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Polygenic score for depression mediates the impact of family history of depression on offspring's psychopathology

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Abstract

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Mental illnesses run in families. Children with a family history of depression are at risk for mental illnesses. Understanding the pathways through which a family history of depression increases the offspring's risk for psychopathology could help identify those at higher risk, aiding in targeting intervention. In this study, we hypothesized polygenic scores (PGSs) of mental illnesses play a role as the genetic mechanism for the impact of a family history of depression. To this end, we analyzed the phenotype and genotype data of 8,111 multiethnic preadolescents (including 6,151 of European ancestry) from the Adolescent Brain Cognitive Development (ABCD) study. A four-level risk variable describing how many prior generations were affected by depression was created, assuming that children with both a parent and grandparent with depression have the highest risk. We estimated the PGSs of 30 psychiatric and cognitive traits. Logistic regression showed that higher familial risk was significantly associated with a higher polygenic risk (adjusted for covariates). PGSs for depression (corrected $P<0.01$; odds ratio [OR] = 1.14) and bipolar disorder (corrected $P<0.05$; OR = 1.12) were significantly associated with a family history of depression. Mediation analysis revealed that PGS for depression significantly mediated the impact of a family history of depression on offspring's psychiatric disorders and suicidality. These findings show an increase in inherited genetic

susceptibility to depression would be a mechanism for intergenerational transmission of depression. Future study is needed to investigate how polygenic risk influences developmental trajectory under the familial risk of mental illness. Such research will pave the way to understanding the pathophysiology of childhood psychopathology and defining children at higher risk for psychiatric conditions.

Keywords: childhood psychopathology, family history, polygenic score, psychiatric disorder, suicidality

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Table of Contents

List of Figures

List of Tables

Chapter 1. Introduction

Mental illnesses have been a global burden, accounting for almost one-third of the years lived with disability (Vigo et al., 2016). Children and adolescents are highly under this burden because half of the first mental disease onset occurs before age 18 (Kim-Cohen et al., 2003; Solmi et al., 2022). Furthermore, in terms of the disability-adjusted life-year (DALY), a metric that reflects early death and disability caused by disease, two mental disorders (i.e., depression and anxiety disorder) are in the top ten diseases for adolescents (Vos et al., 2020). These statistics highlight the importance of identifying early markers for mental illness in childhood and adolescence. Such proper marker identification may lead to early detection of high-risk individuals and appropriate intervention to prevent and reduce maladaptive symptoms. Therefore, understanding the risk factor and the mechanism of psychopathology, especially in childhood, is crucial to lessen the burden of mental conditions worldwide.

1.1. Genetic contributions to mental disorders

Heritability of mental disorders. Mental disorders are highly heritable, influenced by shared genetic factors in families. Each mental trait has some extent of heritability, while the estimated heritability varies across the dimensions of psychopathology, which can be broadly divided into two dimensions: internalizing (e.g., mood disorders) and externalizing (e.g., conduct behaviors and substance use disorders) disorders (Achenbach, 1966; Achenbach & Edelbrock, 1978; Cicchetti & Toth, 1991). According to twin studies, externalizing traits are highly explained by

genetic factors (~80%), whereas the heritability of internalizing traits is relatively low, with an estimated heritability of 26~44% (Blonigen et al., 2005; Gjone & Stevenson, 1997; Hicks et al., 2004). Twin studies on specific disorders have also consistently shown these patterns. For example, the estimated heritability of depression, one of the internalizing problems, is 30~50% (Kendall et al., 2021; Sullivan et al., 2000), and that of attention deficit hyperactivity disorder (ADHD), one of the externalizing problems, is 70~88% (Larsson et al., 2014; Larsson et al., 2011; Thapar et al., 2000).

These heritable problems in childhood are linked to mental health in later life, developing not only nonpsychotic disorders, such as depression, personality disorders, and drug use but to psychotic disorders in adulthood (Copeland et al., 2009; Fisher et al., 2013; Kim-Cohen et al., 2003). Psychotic disorders, where studies have focused on schizophrenia, have high heritability similar to externalizing problems (Hilker et al., 2018; Sullivan et al., 2003). Although there is a slight variance in the heritability of each trait because of differences in phenotypic measurements and populations, it is perceptible that a wide spectrum of psychopathology has considerable genetic effects. Therefore, the genetic components related to psychopathology should be understood more to analyze and solve mental health problems.

Candidate gene studies. Traditional etiology studies focused on several candidate genes that are thought to be engaged in the pathophysiology of mental disorders. This approach was derived from the success of Mendelian disorders, which are genetic disorders resulting from alterations in a single gene. The researchers have paid attention to the variations in the serotonin transporter gene

(Lesch et al., 1996; Murphy et al., 2001) and monoamine oxidase A (MAOA)-encoding gene (Alia-Klein et al., 2008; Shih & Thompson, 1999), associated with mood disorders and externalizing behaviors, respectively.

Although a large body of candidate gene studies have shown significant associations between gene variants and phenotypes of interest, due to the small sample size of these studies relative to the small effect of polymorphism, the results have been in danger of being false-positive (Bosker et al., 2011). Therefore, the findings are hardly robust and insufficient to explain the genetic influences (Hirschhorn et al., 2002). These difficulties reveal the limited power of addressing complex (i.e., polygenic) traits like Mendelian disorders and call for extended methodology more adequate for complex diseases, which include most mental illnesses such as depression and schizophrenia.

Genome-wide association studies. Recent development in genotyping technology and the emergence of large biomedical datasets allow for genome-wide association studies (GWASs). GWAS is a hypothesis-free analysis that aims to identify genetic variants across the genome, mostly single nucleotide polymorphisms (SNPs), associated with a phenotype of interest (Hirschhorn & Daly, 2005; Kunkle et al., 2019). Recent GWASs for educational attainment (Lee et al., 2018), risk tolerance (Karlsson Linnér et al., 2019), and self-regulation and addiction (Karlsson Linnér et al., 2021) included over one million people in the analyses, gaining more statistical power than initial GWASs including tens of thousands. Overcoming the issues of low reproducibility, GWAS enabled us to better understand the genetic architecture of mental and cognitive health and has been identifying new associated loci using large samples. For example, a meta-analysis using three

independent depression GWASs (N = 807,553) has found 102 genome-wide significant variants and 269 putative genes associated with depression (Howard et al., 2019). Since GWAS results revealed that the effect sizes of each SNP are small, researchers have developed a method for risk indicator aggregating the effect of SNPs, called a polygenic scoring method.

1.2. Polygenic prediction for mental disorders

Polygenic scoring. Polygenic score (PGS) is an individual measure of genetic liability for a common disease or trait. The benefit of polygenic scoring is that PGS can represent the risk from tens of thousands of genetic variants in a single value. PGS is calculated from the findings of GWAS (i.e., effect sizes of SNPs) to estimate genetic risk for a certain phenotype (e.g., depression and intelligence) using an individual's genotype. Therefore, the score reflects the number of risk variants that an individual carries. Being represented as a simple equation, the PGS calculated with risk alleles of an individual (α_i) multiplied by the effect size of the corresponding allele (β_i) would be:

$$Polygenic\ Score = \sum_{i}^{n} \alpha_i \beta_i$$

where *n* denotes the number of risk variants in one's genotype.

Polygenic scores in childhood psychopathology. Previous studies have demonstrated that PGSs for psychiatric conditions and cognition correlate with a wide spectrum of childhood psychopathology (i.e., internalizing and externalizing problems). For example, the PGSs of major depression, insomnia, and neuroticism

were positively associated with ADHD and internalizing problems in children and adolescents (aged 6 to 17 years old), and those of subjective well-being and educational attainment had negative associations (Akingbuwa et al., 2020). Among five PGSs (i.e., major depression, bipolar disorder, schizophrenia, ADHD, and anorexia nervosa) tested with Child Behavior Checklist (CBCL) dimensions (Achenbach, 2001), a study using the Adolescent Brain and Cognitive Development (ABCD) study (aged 9 to 10 years old) found that depression PGS has significant associations with both internalizing and externalizing problems, while ADHD PGS is associated specifically with externalizing problems (Wainberg et al., 2022). The findings from another study with CBCL measures at age 10 showed that schizophrenia PGS is positively associated with internalizing scores, higher ADHD PGS with higher externalizing scores, and higher educational attainment PGS with lower externalizing scores (Jansen et al., 2018). In summary, PGSs for psychiatric conditions are likely to increase the risk for overall childhood psychopathology, while those for cognitive ability and well-being are likely to decrease the risk.

PGSs of physical traits have also shown significant associations with mental problems. Specifically, the genetic loadings for body mass index (BMI) are found to be positively associated with ADHD in children (Akingbuwa et al., 2020; Hughes et al., 2022) and disordered eating in adolescence (Abdulkadir et al., 2020).

Limitations of the polygenic score. Despite the evidence for the utility of PGS in the psychiatric field, the results should be interpreted with caution. The proportion of variance that a PGS explains is dependent on the sample size of GWAS and the lifetime prevalence of the disease (Wray et al., 2021). For major depression, affecting 15% of the population, the available PGS to date explains 4% of the

variance, while for schizophrenia, affecting 1% of the population, the PGS explains 11% (Murray et al., 2021). Thus, the top 10% of depression PGS have only 1.6-fold increase in depression risk, which indicates high heterogeneity in risk assessment. The results from several PGS studies showed that PGS hardly indicates absolute risk for diseases; for example, losing its statistical significance after adjusting for confounders (Birmaher et al., 2022). These findings demonstrate the limitation of using PGS as a single, independent predictor for mental disorders.

1.3. Impact of family history of depression on psychopathology

Impact of psychiatric history in family. Family history is a simple yet powerful way to study the intergenerational transmission of psychiatric disorders. Family history reflects the shared genetic and environmental components among biological relatives; thus, the risk or resilience factor for a disease is expected to be transmitted to the next generation. Indeed, one of the most replicated risk factors for mental illness development is having a parent with psychopathology. Longitudinal family studies have shown that the children of a parent affected with depression (Brennan et al., 2002; Klein et al., 2005), ADHD (Larsson et al., 2011), bipolar disorder (Axelson et al., 2015; Birmaher et al., 2022; Duffy et al., 2007; Mesman et al., 2013), schizophrenia (Baron et al., 1985; Mortensen et al., 2010) are likely to develop not only the disorder with the family history but also other psychiatric conditions. The phenotypic variances explained by family history are larger than those explained by PGS, which is known to be approximately 6% for depression in adulthood (Hujoel et al., 2022) and 30% for bipolar disorder in childhood (Birmaher et al., 2022).

Among various familial risks, a family history of depression has been shown to confer a 2- to 5-fold increase in the risk for offspring's psychopathology (Hammen & Brennan, 2003; Weissman, Wickramaratne, et al., 2016; Weissman et al., 2006). The children of depressed parents are at higher rates of anxiety disorders (e.g., panic disorder, agoraphobia), major depression, and substance dependence, and this risk tends to continue as they grow up (Klein et al., 2005; Weissman, 1997; Weissman et al., 2006). This broad impact of family history of depression may result from the pleiotropy of risk variants for depression, which implies that the risk alleles associated with depression also explain other psychiatric disorders (Gale et al., 2016; Gorwood, 2004). In addition, parental depression is associated with offspring's differences at the neurological level, such as thinned cortical thickness (Hao et al., 2017), decreased subcortical volumes (Chen et al., 2010; Pagliaccio et al., 2020), and increased resting-state connectivity (Posner et al., 2016), regardless of offspring's having depression themselves.

Multigenerational effects of depression history. Offspring with two previous generations (i.e., a parent and a grandparent) of depression history are at even higher risk for psychopathology (Weissman, Berry, et al., 2016). They found that children with a depressed grandparent have a 3-fold increased risk of mood disorder and substance dependence and a 2-fold increased risk of suicidal ideation and any anxiety disorder, comparing those with and without a depressed parent. A population-based study demonstrated a 2-fold increase in the mother's major depressive disorder (MDD) diagnosis with the grandmother's MDD diagnosis and a 5-fold increase in the child's MDD diagnosis with both mother and grandmother diagnosed with an MDD (Josefsson et al., 2019).

A recent study replicated these findings in US preadolescents of 9-10-year-old ages using the ABCD study (Van Dijk et al., 2021). The risks for mood disorders and suicidality in children were in the following order: both parent and grandparent affected with depression > only depressed parent > only depressed grandparent > no depression history. This study also showed that the associations between the depression history of two generations and childhood psychopathology are presented across sociodemographic characteristics of the participants, such as sex, socio-economic status (SES), and race/ethnicity. Because each family risk group can be highly heterogeneous when family history indicator is dichotomous (i.e., with and without family history) (Van Sprang et al., 2022), breaking down the familial risk levels with two previous generations reduces the heterogeneity in each risk group; thus, the risk for mental conditions can be stratified better.

Genetic mechanism of family history of depression. Understanding the pathways through which a family history of depression increases the offspring's risk for psychopathology could help identify those at higher risk, aiding in targeting intervention. Polymorphism in the serotonin transporter (5-HTT) promoter region has been suggested as a genetic mechanism for a family history of depression (Cha et al., 2018; Eley et al., 2004; Talati et al., 2015). However, taking only a few genetic variants into account is insufficient to explain the vulnerability because genetic risk loci of mental disorders exist across the genome (Howard et al., 2019; Karlsson Linnér et al., 2019; Stahl et al., 2019). Here polygenic prediction approach would be a better choice because it aggregates the genome-wide risk of the phenotype of interest. Hence, we assume that greater polygenic risk for mental disorders is a mechanism of the impact of familial history of depression on offspring

psychopathology.

1.4. Familial and polygenic risk on mental disorders

Association between psychiatric history and polygenic scores. A few family studies have examined the relationship between a family history of depression and polygenic risk. For example, individuals at high family risk for schizophrenia and bipolar have higher PGS of bipolar disorder than unaffected relatives (Boies et al., 2018). One study (N = 1,425) found an association between depression PGS and a continuous familial score depression from first-degree relatives (i.e., biological parents and siblings) (Van Sprang et al., 2022), while another study (N = 409) found no significant associations between bipolar disorder PGS and parental bipolar disorder history (Birmaher et al., 2022). In addition, studies on autism spectrum disorder (ASD) (Schendel et al., 2022) and alcohol use disorder (AUD) (Lai et al., 2022) tested associations between corresponding PGS and first-degree family history, and the findings implicate the overlap between the two risk factors. However, to date, no studies have reported whether a multigenerational family history of depression is linked to PGSs of mental and cognitive disorders in a large population sample.

