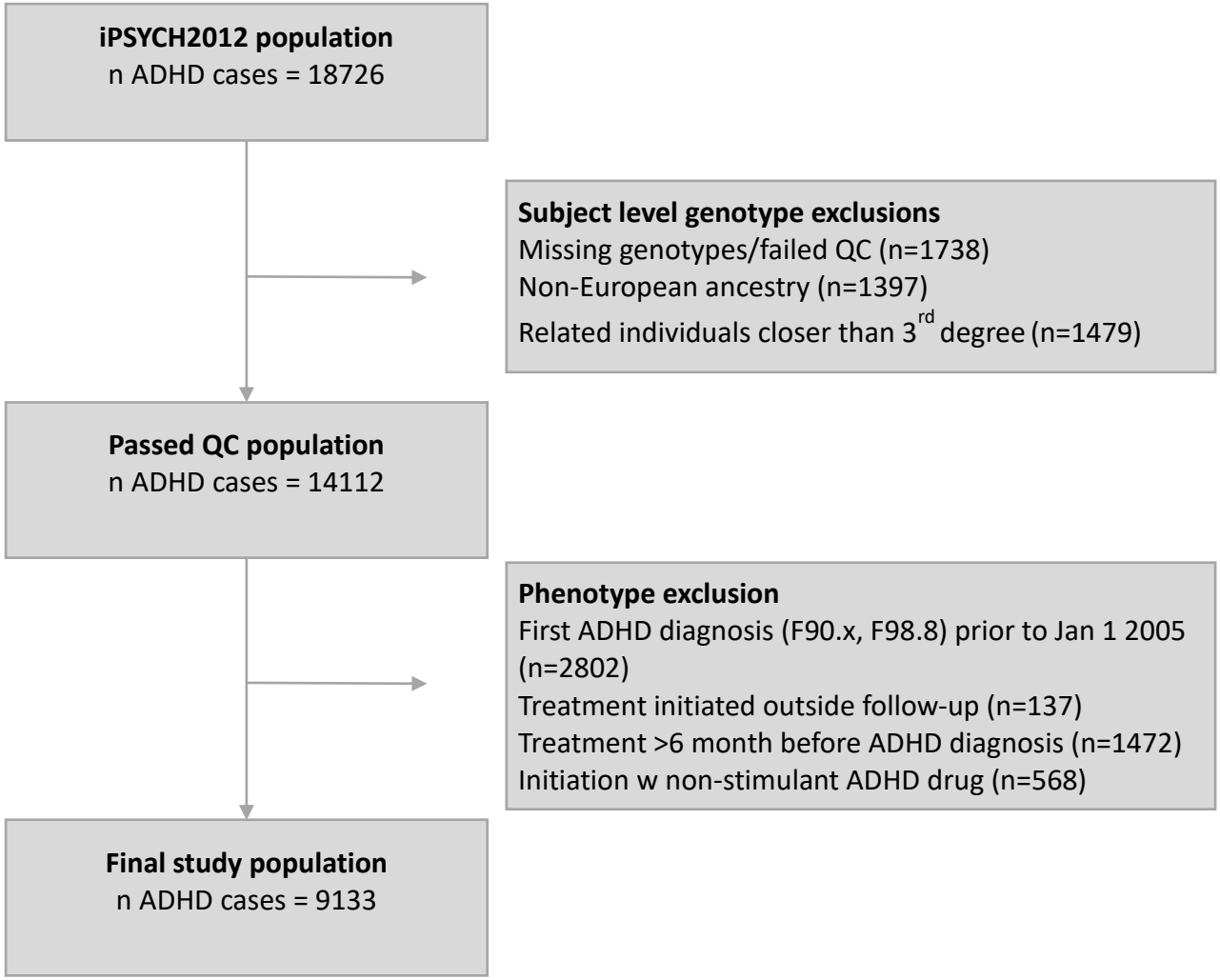
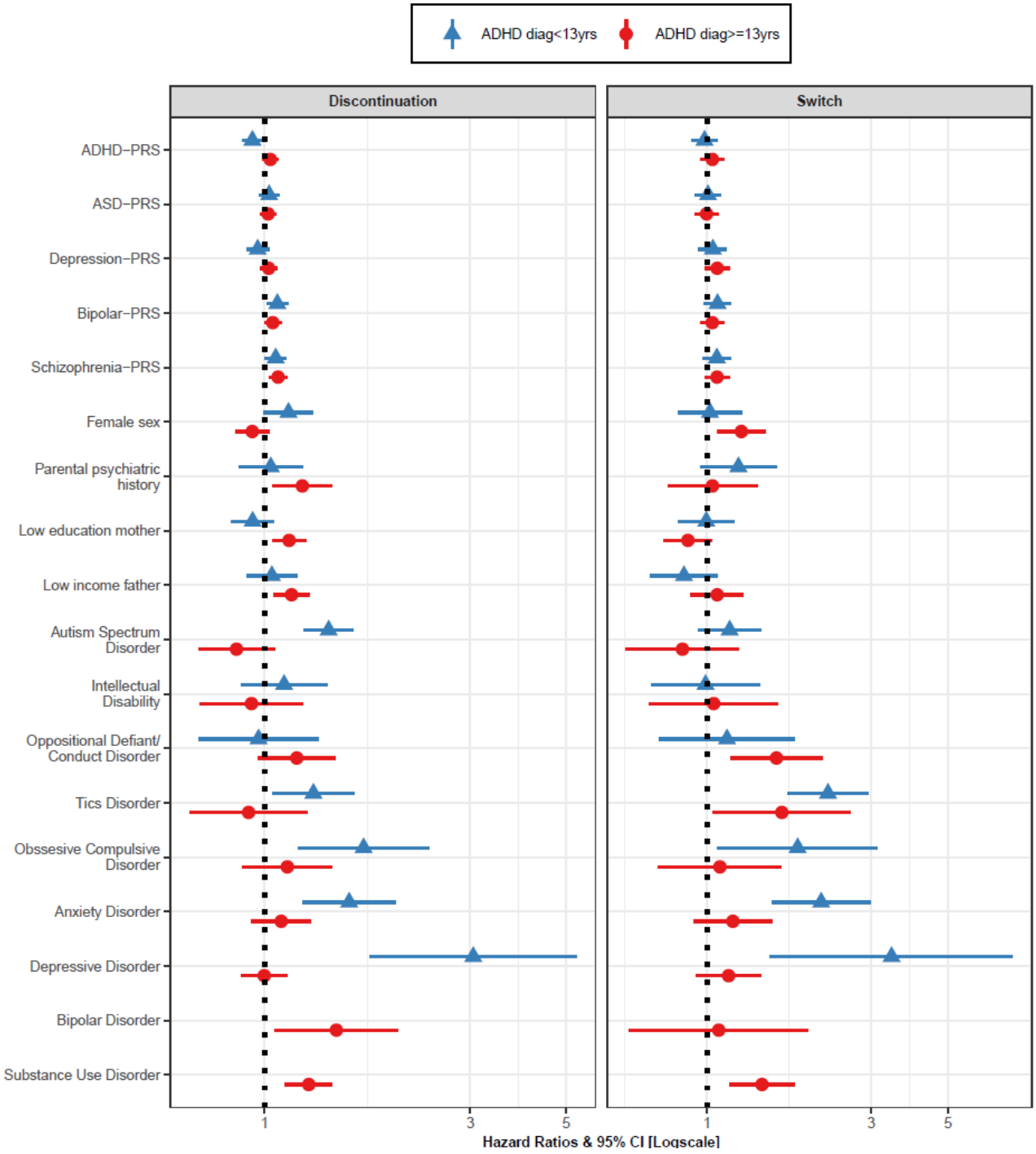
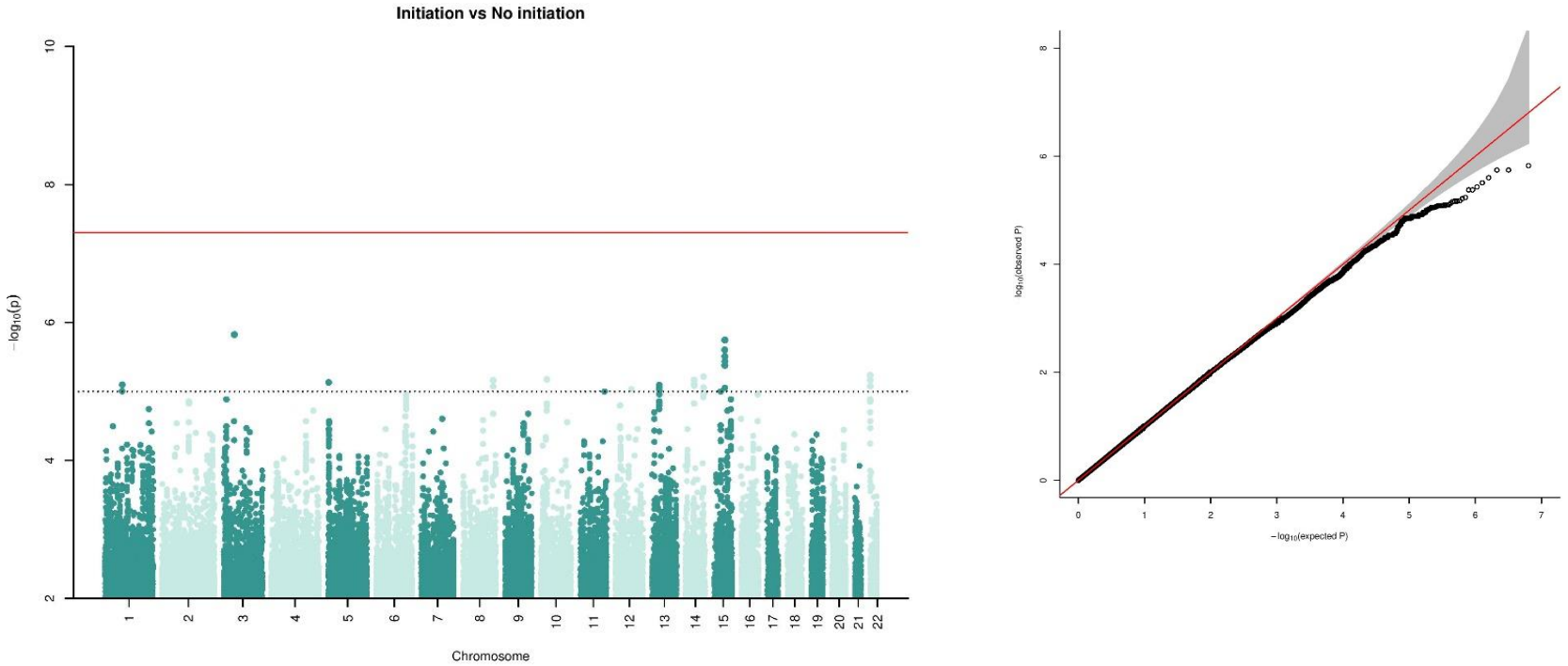


Figure S2. Hazard ratios (HR) & 95% confidence intervals (CIs) of stimulant discontinuation and switch stratified by age at first ADHD diagnosis