Prediction of mental disorders using familial and polygenic risks. Combining PGS and family history would help improve early prediction for mental disorders. Schizophrenia diagnosis was predicted with family history and four multiple PGSs related to schizophrenia (i.e., schizophrenia, bipolar disorder, MDD, and ASD), respectively explaining 3.5% and 6.0% of the diagnosis, while explaining

9.0% together (Lu et al., 2018). A recent study with large British adult samples showed that depression is one of three well-powered diseases (i.e., type 2 diabetes, depression, and hypertension), reporting that the logistic model with PGS and family history attains more predictive accuracy than the model with family history alone (Hujoel et al., 2022). However, the majority of studies integrating PGS and family history have focused on estimating the risk for physical diseases, such as cancer (Kachuri et al., 2020), ischemic stroke (Abraham et al., 2019), and chronic obstructive pulmonary disease (Moll et al., 2020). Considering the detrimental impact of mental illness on quality of life and the early onset age of mental disorders, there is a critical need to investigate psychopathology in children. Therefore, quantifying the contributions of family history and PGS on childhood mental disorders would inform better risk assessment to define high-risk individuals accurately. Also, such an assessment would enable more adequate personalized intervention to prevent mental disorders.

1.5. Objectives and hypotheses

To the best of our knowledge, no studies have examined the relationship between family history of depression and PGS in terms of overall childhood psychopathology that includes internalizing and externalizing problems and suicidality. This study aims to investigate the relationship between multigenerational family risk of depression and PGSs of multiple psychiatric and cognitive traits and whether PGS plays a role as a mechanism of family risk. Accordingly, the following hypotheses are tested:

(1) A higher family risk of depression would correlate with greater polygenic risks. Having more previous generations affected with depression would be associated with higher PGSs of psychiatric disorders and lower PGSs of cognitive ability.

(2) Polygenic risks for psychiatric and physical conditions would confer increased risks for overall childhood psychopathology. The significant effect of PGS would exist under the presence of family risk of depression.

(3) PGSs of psychiatric disorders would mediate the relationship between family risk of depression and psychopathology. This hypothesis will test whether polygenic score plays a crucial role as a genetic mechanism of the effect of depression history on mental disorders.

Chapter 2. Materials and Methods

2.1. Participants and data source

Participants. This study used baseline data of 11,875 participants aged 9-10 years from the ABCD study release 2.01. We obtained children's genetic ancestry to split the sample from release 3.0. The data were collected at 21 research sites in the United States, where a centralized institutional review board (IRB) was approved by the University of California, San Diego IRB. A flowchart that shows the number of participants included at each step of preprocessing is demonstrated in Figure 1. We imputed the missing values of potential confounders. From 8,620 genotyped samples, participants without information of family history (n = 493) and clinical outcomes (n = 507) were excluded. The final samples included 8,111 unrelated multi-ancestry children, consisting of 6,151 European participants, 1,285 African, 315 American, 106 East Asian, and 254 unidentified.

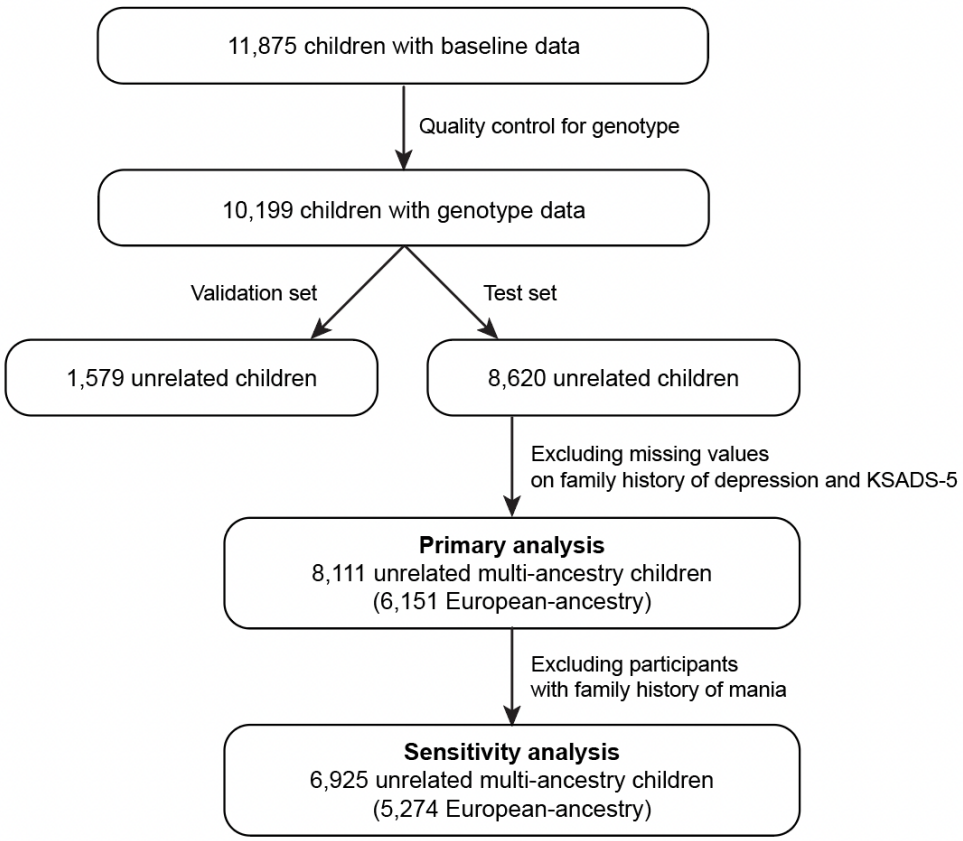

Figure 1. Study flowchart.

Genotype data. Genotypes were collected from saliva samples of ABCD study participants at the baseline visit. The samples were genotyped at the Rutgers University Cell and DNA Repository using the Affymetrix NIDA Smokescreen array (733,293 SNPs). Any SNPs with genotype call rate<95%, sample call rate<95%, and rare variants with minor allele frequency (MAF)<0.01 were removed. The variants were imputed with the Michigan Imputation Server (Das et al., 2016) using the 1000 Genome phase 3 version 5 multiethnic Grch37/hg19 reference panel with Eagle v2.4 phased output (Loh et al., 2016). With the imputed 12,046,090 variants, additional filtering of the data with any individuals with missing genotypes of more than 5%;

with extreme heterozygosity (F coefficients that deviate more than three standard deviations (SDs) from the population mean); and SNPs with imputation quality INFO score<0.4, missingness rate>5%, MAF<0.01 and Hardy-Weinberg equilibrium $p<10^{-6}$. The ABCD release 3.0 provided the genetic ancestry of each participant, determined with the fastSTRUCTURE algorithm (Raj et al., 2014). Considering that the samples had diverse genetic ancestries and included related family members, kinship coefficients (KCs) and ancestrally informative principal components (PCs) were estimated using PC-Air (Conomos et al., 2015) and PC-Relate (Conomos et al., 2016) to control familial relatedness and admixed ancestry. In addition, we removed genetically unrelated participants more distant than 4th-degree relatives (KC>0.022) and any outliers that deviate significantly from the center of PC space (>6 SD limits). Final genotype data consist of 11,301,999 variants in 10,199 unrelated multiethnic samples, including 7,893 European-ancestry participants.

2.2. Measures

Polygenic scores. PGSs of 30 behavioral, psychological, and physical traits related to mental and physical health were constructed using publicly available GWAS summary statistics: Attention-deficit/hyperactivity disorder (ADHD), cognitive performance (CP), educational attainment (EA), major depressive disorder (MDD), insomnia, snoring, intelligence quotient (IQ), post-traumatic stress disorder (PTSD), depression, body mass index (BMI), alcohol dependence, autism spectrum disorder (ASD), automobile speeding propensity (ASP), bipolar disorder, cannabis use during lifetime, ever been a smoker (ever smoker), shared effects on five major

psychiatric disorder (cross disorder), alcoholic drinks consumption per week (alcohol use), eating disorder, neuroticism, obsessive-compulsive disorder (OCD), first principal components of four risky behaviors (risky behaviors), general risk tolerance, schizophrenia, worrying, anxiety, subjective well-being (SWB), general happiness, and general happiness for own health (happiness-health), and belief that own life is meaningful (happiness-life). Detailed information on each GWAS is presented in Table 1.

The posterior effect sizes of single nucleotide polymorphisms (SNPs) were estimated using PRS-CSx (Huang et al., 2021), a Bayesian approach that enables the merging of multiple GWAS summary statistics from diverse populations. This tool uses summary statistics obtained from GWASs and reference panels of each population to estimate more accurate posterior effect sizes of SNPs. What differentiates PRS-CSx from previous tools is that it applies continuous shrinkage (CS) prior to SNP effect sizes. Considering that each SNP has its local LD pattern, PRS-CSx fits the model adaptive to each genetic marker using two parameters on prior function: global shrinkage parameter that decides the common degree of model sparseness and local parameter that follows continuous density function adaptive to each genetic variant. The final scores on the ABCD genotypes were calculated from posterior effect sizes using PLINK version 1.9. For 14 traits that have related phenotype assessments in the ABCD study, PGSs were validated in held-out validation set of 1,579 genetically unrelated participants, which were excluded from the main analyses. The global shrinkage hyperparameter (φ, phi) was optimized with linear regression on phenotype variables related to the traits of each PGS. The regression models included sex, age, genetic ancestry, and the first ten ancestrally

informative PCs as covariates. For example, the linear model of BMI PGS when φ = 1 would be:

$$BMI \sim BMI\ PGS_{\varphi=1} + sex + genetic\ ancestry + 10\ genetic\ PCs$$

and four candidate values of φ (i.e., 10^{-6}, 10^{-4}, 10^{-2}, and 1) were tested. The φ value with the best model performance, evaluated with the R^2 and beta coefficients, was selected.

The discovery GWAS samples consisted of only European participants. Still, the following five traits were additionally available with GWAS from non-European populations: BMI with East Asian samples, PTSD with African and American samples, depression with American samples, alcohol dependence with African samples, and schizophrenia with East Asian samples. Therefore, for these five traits, two different PGSs were estimated: European GWAS-based PGSs and multiethnic GWAS-based PGSs, and these two were used in European-ancestry and multi-ancestry analyses, respectively. The final PGSs were residualized by the first ten genetic PCs for population stratification.

Table 1. List of genome-wide association studies (GWASs) to estimate polygenic scores

Trait	Ancestry	GWAS sample size (study)
Depression	European	500,199 (Howard et al., 2019)
	American	3,308 (Shen et al., 2020)
Major depressive disorder (MDD)	European	480,359 (Wray et al., 2018)
Attention-deficit/hyperactivity disorder (ADHD)	European	53,293 (Demontis et al., 2019)
General happiness	European	125,527 (UK Biobank GWAS)

General happiness with own health (happiness-health)	European	125,870 (UK Biobank GWAS)
A Belief that own life is meaningful (happiness-life)	European	123,223 (UK Biobank GWAS)
Subjective well-being (SWB)	European	128,049 (Okbay et al., 2016)
Insomnia	European	386,533 (Jansen et al., 2019)
Snoring	European	359,916 (Jansen et al., 2019)
Body mass index (BMI)	European	339,224 (Locke et al., 2015)
	East Asian	173,430 (Akiyama et al., 2017)
Post-traumatic stress disorder (PTSD)	European	174,659 (Nievergelt et al., 2019)
	African	15,339 (Nievergelt et al., 2019)
	American	5,703 (Nievergelt et al., 2019)
Cognitive performance	European	1,131,881 (Lee et al., 2018)
Educational attainment	European	1,131,881(Lee et al., 2018)
Intelligence quotient (IQ)	European	269,867 (Savage et al., 2018)
Shared effects on five major psychiatric disorders (cross disorder)	European	61,220 (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013)
Neuroticism	European	390,278 (Nagel et al., 2018)
Automobile speeding propensity (ASP)	European	404,291 (Karlsson Linnér et al., 2019)
The first principal components of four risky behaviors (risky behaviors)	European	315,894 (Karlsson Linnér et al., 2019)
General risk tolerance	European	466,571 (Karlsson Linnér et al., 2019)
Obsessive-compulsive disorder (OCD)	European	6,518 (Arnold et al., 2018)
Worrying	European	348,219 (Nagel et al., 2018)
Alcohol dependence	European	46,568 (Walters et al., 2018)
	African	6,280 (Walters et al., 2018)
Autism spectrum disorder (ASD)	European	46,350 (Grove et al., 2019)
Alcoholic drinks consumption per week (alcohol use)	European	414,343 (Karlsson Linnér et al., 2019)

Anorexia nervosa	European	72,517 (Watson et al., 2019)
Cannabis use during lifetime	European	162,082 (Pasman et al., 2018)
Ever been a smoker during lifetime (ever smoker)	European	518,633 (Karlsson Linnér et al., 2019)
Schizophrenia	European	65,967 (Ruderfer et al., 2018)
	East Asian	58,140 (Lam et al., 2019)
Bipolar disorder	European	51,710 (Stahl et al., 2019)
Anxiety	European	31,060 (Otowa et al., 2016)

Family history of depression. The ABCD Family History Assessment was used to collect the caregivers' reports on the history of biological relatives, including grandparents (generation 1; G1) and parents (generation 2; G2). The question for depression history was, "Has ANY blood relative of your child ever suffered from depression, that is, have they felt so low for a period of at least two weeks that they hardly ate or slept or couldn't work or do whatever they usually do?" From the reports, a four-level depression risk variable was created, adopting from the previous study (Van Dijk et al., 2021), which describes risk levels of depression history from the two generations: neither G1 nor G2 (G1−/G2−), only G1 (G1+/G2−), only G2 (G1−/G2+), and both G1 and G2 (G1+/G2+). Children in G1−/G2− were considered having the lowest familial risk, and those in G1+/G2+ having the highest risk. A dichotomous family history indicator (i.e., G1−/G2− versus G1+ or G2+) and parental history indicator (i.e., G2− versus G2+) were also created to compare with the four-level depression risk indicator (Van Sprang et al., 2022).

Clinical outcomes. The Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS) assessed childhood psychopathology, collecting separate responses by parents and children: major depressive disorder

(MDD), any depressive disorder (including MDD, persistent depressive disorder, and depressive disorder not otherwise specified), social anxiety disorder, generalized anxiety disorder (GAD), any anxiety disorder (including GAD, social anxiety disorder, and specific anxiety disorder not meeting criteria for GAD or social anxiety disorder), bipolar disorder, sleep problems, suicidal plan, suicidal ideation, suicidal attempt, suicidal behaviors (including active or passive ideation, plans/intention/preparation, and attempts), and any psychiatric disorder/condition. In addition, 12 additional diagnoses were derived from parent reports only: self-harm, agoraphobia, simple/specific phobia, eating disorder, separation anxiety disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention-deficit hyperactivity disorder (ADHD), conduct disorder, conduct/oppositional defiant disorder, and psychotic disorder. Parent and child reports were separately analyzed; therefore, total of 36 clinical variables were included in the analyses.

To efficiently present the results, we applied a well-known distinction of psychopathology, categorizing the variables into three groups on the basis of psychological theory (Achenbach & Edelbrock, 1978; Liu, 2004; Liu et al., 2011): internalizing problem, externalizing problem, suicidality, and others. Internalizing problem included MDD, any depressive disorder, social anxiety disorder, GAD, any anxiety disorder, agoraphobia, simple/specific phobia, separation anxiety disorder, OCD, PTSD. Externalizing problem included ADHD, conduct disorder, and conduct/oppositional defiant disorder. The variables that were neither of the two categories above were separated into two categories: suicidality (i.e., suicidal plan, suicidal ideation, suicidal attempt, and suicidal behaviors) and others (i.e., eating

disorder, self-harm, bipolar disorder, sleep problems, psychotic disorder, and any psychiatric disorder/condition.

Potential confounders. The following 13 covariates were included to adjust for potential confounding effects on psychopathology: child's age, sex, race/ethnicity, sexual orientation reported by child and parent, gender identity, religious preference, country of birth, reporter's relationship to the child, total household income, and caregiver's age, education level, and marital status. Multiple imputation method using the R package *'mice'* version 3.14.0 was employed to impute missing values in covariates. The predictive mean matching method was used for continuous variables (i.e., child's age, total household income, caregiver's age, and parental education level), polytomous logistic regression for unordered categorical variables (i.e., marital status of caregiver, sexual orientation, gender identity, relationship with the child, race/ethnicity, and religious preference), and logistic regression for dichotomous variables (i.e., sex and country of birth).

2.3. Analysis

Association testing. In all statistical analyses, 8,111 multi-ancestry samples were primarily analyzed, and the same analyses were performed in 6,151 European-ancestry samples to test without ancestral bias. Child and parent reports of KSADS were separately analyzed because the discrepancies between their responses have been reported (Van Dijk et al., 2021; Weissman et al., 1987). To address multiple comparison issue, Bonferroni and false discovery rate (FDR) corrections for the

number of tests were applied to each analysis, and the associations with corrected $P<0.05$ were considered significant. PGSs and continuous variables of covariates were centered and scaled to obtain standardized estimates from regression analyses. Analyses were conducted with R version 4.2.0.

Kendall's tau (τ) was implemented to test a correlation between family risk ranks and each PGS without covariates (Khamis, 2008). Association testing was performed using multinomial logistic models for categorical four-level familial risk and logistic models for binary risk. The effect size of PGS was reported as odds ratio (OR). Firth logistic regression was used for KSADS as outcome variables with family risk and/or PGS as predictors including covariates (Firth, 1993). Firth's approach helps reduce bias in sparse data with rare events by penalizing the likelihood function. We computed 95% confidence intervals (CIs) and McFadden's pseudo R^2 with penalized log-likelihood (McFadden, 1974). When the likelihood of a null model is L_0, and that of a fitted model is L_M, McFadden's R^2 is:

$$1 - ln(L_0)/\, ln(L_M)$$

The proportion of variance of the KSADS variable explained by predictors was reported as ΔMcFadden's R^2, which is McFadden's R^2 from the full model minus McFadden's R^2 from a baseline model that includes covariates only.

Mediation analysis. KSADS diagnoses and candidate PGS mediators were selected from Bonferroni-significant results of Firth logistic regressions. In the mediation models, the treatment was the familial risk, considering the lowest risk (G1−/G2−) as a control condition and the others as a treatment condition. The same

covariates with regression analyses were adjusted in the mediation models. Additionally, models with parental history only were tested, considering G2− as a control condition and G2+ as a treatment condition. The direct effects of familial risk and the mediation effects of PGSs were estimated with one thousand bootstrap standard errors. Likewise, multiple comparison corrections were applied to adjust for the number of mediation analyses. The R package '*mediation*' version 4.5.0 was used for mediation analyses.

Sensitivity analysis. The question for depression history in the ABCD study does not discriminate depression from maniac symptoms. Therefore, to filter out the effect of mania history, we also tested the association between familial depression history and PGSs, removing children who have parents or grandparents with mania. We obtained a family history of mania from the ABCD Parent Family History Summary Scores. The final samples in sensitivity analysis included 6,925 multi-ancestry participants, including 5,274 European-ancestry participants (Figure 1).

Chapter 3. Results

3.1. Participants

The final samples were 8,111 unrelated multi-ancestry children, including 6,151 European-ancestry children. Multi-ancestry children consist of 3,832 (47.2%) females with a mean (SD) age at baseline of 9.48 (0.51) years. Of European children, 2,860 (46.5%) were female, and the mean (SD) age was 9.48 (0.51) years (Table 2). No group differences between multi-ancestry and European-ancestry samples were found in age, sex, child report sexual orientation, country of birth, caregiver's age, household income, and parental education.

Table 2. Demographics and family history of depression for multi-ancestry and European-ancestry participants

	Multi-ancestry (n=8,111)		**European-ancestry (n=6,151)**		**Test statistics**	
Child's demographics	N (%)	Mean (SD)	N (%)	Mean (SD)	t / χ^2	P
Age		9.48 (0.51)		9.48 (0.51)	0.1194	0.9049
Sex						
Male	4,279 (52.76)		3,291 (53.50)		0.7858	0.3754
Female	3,832 (47.24)		2,860 (46.50)			
Race/Ethnicity						
Hispanic	1,772 (21.85)		1,204 (19.57)		958.46	<0.0001
Non-Hispanic black	1,203 (14.83)		45 (0.73)			
Non-Hispanic white	4,996 (61.60)		4,833 (78.57)			
Other	140 (1.73)		69 (1.12)			

"Is your child gay?" (parent report)						
Yes	3 (0.04)		1 (0.02)			
Maybe/Don't know	648 (7.99)		595 (9.67)			
No	7,390 (91.11)		5,499 (89.40)		13.141	0.004
Decline to answer	70 (0.86)		56 (0.91)			
"Are you gay or bisexual?" (child report)						
Yes	31 (0.38)		26 (0.42)			
Maybe	72 (0.89)		61 (0.99)			
No	6,006 (74.05)		4,488 (72.96)		2.3383	0.5052
I do not understand this question	2,002 (24.68)		1,576 (25.62)			
Gender identity (parent report)						
Male	4,276 (52.72)		3,288 (53.45)			
Female	3,828 (47.20)		2,856 (46.43)			
Trans male	0 (0.00)		0 (0.00)		1.0623	0.9002
Trans female	2 (0.02)		2 (0.03)			
Gender queer	1 (0.01)		1 (0.02)			
Other identity	4 (0.05)		4 (0.07)			
Religious preference						
Agnostic/Atheist	379 (4.67)		366 (5.95)			
Denominational	5,889 (72.61)		4,316 (70.17)		15.863	0.0004
Non-denominational	1,843 (22.72)		1,469 (23.88)			
Country of birth						
USA and territories	7,887 (97.24)		5,994 (97.45)		0.5891	0.4428
Other	224 (2.76)		157 (2.55)			
Caregiver's demographics	N (%)	Mean (SD)	N (%)	Mean (SD)	t / χ^2	P
Relationship with child						
Biological mother	6,970 (85.93)		5,284 (85.90)		12.389	0.01468

Biological father	803 (9.90)	668 (10.86)			
Adoptive parent	158 (1.95)	85 (1.38)			
Custodial parent	78 (0.96)	45 (0.73)			
Other	102 (1.26)	69 (1.12)			
Age	39.96 (6.78)		40.72 (6.36)	0.1232	0.902
Marital status					
Married	5,537 (68.27)	4,727 (76.85)		211.72	<0.0001
Widowed	60 (0.74)	41 (0.67)			
Divorced	742 (9.15)	571 (9.28)			
Separated	305 (3.76)	189 (3.07)			
Never married	968 (11.93)	342 (5.56)			
Living with partner	499 (6.15)	281 (4.57)			
Household income	7.16 (2.44)		7.77 (2.01)	0.7359	0.4618
Parental education	16.63 (2.75)		17.18 (2.34)	1.0372	0.2996
Family history of depression					
G1−/G2−	4,658 (57.43)	3,284 (53.39)		30.87	<0.0001
G1+/G2−	1,092 (13.46)	967 (15.72)			
G1−/G2+	882 (10.87)	650 (10.57)			
G1+/G2+	1,479 (18.23)	1,250 (20.32)			

G1, generation 1; G2, generation 2

3.2. Association between familial risk and polygenic scores

The children with high familial risk showed a descriptive tendency to have high polygenic risks of psychiatric conditions (Table 3). Of the 30 tested PGSs, family history was significantly correlated with the PGSs for depression (Kendall's τ = 0.0395), neuroticism (τ = 0.0279), bipolar disorder (τ = 0.0262), IQ (τ = 0.0254), cognitive performance (τ = 0.0242), ever smoker (τ = 0.0230), and ADHD (τ =

0.0218; FDR-corrected P<0.05). The same PGSs were significantly associated with family history in European samples (Table 4).

Considering great impact of demographic and socioeconomic status on depression, it is important to adjust the covariates to examine (nearly) genuine relationship between PGS and familial risk of depression. The multinomial logistic regressions showed that higher PGSs for depression and bipolar disorder were significantly associated with depression history of two generations being affected after adjusting for covariates (OR of depression PGS, 1.1425 [95% CI, 1.0756-1.2136]; OR of bipolar disorder PGS, 1.1188 [95% CI, 1.0539-1.1877]; FDR-corrected P<0.05; Figure 2A). Depression PGS showed the most significant effect in the logistic regression models on the dichotomous family risk (OR, 1.1055 [95% CI, 1.0564-1.1571]; FDR-corrected P<0.05; Figure 2B). The proportion of variance explained by depression PGS and covariates was 7.51%, which was 0.29% larger than the proportion explained only by covariates. The other PGSs, except for depression PGS, were not significantly associated with binary family risk. Likewise, the depression PGS was the only significant PGS in the logistic models on parental depression history (OR, 1.0948 [95% CI, 1.0420-1.1503]; FDR-corrected P<0.05; Figure 2C).

In European-ancestry samples, association patterns between the family risk of depression and PGSs were similar. Results of multinomial logistic regressions showed that PGSs for depression and bipolar disorder were significantly higher in the G1+/G2+ group (OR of depression PGS, 1.1535 [95% CI, 1.0756-1.2136]; OR of bipolar disorder PGS, 1.1416 [95% CI, 1.0539-1.1877]; FDR-corrected P<0.05; Figure 3A). While only depression PGS had a significant association with binary

family risk in multi-ancestry samples, PGSs for depression (OR, 1.1028 [95% CI, 1.0470-1.1606]), IQ (OR, 1.0965 [95% CI, 1.0403-1.1560]), and cognitive performance (OR, 1.0878 [95% CI, 1.0326-1.1463]) were significantly associated in European samples (FDR-corrected $P<0.05$; Figure 3B). There were no significant associations between PGS and parental depression history in European samples (Figure 3C).

As a sensitivity analysis to reduce the heterogeneity of familial risk, the same analyses were performed with children without a family history of mania. Only depression PGS was significantly associated with four-level family risk (OR, 1.1240 [95% CI, 1.0493-1.1775]; FDR-corrected $P<0.05$) and binary family risk (OR, 1.1030 [95% CI, 1.0499-1.1591]; FDR-corrected $P<0.05$). No significant association was found in the logistic models on parental depression history. The same analyses in European samples excluding participants with mania history revealed moderately different results. Regression on four-level family risk showed that PGSs for depression (OR, 1.1406 [95% CI, 1.0570-1.2307]), bipolar disorder (OR, 1.1480 [95% CI, 1.0631-1.2396]), neuroticism (OR, 1.1325 [95% CI, 1.0492-1.2223]), and cognitive performance (OR, 1.1316 [95% CI, 1.0474-1.2227]) have significant effects (FDR-corrected $P<0.05$). However, there was no significant PGS on binary and parental depression history in the same samples.

Table 3. Kendall's rank correlation between family history of depression and polygenic scores in multi-ancestry samples

Polygenic score	τ (tau) estimate	Statistic	FDR-corrected *P*	Bonferroni-corrected *P*
Depression	0.0395	4.6451	<0.0001	<0.001
Neuroticism	0.0279	3.2808	0.0155	0.031
Bipolar disorder	0.0262	3.0824	0.0205	n.s.
IQ	0.0254	2.9883	0.0210	n.s.
CP	0.0242	2.8410	0.0269	n.s.
Ever smoker	0.0230	2.7028	0.0344	n.s.
ADHD	0.0218	2.5594	0.0449	n.s.

Multiple comparison correction for 30 tests; IQ, intelligence quotient; CP, cognitive performance; ADHD, attention-deficit/hyperactivity disorder; n.s., not significant

Table 4. Kendall's rank correlation between family history of depression and polygenic scores in European-ancestry samples

Polygenic score	τ (tau) estimate	Statistic	FDR-corrected *P*	Bonferroni-corrected *P*
Depression	0.0434	4.4641	0.0002	0.0002
Neuroticism	0.0340	3.4951	0.0071	0.0142
Bipolar disorder	0.0323	3.3248	0.0088	0.0265
IQ	0.0315	3.2386	0.0090	0.0360
CP	0.0291	2.9898	0.0168	n.s.
Ever smoker	0.0267	2.7485	0.0299	n.s.
ADHD	0.0254	2.6074	0.0391	n.s.