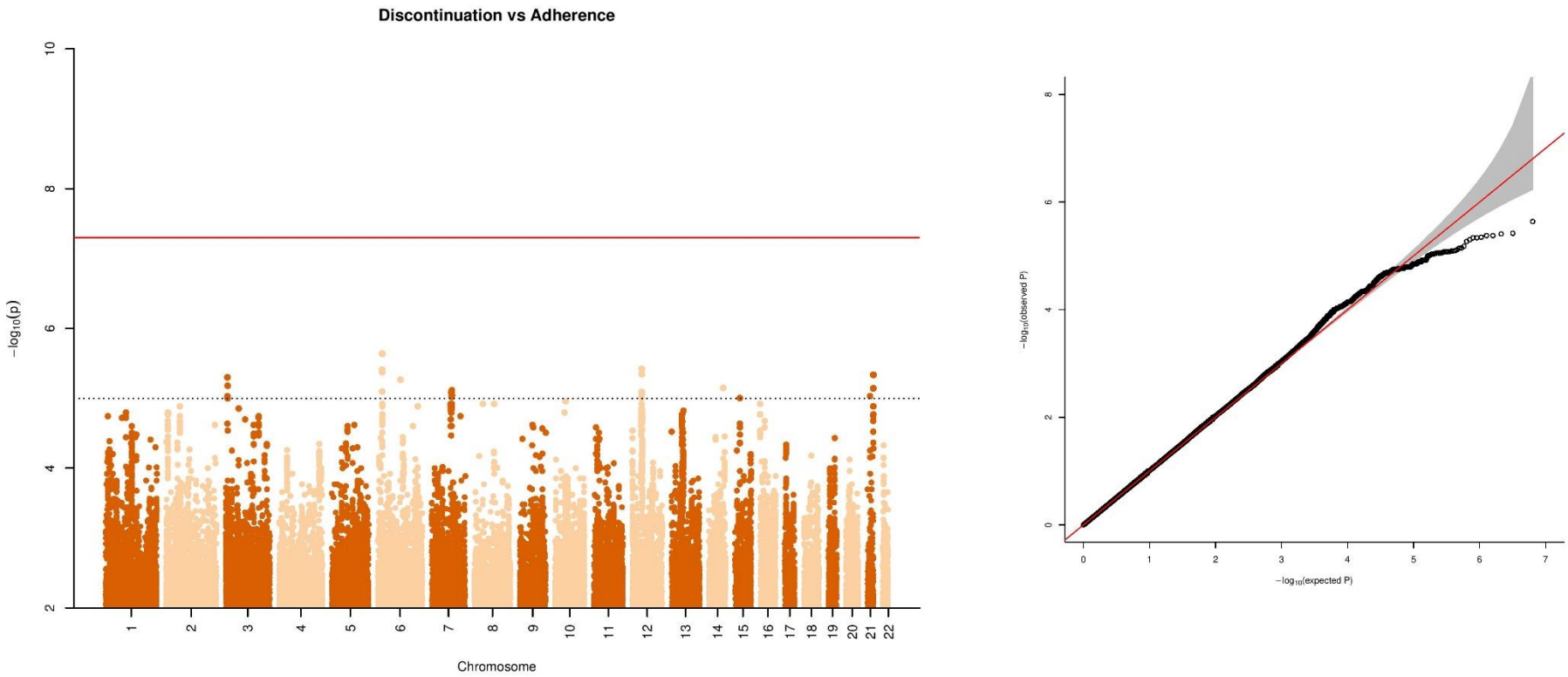
Note: Hazard ratios (HRs) and 95% confidence intervals (95%CIs) are shown for treatment discontinuation and switch, stratified by age at first ADHD diagnosis (before or after 13 years-of-age). There were too few cases with comorbid bipolar or substance