Multiple comparison correction for 30 tests; IQ, intelligence quotient; CP, cognitive performance; ADHD, attention-deficit/hyperactivity disorder; n.s., not significant

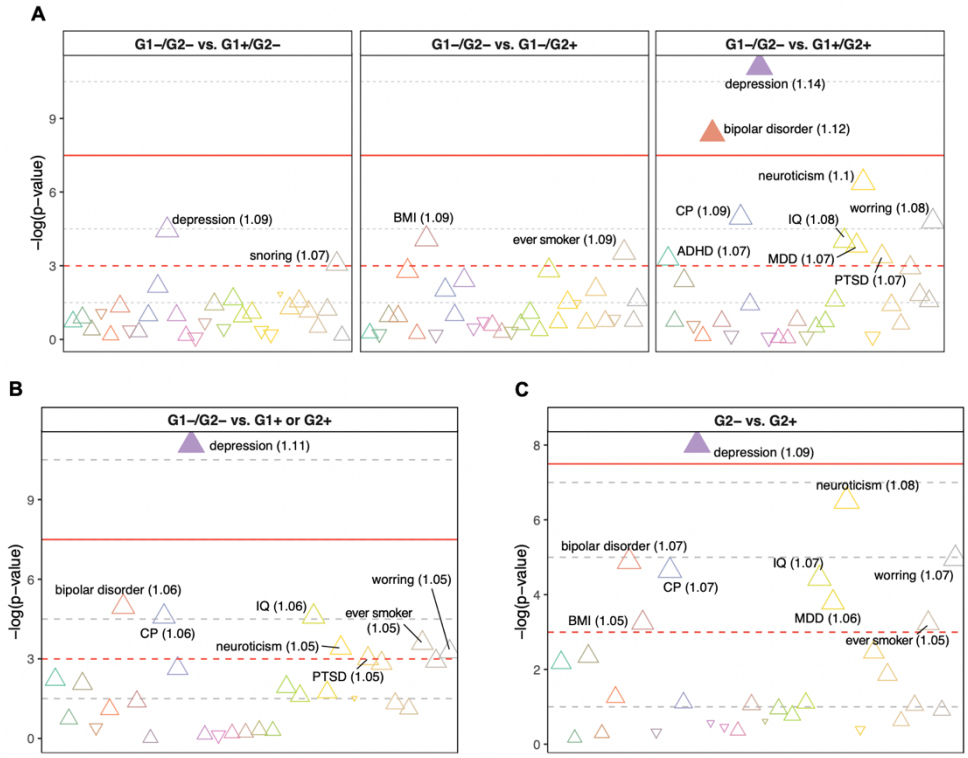

Figure 2. Logistic regressions of polygenic scores on family history of depression in multi-ancestry samples. Dashed red line indicates 0.05 of unadjusted *P*. Solid red line indicates 0.05 of Bonferroni-corrected *P*. Each triangle represents a PGS with its odds ratio (OR). Triangles filled with color denote PGSs with FDR-corrected $P<0.05$. *P* values were adjusted for 30 tests. **(A)** Regression on four risk levels of depression history from the two generations: no depression history (G1−/G2–; reference group), only grandparent (G1+/G2−), only parent (G1−/G2+), and both generations (G1+/G2+). **(B)** Regression on two-level familial risk: no depression history (G1−/G2–; reference group) and the rest of the groups (G1+ or G2+). **(C)** Regression on parental depression history: no history in the parent (G2–; reference group) and depression in the parent (G2+).

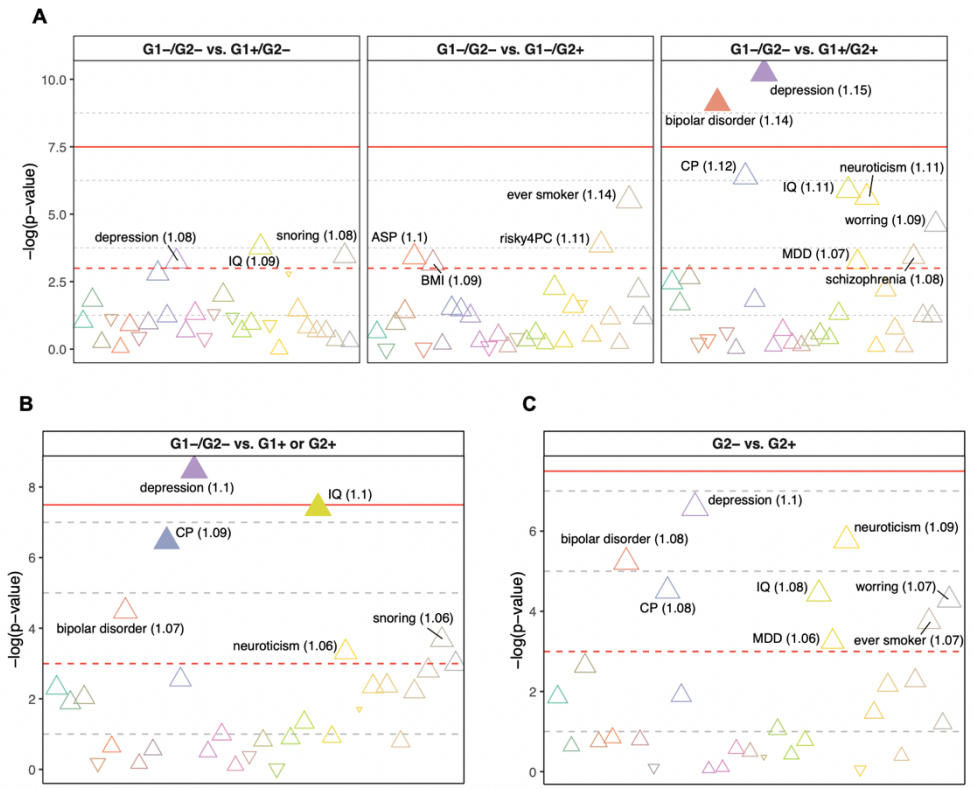

Figure 3. Logistic regressions of polygenic scores on family history of depression in European-ancestry samples. Dashed red line indicates 0.05 of unadjusted *P*. Solid red line indicates 0.05 of Bonferroni-corrected *P*. Each triangle represents a PGS with its odds ratio (OR). Triangles filled with color denote PGSs with FDR-corrected $P<0.05$. *P* values were adjusted for 30 tests. **(A)** Regression on four risk levels of depression history from the two generations: no depression history (G1−/G2–; reference group), only grandparent (G1+/G2−), only parent (G1−/G2+), and both generations (G1+/G2+). **(B)** Regression on two-level familial risk: no depression history (G1−/G2–; reference group) and the rest of the groups (G1+ or G2+). **(C)** Regression on parental depression history: no history in the parent (G2–; reference group) and depression in the parent (G2+).

3.3. Association of psychopathology with polygenic scores and family history of depression

We first tested the associations between PGSs and 36 KSADS diagnoses. Among 1,080 combinations of PGS and clinical outcome, 52 associations were significant with FDR-corrected $P<0.05$ (Firth logistic regression adjusted for covariates; Figure 4; Supplementary 1). Higher depression PGS and PGSs related to risky behaviors (i.e., ever smoker, ADHD, general risk tolerance, cannabis use) were linked to internalizing and externalizing problems and suicidal behaviors. Besides depression PGS and PGSs related to risky behaviors, externalizing problems were negatively associated with PGSs of educational attainment, IQ, and cognitive performance. Higher PGSs of worrying and neuroticism and lower automobile speed propensity PGS were associated with internalizing problems. Suicidality in childhood was positively associated with insomnia and neuroticism PGSs. Within the regression models with significant PGS, the proportions of variance explained by PGS ranged from 0.09% to 1.39%. Five PGSs significant after the Bonferroni correction (i.e., BMI, ADHD, ever smoker, educational attainment, and depression) were candidate mediators in mediation analyses.

In European samples, 49 out of 1,080 associations between PGS and clinical outcome were with significant effect of PGS (Figure 5; Supplementary 2). The overall trend in the relationship between PGS and psychopathology in European samples was similar to multi-ancestry samples. What has not been observed in multi-ancestry results were negative associations between educational attainment PGS and internalizing problems and positive associations between PTSD PGS and internalizing problems and suicidality. Four PGSs significant after the Bonferroni

correction (i.e., BMI, ADHD, ever smoker, and depression) were candidate mediators in mediation analyses. The proportions of the phenotypic variance explained by PGS in significant associations ranged from 0.18% to 1.18%.

Incorporating family history into the models, 34 associations still had significant effects of PGSs (FDR-corrected $P<0.05$; Figure 6; Supplementary 3). PGSs significantly associated with KSADS diagnoses, such as BMI, ever smoker, and depression, were also significant under the presence of family history term. The family history indicator was significant after the FDR correction in all logistic models with significant PGS, except for three models: eating disorder with BMI PGS, any anxiety disorder of the child report with general risk tolerance PGS, and any depressive disorder of the child report with ever smoker PGS. Figure 6 also shows that the proportion of variance explained by both PGS and family history increased compared to the proportion explained only by family history of depression. The increases in explained proportion ranged from 0.17% to 0.71%.

Likewise, 42 models in European samples, including both family history and PGS, had significant effects of PGSs (FDR-corrected $P<0.05$; Figure 7; Supplementary 4). Significant PGSs in these models were similar to those significant in models with PGS alone. The explained variances by family history and PGS ranged from 0.15% to 1.00%, which increased from the models with family history alone.

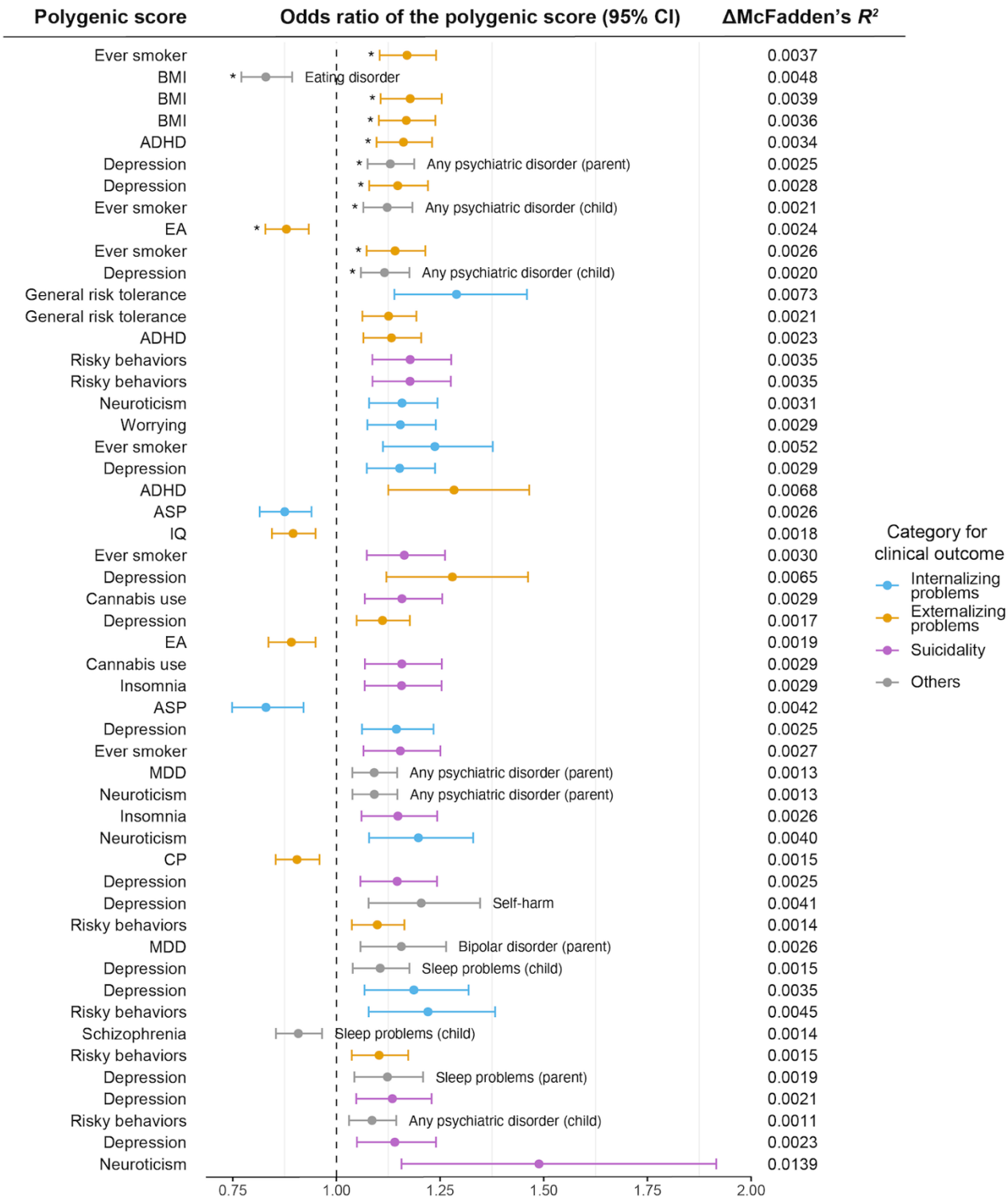
Polygenic score
Odds ratio of the polygenic score (95% CI)
ΔMcFadden's R^2
Ever smoker 0.0037
BMI 0.0048
BMI 0.0039
BMI 0.0036
ADHD 0.0034
Depression 0.0025
Depression 0.0028
Ever smoker 0.0021
EA 0.0024
Ever smoker 0.0026
Depression 0.0020
General risk tolerance 0.0073
General risk tolerance 0.0021
ADHD 0.0023
Risky behaviors 0.0035
Risky behaviors 0.0035
Neuroticism 0.0031
Worrying 0.0029
Ever smoker 0.0052
Depression 0.0029
ADHD 0.0068
ASP 0.0026
IQ 0.0018
Ever smoker 0.0030
Depression 0.0065
Cannabis use 0.0029
Depression 0.0017
EA 0.0019
Cannabis use 0.0029
Insomnia 0.0029
ASP 0.0042
Depression 0.0025
Ever smoker 0.0027
MDD 0.0013
Neuroticism 0.0013
Insomnia 0.0026
Neuroticism 0.0040
CP 0.0015
Depression 0.0025
Depression 0.0041
Risky behaviors 0.0014
MDD 0.0026
Depression 0.0015
Depression 0.0035
Risky behaviors 0.0045
Schizophrenia 0.0014
Risky behaviors 0.0015
Depression 0.0019
Depression 0.0021
Risky behaviors 0.0011
Depression 0.0023
Neuroticism 0.0139
Eating disorder
Any psychiatric disorder (parent)
Any psychiatric disorder (child)
Any psychiatric disorder (child)
Any psychiatric disorder (parent)
Any psychiatric disorder (parent)
Self-harm
Bipolar disorder (parent)
Sleep problems (child)
Sleep problems (child)
Sleep problems (parent)
Any psychiatric disorder (child)
0.75
1.00
1.25
1.50
1.75
2.00
Category for clinical outcome
Internalizing problems
Externalizing problems
Suicidality
Others

Figure 4. Firth logistic regressions on clinical outcomes with polygenic scores in multi-ancestry samples. All presented results were models with significant PGS after the FDR correction. Asterisk indicates a PGS with Bonferroni-corrected $P<0.05$. P values were adjusted for 1,080 tests. ΔMcFadden's R^2, proportion of variance explained by polygenic score; BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; MDD, major depressive disorder; CP, cognitive performance.