use disorder among individuals with ADHD diagnosed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

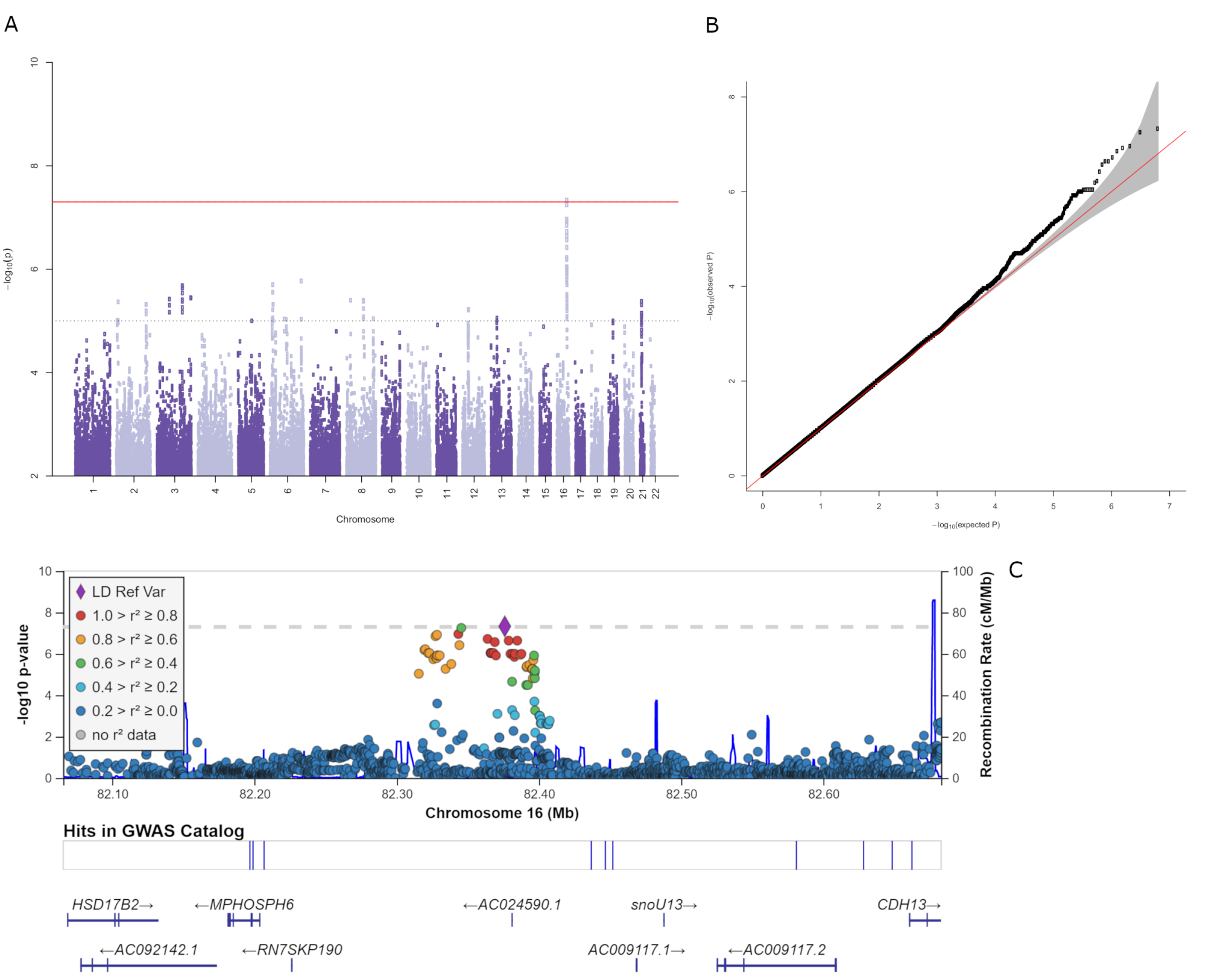


Note: Individuals with ADHD who initiated stimulant treatment (n=7427) were compared to those who did not (n=1706) (i.e. no prescription for any ADHD drugs within two years of first ADHD diagnosis). In the Manhattan plot, the -log^{10} of the *p*-value for each of SNPs is plotted against the genomic 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.


A
B
C
−log10(p)
Chromosome
−log10(observed P)
−log10(expected P)
LD Ref Var
1.0 > r² ≥ 0.8
0.8 > r² ≥ 0.6
0.6 > r² ≥ 0.4
0.4 > r² ≥ 0.2
0.2 > r² ≥ 0.0
no r² data
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 16 (Mb)
Hits in GWAS Catalog
HSD17B2→
←MPHOSPH6
←AC024590.1
snoU13→
CDH13→
←AC092142.1
←RN7SKP190
AC009117.1→
←AC009117.2