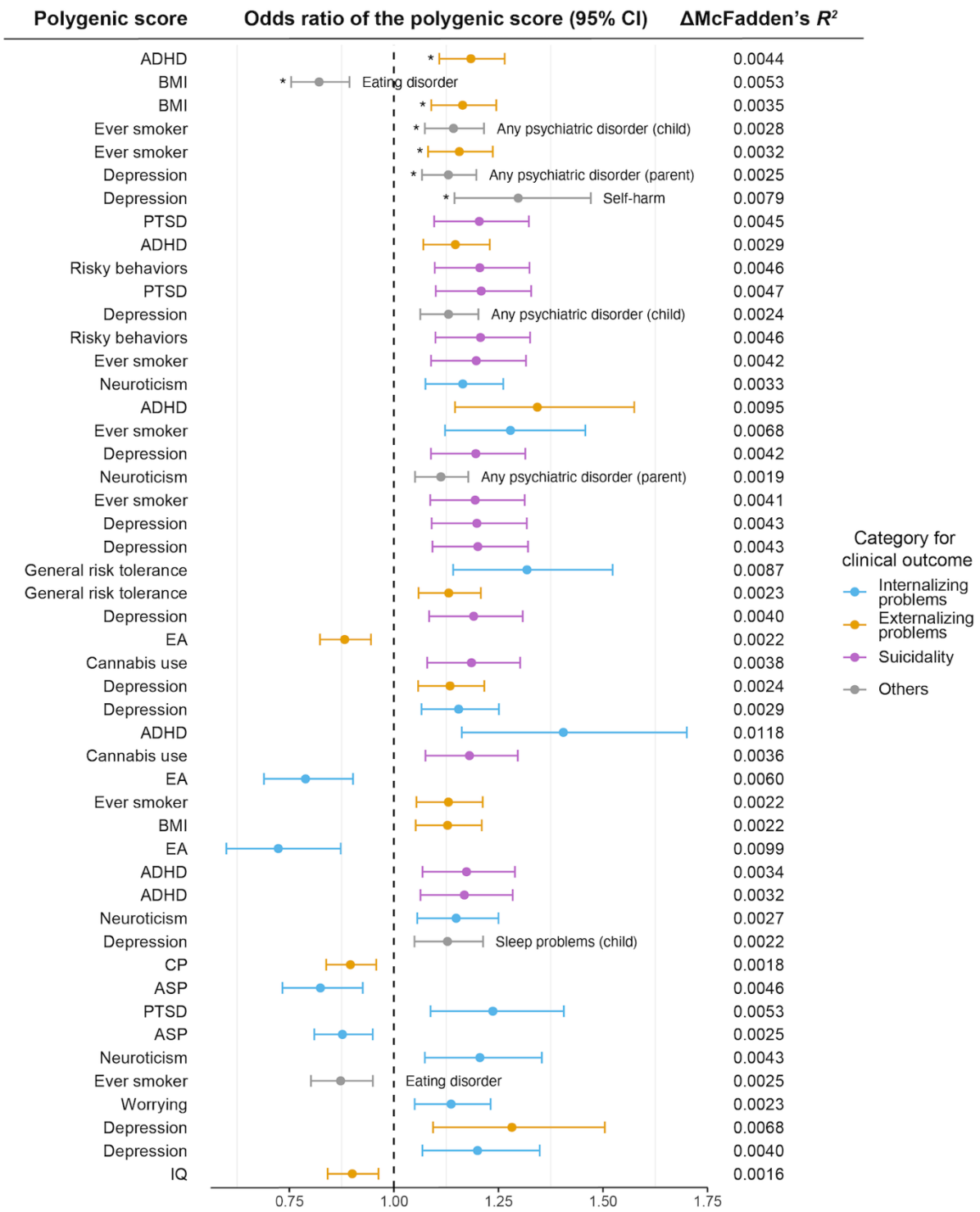
Polygenic score
Odds ratio of the polygenic score (95% CI)
ΔMcFadden's R^2
ADHD 0.0044
BMI * Eating disorder 0.0053
BMI 0.0035
Ever smoker * Any psychiatric disorder (child) 0.0028
Ever smoker 0.0032
Depression * Any psychiatric disorder (parent) 0.0025
Depression * Self-harm 0.0079
PTSD 0.0045
ADHD 0.0029
Risky behaviors 0.0046
PTSD 0.0047
Depression Any psychiatric disorder (child) 0.0024
Risky behaviors 0.0046
Ever smoker 0.0042
Neuroticism 0.0033
ADHD 0.0095
Ever smoker 0.0068
Depression 0.0042
Neuroticism Any psychiatric disorder (parent) 0.0019
Ever smoker 0.0041
Depression 0.0043
Depression 0.0043
General risk tolerance 0.0087
General risk tolerance 0.0023
Depression 0.0040
EA 0.0022
Cannabis use 0.0038
Depression 0.0024
Depression 0.0029
ADHD 0.0118
Cannabis use 0.0036
EA 0.0060
Ever smoker 0.0022
BMI 0.0022
EA 0.0099
ADHD 0.0034
ADHD 0.0032
Neuroticism 0.0027
Depression Sleep problems (child) 0.0022
CP 0.0018
ASP 0.0046
PTSD 0.0053
ASP 0.0025
Neuroticism 0.0043
Ever smoker Eating disorder 0.0025
Worrying 0.0023
Depression 0.0068
Depression 0.0040
IQ 0.0016
0.75
1.00
1.25
1.50
1.75
Category for clinical outcome
Internalizing problems
Externalizing problems
Suicidality
Others

Figure 5. Firth logistic regressions on clinical outcomes with polygenic scores in European-ancestry samples. All presented results were models with significant PGS after the FDR correction. Asterisk indicates a PGS with Bonferroni-corrected $P<0.05$. P values were adjusted for 1,080 tests. ΔMcFadden's R^2, proportion of variance explained by polygenic score; BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; PTSD, post-traumatic stress disorder; CP, cognitive performance.

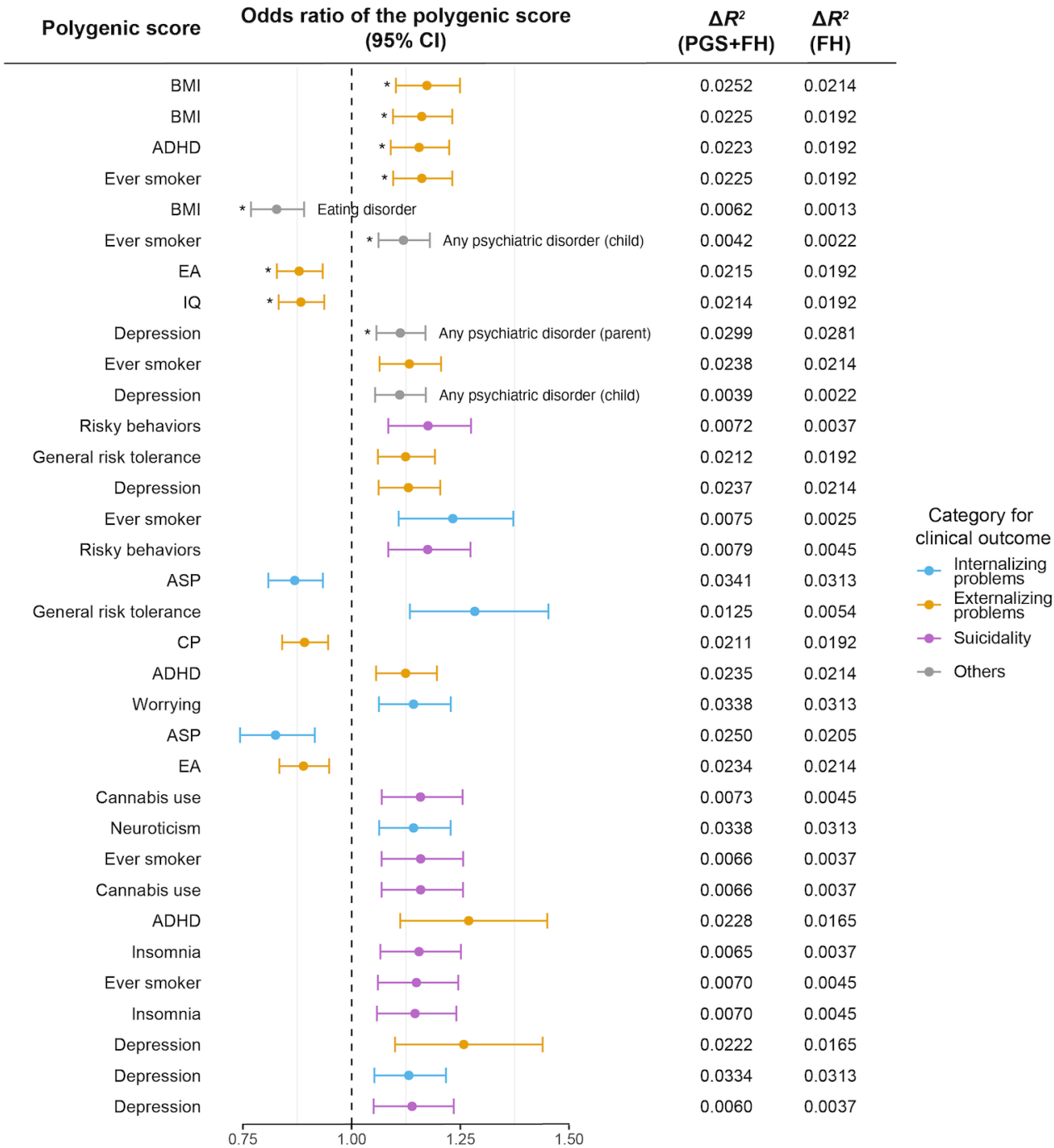

Figure 6. Firth logistic regressions on clinical outcomes with polygenic scores and family history of depression in multi-ancestry samples. All presented results were models with significant PGS after the FDR correction. Asterisk indicates a PGS with Bonferroni-corrected $P<0.05$. P values were adjusted for 1,080 tests. ΔR^2

(PGS+FH), the proportion of variance explained by polygenic score and family history of depression; ΔR^2 (FH), the proportion of variance explained by family history of depression; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; CP, cognitive performance.

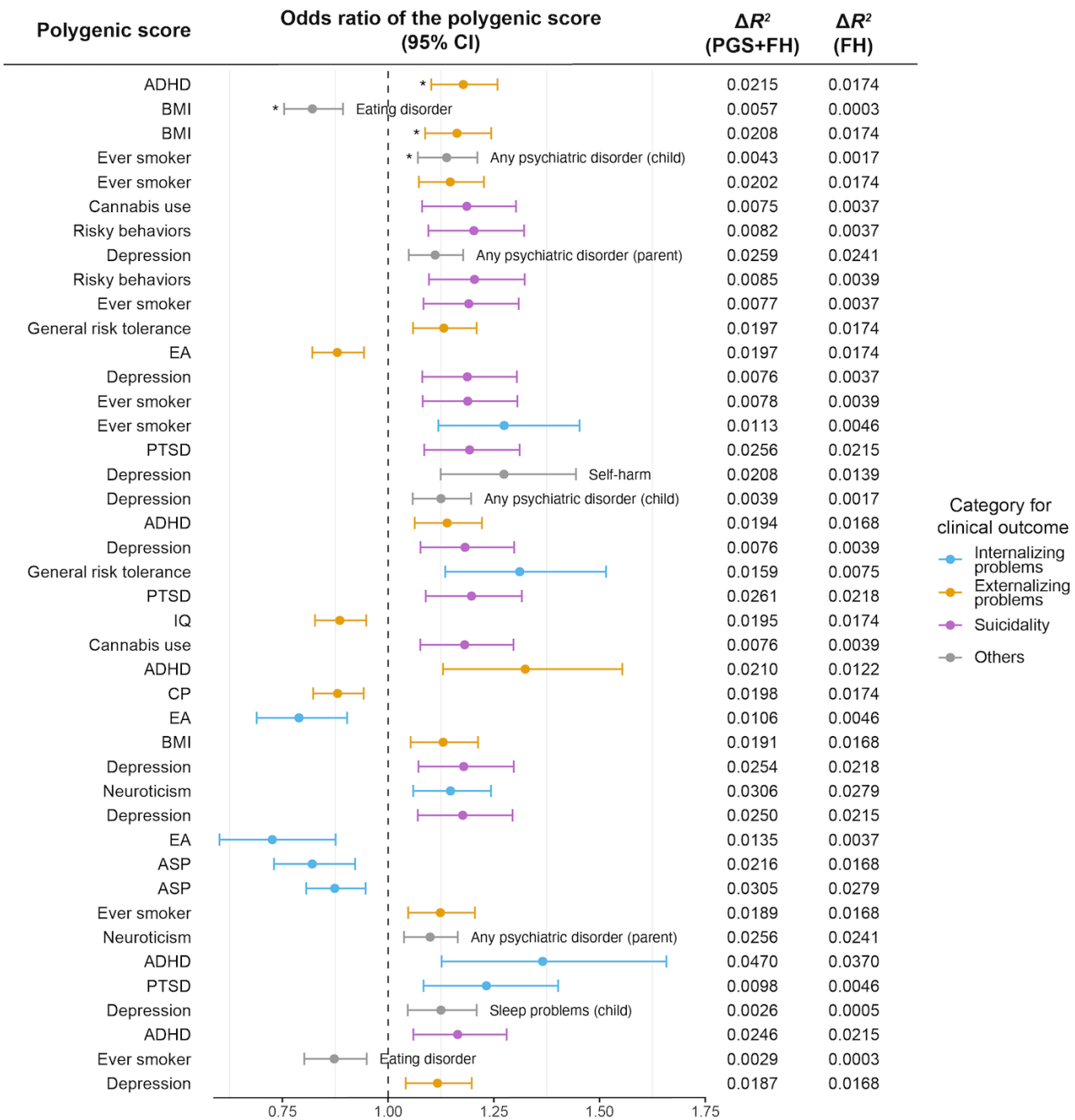

Figure 7. Firth logistic regressions on clinical outcomes with polygenic scores and family history of depression in European-ancestry samples. All presented results were models with significant PGS after the FDR correction. Asterisk indicates a PGS with Bonferroni-corrected $P<0.05$. P values were adjusted for 1,080 tests. ΔR^2 (PGS+FH), the proportion of variance explained by polygenic score and

family history of depression; ΔR^2 (FH), the proportion of variance explained by family history of depression; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; BMI, body mass index; ASP, automobile speed propensity; PTSD, post-traumatic stress disorder; IQ, intelligence quotient; CP, cognitive performance.

3.4. Mediating role of polygenic scores

The mediation models with PGS as mediator were tested (Figure 8A). The treatments in the mediation models were multigenerational depression history with two risk levels (e.g., G1−/G2− as a control group) and parental depression history. Twenty-seven clinical variables significantly associated with depression history were tested as outcomes.

Among the tested PGSs, depression PGS was the only mediator that had significant mediating effects in the relationship between familial risk and psychiatric disorders (Figure 8B). The mediation models with multigenerational depression history showed that depression PGS had significant mediation effects on ADHD (estimate, 0.0014 [95% CI, 0.0005-0.0018]), conduct/oppositional defiant disorder (estimate, 0.0016 [95% CI, 0.0006-0.0027]), conduct disorder (estimate, 0.0007 [95% CI, 0.0002-0.0013]), parent-reported any anxiety disorder (estimate, 0.0012 [95% CI, 0.0005-0.0007]), self-harm (estimate, 0.0007 [95% CI, 0.0002-0.0013]), and parent- (estimate, 0.0021 [95% CI, 0.0009-0.0037]) and child-reported (estimate, 0.0019 [95% CI, 0.0008-0.0033]) any psychiatric disorder/condition. The direct effects of multigenerational depression history were significant on all clinical variables except for suicidality of the child report. The largest direct effects were observed on parent-reported any psychiatric disorder/condition (estimate, 0.1441 [95% CI, 0.1242-0.1642]; Bonferroni-corrected $P<0.05$).

Similar results were observed with the mediation models of parental depression history. Parental depression history had significant direct effects on the KSADS outcomes except for child-reported any anxiety disorder. Depression PGS had

significant mediating effects on ADHD, conduct/oppositional defiant disorder, conduct disorder, child-reported any psychiatric disorder/condition, and child-reported suicidal ideation. Mediation models with ever smoker, ADHD, BMI, and educational attainment PGSs had similar direct effects of depression history compared to depression PGS models. However, there was no significant mediation effect within the models. Similar results were found in European samples: Four PGSs (i.e., depression, ever smoker, BMI, and ADHD PGSs) were candidate mediators, and depression PGS was the only significant mediator.

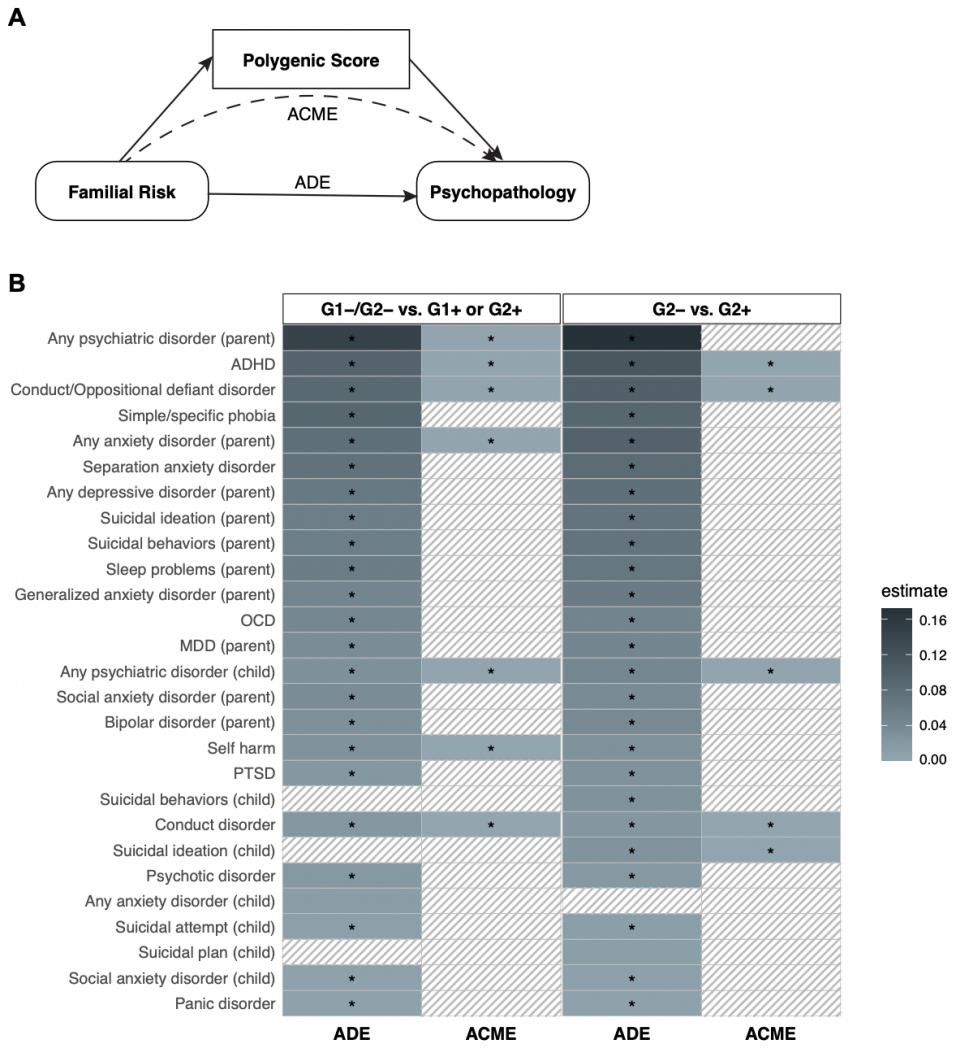

Figure 8. Mediation analysis with depression PGS as a mediator in multi-ancestry samples. ADE, average direct effect; ACME, average causal mediation effect. PGS was included as a mediator, family history of depression as treatment, and clinical report as the outcome. **(A)** Mediation model. Five PGSs with significant effects on clinical outcomes and 27 clinical outcomes of significant ADE were tested in the mediation model. Two versions of depression history were included: two-level risk of multigenerational history and parental history. **(B)** Results from mediation analyses with depression PGS as a mediator in multi-ancestry samples. Boxes with color indicate effects with FDR-corrected $P<0.05$. Asterisks indicate effects with Bonferroni-corrected $P<0.05$. P values were adjusted for 270 tests (2 versions of family history x 5 PGSs x 27 clinical outcomes).

Chapter 4. Discussion

This study demonstrates that having multiple prior generations affected with depression is associated with higher PGSs for depression and bipolar disorder. PGSs for mental and cognitive traits were also significantly associated with a wide range of children's psychopathology, even under the presence of familial risk of depression. This is the first study to show that depression PGS mediated associations between family history of depression and higher rates of childhood psychiatric disorders. Taken together, the results suggest that having multiple generations affected with depression is associated with a higher genetic load specific to depression and contributes to the increased rates of psychiatric disorders in preadolescents across diverse ancestry groups.

4.1. PGSs associated with multigenerational depression history

Depression and bipolar disorder PGSs and depression history. With the adjustment of covariates, the children with two previous generations affected had the highest depression PGS (OR = 1.14), which may indicate that their genetic burden is exceptionally high compared to those with one or no previous generation affected. We found a similar association for bipolar disorder PGS. These results imply that the more genetic risk variants for depression and bipolar disorder an individual have, the more likely these variants are to be inherited by the next generation, and thereby, the risk of developing mental conditions would increase in offspring. Indeed, our findings are in line with the previous study that showed

increased risk of overall psychopathology in children with more previous generations affected with depression (Van Dijk et al., 2021), and also, partially consistent with the study showing that familial risk is related to genetic vulnerability for depression and anxiety (Smoller, 2016).

We also conducted sensitivity analysis limiting the sample to children of parents and grandparents with a history of depression without mania in order to increase homogeneity of depression history data. In our sensitivity analysis, bipolar disorder PGS lost its significance on family history of depression. This result suggests that the significant associations with bipolar disorder PGS might be due to including children with a family history of bipolar disorder, as family history of bipolar disorder is associated with higher bipolar disorder PGS in offspring (Andlauer et al., 2021; Birmaher et al., 2022; Fullerton et al., 2015).

Cognitive ability PGSs and depression history. Not in the multi-ancestry group but in the European-only sample, positive relationships between multigenerational depression history and PGSs for cognitive ability (i.e., cognitive performance and IQ) were observed, even after adjusting for the confounders. No significant associations were found with parental depression history. Although these PGSs had marginal effects (OR = ~1.10), these findings seem contradictory with previous reports on the phenotypic association between depression and cognitive impairment (Meijsen et al., 2018; Rock et al., 2014; Semkovska et al., 2019). These disagreements may come from the genetic liability for cognitive ability that reflects a variety of heritable traits, such as personality and behavioral problems (Krapohl et al., 2014). In other words, the genetic variants associated with cognitive ability contribute to mental and behavioral traits, not just cognitive ability itself, sharing

biological or other indirect pathways (e.g., gene-by-environment interaction) across the phenotypes.

Despite the phenotypic correlation between depression and cognitive impairment, the genetic correlation between these phenotypes has hardly been observed (Savage et al., 2018). One study also reported a non-significant genetic correlation between depression and general intelligence but observed over 90 genetic variants associated with these two traits overlapping (Bahrami et al., 2021). The association of cognitive ability PGS with family history of depression has not been reported to our knowledge. Therefore, the role of genetic variation related to cognitive ability in the intergenerational transmission of depression should be further investigated in European and non-European cohorts.

4.2. Polygenic risks for childhood psychopathology

We extend recent findings from the ABCD study that examined the associations of psychiatric family history and PGS with children's psychopathology, respectively (Wainberg et al., 2022). PGSs were significant under the presence of family history term and covariates in the logistic models, explaining about 0.7% of the phenotypic variances, while family history alone explained 2%. Considering the correlation between PGSs and family history of depression, these findings show that PGSs reflect the risk for mental conditions in children beyond the familial risk for depression.

Childhood externalizing problem and its genetic liability. We found that a notable number of significant associations were with externalizing disorders (i.e.,

conduct/oppositional defiant disorder and ADHD). Two possible explanations for these findings can be discussed. First, in line with the age of the participants, the higher prevalence of externalizing problems than other mental conditions in children (Chan et al., 2008; Danielson et al., 2021) may have gained more statistical power in our models. There have been consistent reports that childhood conduct and oppositional problems tend to precede mental disorders in later life (Burke et al., 2005; Hofstra et al., 2002; Zoccolillo, 1992). In tandem with these findings, externalizing disorders (e.g., conduct disorder and oppositional defiant disorder) in children and adolescents have been considered as a major intervention target in terms of the development of psychiatric disorders (Kim-Cohen et al., 2003).

The second explanation is that externalizing disorders are well known to be highly heritable (Hicks et al., 2004), so more associations with PGSs were found than other traits. This explanation is also linked to our findings that the majority of significant associations were with polygenic risks for risk-taking behaviors (i.e., ever smoker, cannabis use, general risk tolerance, and risky behaviors). These results may imply that higher inherited risks for risk-taking traits increase the risk for psychopathology in preadolescence. Several family studies support the transmission of these risks revealing that the parental history of substance use and antisocial problems confers the risk for mental problems in offspring (Coley et al., 2011; Eiden et al., 2007; Giancola, 2000; Rhule et al., 2004). Therefore, although we suggested associations of childhood psychopathology with PGS of individual externalizing traits, common genetic components underlying a wide array of externalizing traits (Karlsson Linnér et al., 2021) may be a putative mechanism for the intergenerational transmission of externalizing disorders.

Genetic influences on suicidality. Although suicidal behaviors were much rarer than externalizing problems in our clinical data, significant associations were found between PGSs and suicidal behaviors, such as suicidal ideation and plan. The association testing in this study showed that PGSs of depression, insomnia, neuroticism, and risk-taking behaviors (i.e., ever smoker, cannabis use, and risky behaviors) have influences on suicidal behaviors in children.

Traditionally, suicide risk has been examined and understood in relation to psychiatric disorders (Baxter & Appleby, 1999; Lawrence et al., 1999; Qin et al., 2003). As genetic studies found that suicidality itself is a heritable trait with heritability estimates ranging between 30%-55% (Voracek & Loibl, 2007), the growing body of research has been investigating the genetic architecture of suicidality outcomes (Sokolowski et al., 2014). In addition, several GWASs of suicidal behaviors and death in adult samples found genetic correlations between suicidality and psychiatric disorders, especially depression and behavioral disinhibition (Docherty et al., 2020; Mullins et al., 2019; Strawbridge et al., 2019). Our findings confirm these correlations with children's suicidality measures and extend previous findings by suggesting genetic associations with insomnia, neuroticism, and substance use. Such findings in children may have an important meaning because suicidal behaviors in youth are becoming more common in recent years (Barzilay & Apter, 2022).

Depression PGS and psychopathology. Depression PGS predicted internalizing and externalizing disorders and suicidality at ages 9 and 10, as well as self-harm and any psychiatric disorder after multiple comparison correction. Previous studies have shown that depression in adults is genetically correlated with

bipolar disorder, schizophrenia, ADHD, and earlier smoking initiation (Howard et al., 2019; Howard et al., 2018; Wray et al., 2018). Our depression PGS was calculated from the largest genome-wide meta-analysis for depression integrating three GWASs of differently defined depression, from clinically diagnosed depression to self-reported depressive symptoms (Howard et al., 2019). Recent studies with depression PGS estimated from this meta-analysis study demonstrated associations of depression PGS with perinatal (Kiewa et al., 2022; Rantalainen et al., 2020) and youth (Perret et al., 2022; Rabinowitz et al., 2020) depressive symptoms, externalizing and internalizing problems in children (Wainberg et al., 2022), and various medical conditions in adults (Fang et al., 2022). Our results extend these findings to clinical diagnosis of psychiatric conditions and suicidal behaviors in children. Overall, the genetic risk variants for depression seem to contribute to multidimensional health outcomes throughout the lifetime.

The possible pathway from the risk variants of depression to mental problems in childhood is through neurobiological endophenotypes. When the genetic variants that contribute to the heritability of depression were partitioned by cell type, the variants were enriched in brain regions such as the anterior cingulate cortex (ACC) and frontal cortex (Howard et al., 2019). Transcriptomic and proteomic studies have also highlighted that genes expressed in the prefrontal cortex and ACC are related to depression (Wang et al., 2012; Wingo et al., 2021). Accordingly, the risk variants for depression may involve the regulation of genes particularly expressed in the prefrontal cortex and ACC, and the differentially expressed genes may influence the individual variation in mental status.

Cognitive ability PGSs and externalizing problems. In our result, PGSs for

IQ, cognitive performance, and educational attainment were negatively associated with externalizing problems in children, regardless of family history term in the model. Our observation is in line with a previous finding that higher educational attainment PGS is correlated with lower externalizing scores at the age of 3, 6, and 10 (Jansen et al., 2018). Indeed, prospective studies have reported that externalizing traits like inattentiveness and hyperactivity may lead to lower academic performance in children (Polderman et al., 2010). The association between externalizing problems and PGSs for cognitive ability and their phenotypic association imply that these phenotypes may bidirectionally influence each other at both genotype level and phenotype level.

BMI PGS and externalizing problems. Our results consistently showed positive correlations between BMI PGS and externalizing problems in children. These associations are partially consistent with prior studies that found positive associations of ADHD and conduct disorder with obesity (Cortese et al., 2016; Khalife et al., 2014). These phenotypic associations have been thought to be come from the impulsivity and inattention of externalizing problems that may increase dysregulated eating habits (Cortese & Vincenzi, 2011).

Our findings imply that the genetic liability of obesity may have an influence on externalizing problems in children. A Mendelian randomization (MR) study supports our findings showing a causal genetic effect of BMI on ADHD but not vice versa (Martins-Silva et al., 2019). However, more recent genetic studies have reported a positive association between BMI PGS and ADHD PGS, implying the bidirectional effects on one trait to another (Barker et al., 2021; Karhunen et al., 2021; Liu et al., 2021). The putative mechanism underlying the link between ADHD and

obesity may be shared neural substrates between the two traits (Barker et al., 2021) and abnormal brain functioning triggered by obesity or ADHD (Cortese, 2019; Furman et al., 2019). The bidirectional pathway between externalizing problems and obesity needs to be further investigated since these two traits can be variously assessed; for example, obesity can be measured as BMI, waist circumference, and waist-to-height ratio (Savva et al., 2000).

4.3. Mediating effect of depression PGS in the relationship between depression history and offspring psychopathology

Only PGS for depression, but not other PGSs, showed a significant mediation effect on the impact of family risk for depression on offspring's psychiatric diagnoses. Our findings implicate the polygenic mechanism for family history of depression, which was specific to polygenic risk for depression.

As seen in our association results, the large direct effect of depression history compared to the indirect effect of PGS was discovered. Family history can affect mental health through genetic and environmental components. Interpersonal stress (Hammen et al., 2004), early life stress (Luby et al., 2006), and dysfunctional family environment (Gutierrez-Galve et al., 2015; Hammen et al., 2004) have been suggested as environmental mediators of the impact of parental depression. Also, other interactions between genes and environment (Eley et al., 2004; Feurer et al., 2022) and genes themselves (Garvert et al., 2022; Ressler et al., 2009) could partially explain the mechanism of intergenerational transmission of depression. Further efforts are needed to dissect gene-environment interactions within childhood psychopathology, especially in children with a high polygenic risk for depression.

Our findings show that both parental and multigenerational family history of depression was mediated by depression PGS. Depression PGS mediated early childhood outcomes like conduct/oppositional defiant disorder, anxiety disorder, and suicidal thoughts and behaviors. Even though bipolar disorder has a higher heritability than depression, a family study showed that the effect of parental bipolar disorder on the offspring's bipolar disorder is not mediated by the offspring's bipolar disorder PGS (Birmaher et al., 2022). Therefore, the significant mediating effect of depression PGS shown in our results highlights the specific role of genetic liability of depression in childhood psychopathology. Still, the indirect effect of depression PGS in the mediation model was marginal relative to the direct effect of depression history. This may be because the participants are younger than the median onset age of psychiatric disorder, so psychiatric symptoms have yet to manifest in children. As the children pass through the median age of onset, associations between depression PGS and psychiatric phenotypes will become stronger as these associations have been shown in other studies (Mistry et al., 2018; Musliner et al., 2019), so will the indirect effect of depression PGS.

4.4. Implications and future directions

Recently, a growing number of studies incorporate familial and polygenic risk to predict and stratify better the risk for target diseases. While the family history of depression as a strong risk factor for mental illness is well replicated, its association with polygenic risks has been understudied. Also, studies have focused on the depression history of first-degree family members, such as parents and siblings. Adding to the existing literature, this study examined the risk for a broad array of

childhood psychopathology using multigenerational family history of depression and multiple polygenic scores in a large, diverse multi-ancestry sample. The present study has important implications in the trend of discussing how PGS can be implemented in clinical practice (Murray et al., 2021; Wray et al., 2021).

This is the first study to demonstrate that depression PGS mediated the impact of multigenerational family history of depression toward increased risk of overall psychopathology in multi-ancestry children. The mediating effect of depression PGS implicates the polygenic mechanism of the family history of depression. In addition, unlike previous studies that failed to find significant associations between first-degree depression history and genetic risk for psychiatric disorders, this study revealed that parental and multigenerational history of depression represents the genetic vulnerability to depression and bipolar disorder. Also, these associations and mediation effects of depression PGS remained significant under adjustment for potential confounders and multiple comparison correction. Because the risk indicated by PGS should be interpreted as a relative scale, future studies would benefit from incorporating PGS with other neurobiological factors that are thought to lie in between polygenic risks and manifestations of psychopathology. For example, incorporating neuroimaging substrates with polygenic risk would bring about more powerful predictive utility, bridging the gap between genetic risk and the expression of mental conditions.

Some limitations should be noted for this study. First, most PGSs were derived from GWAS that was conducted in European-ancestry samples. Since there has been an issue of transferability of PGS across the ancestries (Martin et al., 2019), European GWAS-based PGSs might not be the optimal summary statistics to work

with for multi-ancestry populations. To complement this limitation, we conducted same analyses in both multi-ancestry and European-ancestry samples and presented similar results. The second limitation is that we relied on the clinical diagnosis and family history reported by the caregivers or children themselves. The clinical information collected from the participants would be less accurate than the diagnoses based on clinician's interview. For family history of depression, it was unable to identify whether or when the affected grandparents or parents were remitted from a depressive episode, which may influence the offspring's behavioral problems (Shaw et al., 2009). The effect of depression PGS on offspring's psychopathology should be further studied considering grandparent's or parent's remission from the depression. In addition, the sample was preadolescents at ages 9 and 10, so the mental conditions would not have been fully expressed. Only 2.5% of mood disorders and 3% of psychotic traits occur before the age 14, and when it comes to age 18, the proportions rise to 11.5% and 12.3%, respectively. We expect in follow-up waves of the ABCD study, clinical diagnoses to become more prevalent as the children go through the median age of onset of psychiatric disorders.

Supplementary Material

Supplementary 1. Firth logistic regressions on clinical outcomes with polygenic scores in multi-ancestry samples

Polygenic score	Clinical outcome	OR [95% CI]	FDR-corrected *P*	Bonferroni-corrected *P*	ΔMcFadden's R^2
Ever smoker	ADHD	1.1702 [1.1042, 1.2404]	0.0001	0.0001	0.0037
BMI	ADHD	1.1684 [1.1023, 1.2387]	0.0001	0.0002	0.0036
BMI	Conduct/Oppositional defiant disorder	1.1779 [1.1067, 1.2539]	0.0001	0.0003	0.0039
ADHD	ADHD	1.1616 [1.0967, 1.2305]	0.0001	0.0003	0.0034
BMI	Eating disorder	0.8297 [0.7707, 0.8931]	0.0001	0.0007	0.0048
Depression	Any psychiatric disorder (parent)	1.1299 [1.0752, 1.1875]	0.0003	0.0015	0.0025
Depression	Conduct/Oppositional defiant disorder	1.1477 [1.0790, 1.2208]	0.0018	0.0128	0.0028
Ever smoker	Any psychiatric disorder (child)	1.1224 [1.0649, 1.1832]	0.0022	0.0179	0.0021
EA	ADHD	0.8794 [0.8286, 0.9331]	0.0025	0.0226	0.0024
Ever smoker	Conduct/Oppositional defiant disorder	1.1414 [1.0728, 1.2145]	0.0031	0.0306	0.0026
Depression	Any psychiatric disorder (child)	1.1160 [1.0591, 1.1760]	0.0038	0.0414	0.0020
Neuroticism	Any anxiety disorder (parent)	1.1582 [1.0787, 1.2437]	0.0046	n.s.	0.0031
General risk tolerance	Any anxiety disorder (child)	1.2896 [1.1398, 1.4595]	0.0044	n.s.	0.0073
General risk tolerance	ADHD	1.1257 [1.0626, 1.1927]	0.0044	n.s.	0.0021
Risky behaviors	Suicidal behaviors (child)	1.1775 [1.0868, 1.2759]	0.0046	n.s.	0.0035

Risky behaviors	Suicidal ideation (child)	1.1778 [1.0866, 1.2769]	0.0046	n.s.	0.0035
ADHD	Conduct/Oppositional defiant disorder	1.1327 [1.0651, 1.2047]	0.0045	n.s.	0.0023
Worrying	Any anxiety disorder (parent)	1.1542 [1.0747, 1.2398]	0.0048	n.s.	0.0029
Ever smoker	Any depressive disorder (child)	1.2373 [1.1121, 1.3769]	0.0051	n.s.	0.0052
Depression	Any anxiety disorder (parent)	1.1525 [1.0731, 1.2380]	0.0053	n.s.	0.0029
ADHD	Conduct disorder	1.2837 [1.1251, 1.4652]	0.0104	n.s.	0.0068
IQ	ADHD	0.8955 [0.8444, 0.9496]	0.0109	n.s.	0.0018
Ever smoker	Suicidal ideation (child)	1.1636 [1.0732, 1.2617]	0.0111	n.s.	0.0030
ASP	Any anxiety disorder (parent)	0.8752 [0.8150, 0.9398]	0.0108	n.s.	0.0026
Depression	Conduct disorder	1.2797 [1.1202, 1.4621]	0.0121	n.s.	0.0065
Cannabis use	Suicidal behaviors (child)	1.1577 [1.0687, 1.2542]	0.0137	n.s.	0.0029
Insomnia	Suicidal ideation (child)	1.1571 [1.0682, 1.2536]	0.0138	n.s.	0.0029
Depression	ADHD	1.1110 [1.0487, 1.1770]	0.0134	n.s.	0.0017
Cannabis use	Suicidal ideation (child)	1.1580 [1.0684, 1.2552]	0.0131	n.s.	0.0029
EA	Conduct/Oppositional defiant disorder	0.8912 [0.8361, 0.9497]	0.0137	n.s.	0.0019
ASP	Social anxiety disorder (parent)	0.8300 [0.7483, 0.9205]	0.0144	n.s.	0.0042
Depression	Separation Anxiety disorder	1.1446 [1.0616, 1.2341]	0.0146	n.s.	0.0025
Ever smoker	Suicidal behaviors (child)	1.1542 [1.0652, 1.2508]	0.0150	n.s.	0.0027
Neuroticism	Any psychiatric disorder (parent)	1.0913 [1.0385, 1.1469]	0.0175	n.s.	0.0013

MDD	Any psychiatric disorder (parent)	1.0910 [1.0383, 1.1464]	0.0174	n.s.	0.0013
Insomnia	Suicidal behaviors (child)	1.1481 [1.0605, 1.2431]	0.0194	n.s.	0.0026
Neuroticism	Generalized anxiety disorder (parent)	1.1976 [1.0787, 1.3299]	0.0210	n.s.	0.0040
CP	ADHD	0.9048 [0.8534, 0.9591]	0.0219	n.s.	0.0015
Depression	Suicidal ideation (child)	1.1464 [1.0578, 1.2425]	0.0242	n.s.	0.0025
Depression	Self-harm	1.2045 [1.0774, 1.3466]	0.0290	n.s.	0.0041
MDD	Bipolar disorder (parent)	1.1565 [1.0580, 1.2645]	0.0360	n.s.	0.0026
Risky behaviors	ADHD	1.0986 [1.0371, 1.1639]	0.0356	n.s.	0.0014
Depression	Sleep problems (child)	1.1055 [1.0393, 1.1760]	0.0364	n.s.	0.0015
Depression	Generalized anxiety disorder (parent)	1.1866 [1.0677, 1.3187]	0.0366	n.s.	0.0035
Risky behaviors	Any anxiety disorder (child)	1.2207 [1.0778, 1.3828]	0.0404	n.s.	0.0045
Risky behaviors	Conduct/Oppositional defiant disorder	1.1029 [1.0370, 1.1731]	0.0428	n.s.	0.0015
Depression	Suicidal behaviors (child)	1.1349 [1.0478, 1.2293]	0.0435	n.s.	0.0021
Depression	Suicidal ideation (parent)	1.1408 [1.0495, 1.2401]	0.0440	n.s.	0.0023
Neuroticism	Suicidal plan (parent)	1.4885 [1.1567, 1.9161]	0.0441	n.s.	0.0139
Risky behaviors	Any psychiatric disorder (child)	1.0858 [1.0305, 1.1442]	0.0438	n.s.	0.0011
Depression	Sleep problems (parent)	1.1230 [1.0432, 1.2090]	0.0431	n.s.	0.0019
Schizophrenia	Sleep problems (child)	0.9080 [0.8540, 0.9654]	0.0427	n.s.	0.0014

Multiple comparison correction for 1,080 tests; Clinical outcomes without reporter are of parent report; OR, odds ratio; ΔMcFadden's R^2, proportion of variance explained by polygenic score; BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; MDD, major depressive disorder; CP, cognitive performance; n.s., not significant

Supplementary 2. Firth logistic regressions on clinical outcomes with polygenic scores in European-ancestry samples

Polygenic score	Clinical outcome (reporter)	OR [95% CI]	FDR-corrected *P*	Bonferroni-corrected *P*	ΔMcFadden's R^2
ADHD	ADHD	1.1840 [1.1085, 1.2648]	0.0005	0.0005	0.0044
BMI	Eating disorder	0.8210 [0.7542, 0.8936]	0.0026	0.0052	0.0053
BMI	ADHD	1.1642 [1.0893, 1.2446]	0.0027	0.0080	0.0035
Ever smoker	ADHD	1.1563 [1.0818, 1.2362]	0.0051	0.0204	0.0032
Ever smoker	Any psychiatric disorder (child)	1.1424 [1.0739, 1.2154]	0.0051	0.0254	0.0028
Depression	Any psychiatric disorder (parent)	1.1301 [1.0672, 1.1970]	0.0051	0.0306	0.0025
Depression	Self-harm	1.2972 [1.1447, 1.4707]	0.0068	0.0475	0.0079
Risky behaviors	Suicidal behaviors (child)	1.2070 [1.0993, 1.3256]	0.0106	n.s.	0.0046
PTSD	Suicidal ideation (parent)	1.2087 [1.1000, 1.3283]	0.0095	n.s.	0.0047
Depression	Any psychiatric disorder (child)	1.1304 [1.0631, 1.2021]	0.0097	n.s.	0.0024
Risky behaviors	Suicidal ideation (child)	1.2053 [1.0975, 1.3242]	0.0092	n.s.	0.0046
ADHD	Conduct/Oppositional defiant disorder	1.1469 [1.0703, 1.2293]	0.0091	n.s.	0.0029
PTSD	Suicidal behaviors (parent)	1.2040 [1.0961, 1.3228]	0.0088	n.s.	0.0045
Depression	Suicidal ideation (parent)	1.2006 [1.0920, 1.3205]	0.0119	n.s.	0.0043
General risk tolerance	Any anxiety disorder (child)	1.3182 [1.1415, 1.5230]	0.0120	n.s.	0.0087
Depression	Suicidal behaviors (parent)	1.1983 [1.0902, 1.3176]	0.0118	n.s.	0.0043

Neuroticism	Any anxiety disorder (parent)	1.1646 [1.0754, 1.2615]	0.0112	n.s.	0.0033
Depression	Suicidal ideation (child)	1.1958 [1.0884, 1.3141]	0.0115	n.s.	0.0042
Ever smoker	Suicidal ideation (child)	1.1968 [1.0888, 1.3158]	0.0110	n.s.	0.0042
Ever smoker	Suicidal behaviors (child)	1.1943 [1.0869, 1.3126]	0.0118	n.s.	0.0041
Ever smoker	Any depressive disorder (child)	1.2786 [1.1220, 1.4577]	0.0115	n.s.	0.0068
General risk tolerance	ADHD	1.1309 [1.0588, 1.2080]	0.0121	n.s.	0.0023
Depression	Suicidal behaviors (child)	1.1907 [1.0842, 1.3080]	0.0121	n.s.	0.0040
Neuroticism	Any psychiatric disorder (parent)	1.1123 [1.0506, 1.1779]	0.0116	n.s.	0.0019
ADHD	Conduct disorder	1.3430 [1.1462, 1.5747]	0.0113	n.s.	0.0095
EA	ADHD	0.8821 [0.8233, 0.9449]	0.0144	n.s.	0.0022
Cannabis use	Suicidal ideation (child)	1.1854 [1.0796, 1.3019]	0.0144	n.s.	0.0038
Depression	Conduct/Oppositional defiant disorder	1.1342 [1.0580, 1.2160]	0.0146	n.s.	0.0024
Depression	Any anxiety disorder (parent)	1.1547 [1.0659, 1.2512]	0.0157	n.s.	0.0029
ADHD	PTSD	1.4051 [1.1623, 1.7004]	0.0157	n.s.	0.0118
Cannabis use	Suicidal behaviors (child)	1.1805 [1.0754, 1.2961]	0.0168	n.s.	0.0036
EA	Any depressive disorder (child)	0.7886 [0.6890, 0.9022]	0.0181	n.s.	0.0060
Ever smoker	Conduct/Oppositional defiant disorder	1.1302 [1.0538, 1.2123]	0.0196	n.s.	0.0022
EA	MDD (child)	0.7234 [0.5992, 0.8726]	0.0223	n.s.	0.0099
BMI	Conduct/Oppositional defiant disorder	1.1282 [1.0521, 1.2100]	0.0218	n.s.	0.0022

ADHD	Suicidal behaviors (parent)	1.1735 [1.0683, 1.2893]	0.0251	n.s.	0.0034
ASP	Social anxiety disorder (parent)	0.8241 [0.7334, 0.9256]	0.0319	n.s.	0.0046
Depression	Sleep problems (child)	1.1280 [1.0491, 1.2131]	0.0318	n.s.	0.0022
ASP	Any anxiety disorder (parent)	0.8767 [0.8095, 0.9493]	0.0327	n.s.	0.0025
PTSD	Any depressive disorder (child)	1.2365 [1.0875, 1.4064]	0.0320	n.s.	0.0053
ADHD	Suicidal ideation (parent)	1.1684 [1.0634, 1.2841]	0.0314	n.s.	0.0032
CP	ADHD	0.8959 [0.8380, 0.9577]	0.0318	n.s.	0.0018
Neuroticism	Separation Anxiety disorder	1.1487 [1.0558, 1.2500]	0.0316	n.s.	0.0027
Neuroticism	Generalized anxiety disorder (parent)	1.2055 [1.0738, 1.3538]	0.0377	n.s.	0.0043
Ever smoker	Eating disorder	0.8725 [0.8016, 0.9496]	0.0380	n.s.	0.0025
Worrying	Any anxiety disorder (parent)	1.1366 [1.0495, 1.2312]	0.0383	n.s.	0.0023
Depression	Generalized anxiety disorder (parent)	1.1999 [1.0680, 1.3486]	0.0491	n.s.	0.0040
Depression	Conduct disorder	1.2821 [1.0936, 1.5045]	0.0488	n.s.	0.0068
IQ	ADHD	0.9003 [0.8414, 0.9631]	0.0499	n.s.	0.0016

Multiple comparison correction for 1,080 tests; Clinical outcomes without reporter are of parent report; OR, odds ratio; ΔMcFadden's R^2, proportion of variance explained by polygenic score; BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; PTSD, post-traumatic stress disorder; CP, cognitive performance; n.s., not significant

Supplementary 3. Firth logistic regressions on clinical outcomes with polygenic scores and family history of depression in multi-ancestry samples

Polygenic score	Clinical outcome (reporter)	OR [95% CI]	FDR-corrected *P*	Bonferroni-corrected *P*	ΔR^2 (PGS+FH)	ΔR^2 (FH)
BMI	Eating disorder	0.8277 [0.7688, 0.8909]	0.0005	0.0005	0.0062	0.0013
Ever smoker	ADHD	1.1615 [1.0956, 1.2317]	0.0003	0.0005	0.0225	0.0192
BMI	ADHD	1.1613 [1.0951, 1.2317]	0.0002	0.0006	0.0225	0.0192
BMI	Conduct/oppositional defiant disorder	1.1731 [1.1018, 1.2493]	0.0002	0.0006	0.0252	0.0214
ADHD	ADHD	1.1552 [1.0901, 1.2244]	0.0002	0.0011	0.0223	0.0192
EA	ADHD	0.8794 [0.8281, 0.9336]	0.0046	0.0273	0.0215	0.0192
Ever smoker	Any psychiatric disorder (child)	1.1193 [1.0619, 1.1799]	0.0041	0.0289	0.0042	0.0022
Depression	Any psychiatric disorder (parent)	1.1120 [1.0571, 1.1699]	0.0053	0.0424	0.0299	0.0281
IQ	ADHD	0.8833 [0.8323, 0.9372]	0.0048	0.0429	0.0214	0.0192
General risk tolerance	Any anxiety disorder (child)	1.2833 [1.1340, 1.4528]	0.0082	n.s.	0.0125	0.0054
Risky behaviors	Suicidal behaviors (child)	1.1750 [1.0844, 1.2734]	0.0080	n.s.	0.0079	0.0045
General risk tolerance	ADHD	1.1242 [1.0605, 1.1918]	0.0074	n.s.	0.0212	0.0192
Risky behaviors	Suicidal ideation (child)	1.1757 [1.0845, 1.2747]	0.0070	n.s.	0.0072	0.0037
Depression	Any psychiatric disorder (child)	1.1107 [1.0540, 1.1706]	0.0066	n.s.	0.0039	0.0022
Ever smoker	Conduct/oppositional defiant disorder	1.1328 [1.0643, 1.2059]	0.0064	n.s.	0.0238	0.0214

Ever smoker	Any depressive disorder (child)	1.2328 [1.1082, 1.3718]	0.0078	n.s.	0.0075	0.0025
Depression	Conduct/oppositional defiant disorder	1.1307 [1.0622, 1.2038]	0.0074	n.s.	0.0237	0.0214
ASP	Any anxiety disorder (parent)	0.8692 [0.8087, 0.9341]	0.0080	n.s.	0.0341	0.0313
CP	ADHD	0.8918 [0.8405, 0.9461]	0.0082	n.s.	0.0211	0.0192
ADHD	Conduct/oppositional defiant disorder	1.1242 [1.0565, 1.1963]	0.0117	n.s.	0.0235	0.0214
Neuroticism	Any anxiety disorder (parent)	1.1425 [1.0633, 1.2277]	0.0141	n.s.	0.0338	0.0313
ASP	Social anxiety disorder (parent)	0.8251 [0.7435, 0.9154]	0.0138	n.s.	0.0250	0.0205
Worrying	Any anxiety disorder (parent)	1.1424 [1.0629, 1.2281]	0.0138	n.s.	0.0338	0.0313
Cannabis use	Suicidal behaviors (child)	1.1585 [1.0694, 1.2552]	0.0140	n.s.	0.0073	0.0045
Cannabis use	Suicidal ideation (child)	1.1588 [1.0691, 1.2562]	0.0143	n.s.	0.0066	0.0037
Ever smoker	Suicidal ideation (child)	1.1589 [1.0690, 1.2565]	0.0142	n.s.	0.0066	0.0037
EA	Conduct/oppositional defiant disorder	0.8894 [0.8339, 0.9485]	0.0140	n.s.	0.0234	0.0214
Insomnia	Suicidal ideation (child)	1.1551 [1.0663, 1.2515]	0.0158	n.s.	0.0065	0.0037
ADHD	Conduct disorder	1.2693 [1.1118, 1.4501]	0.0155	n.s.	0.0228	0.0165
Ever smoker	Suicidal behaviors (child)	1.1491 [1.0606, 1.2452]	0.0243	n.s.	0.0070	0.0045
Insomnia	Suicidal behaviors (child)	1.1459 [1.0584, 1.2409]	0.0271	n.s.	0.0070	0.0045
Depression	Conduct disorder	1.2580 [1.0999, 1.4392]	0.0274	n.s.	0.0222	0.0165
Depression	Any anxiety disorder (parent)	1.1316 [1.0523, 1.2170]	0.0278	n.s.	0.0334	0.0313
Depression	Suicidal ideation (child)	1.1391 [1.0508, 1.2349]	0.0496	n.s.	0.0060	0.0037

Multiple comparison correction for 1,080 tests; Clinical outcomes without reporter are of parent report; OR, odds ratio; ΔR^2 (PGS+FH), the proportion of variance explained by polygenic score and family history of depression; ΔR^2 (FH), the proportion of variance explained by family history of depression; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; ASP, automobile speed propensity; IQ, intelligence quotient; CP, cognitive performance; n.s., not significant

Supplementary 4. Firth logistic regressions on clinical outcomes with polygenic scores and family history of depression in European-ancestry samples

Polygenic score	Clinical outcome (reporter)	OR [95% CI]	FDR-corrected *P*	Bonferroni-corrected *P*	ΔR^2 (PGS+FH)	ΔR^2 (FH)
ADHD	ADHD	1.1778 [1.1023, 1.2587]	0.0014	0.0014	0.0215	0.0174
BMI	Eating disorder	0.8209 [0.7541, 0.8933]	0.0025	0.0050	0.0057	0.0003
BMI	ADHD	1.1629 [1.0875, 1.2438]	0.0036	0.0108	0.0208	0.0174
Ever smoker	Any psychiatric disorder (child)	1.1385 [1.0704, 1.2111]	0.0099	0.0394	0.0043	0.0017
Ever smoker	ADHD	1.1470 [1.0729, 1.2266]	0.0123	n.s.	0.0202	0.0174
Risky behaviors	Suicidal behaviors (child)	1.2044 [1.0968, 1.3229]	0.0174	n.s.	0.0085	0.0039
Risky behaviors	Suicidal ideation (child)	1.2029 [1.0952, 1.3216]	0.0173	n.s.	0.0082	0.0037
Depression	Self-harm	1.2740 [1.1244, 1.4443]	0.0191	n.s.	0.0208	0.0139
Depression	Any psychiatric disorder (child)	1.1251 [1.0583, 1.1963]	0.0191	n.s.	0.0039	0.0017
PTSD	Suicidal ideation (parent)	1.1972 [1.0891, 1.3162]	0.0205	n.s.	0.0261	0.0218
CP	ADHD	0.8806 [0.8229, 0.9422]	0.0219	n.s.	0.0198	0.0174
General risk tolerance	Any anxiety disorder (child)	1.3113 [1.1352, 1.5155]	0.0204	n.s.	0.0159	0.0075
ADHD	Conduct/Oppositional defiant disorder	1.1396 [1.0630, 1.2219]	0.0191	n.s.	0.0194	0.0168
PTSD	Suicidal behaviors (parent)	1.1927 [1.0854, 1.3110]	0.0190	n.s.	0.0256	0.0215
Ever smoker	Any depressive disorder (child)	1.2745 [1.1188, 1.4527]	0.0186	n.s.	0.0113	0.0046

General risk tolerance	ADHD	1.1316 [1.0589, 1.2095]	0.0176	n.s.	0.0197	0.0174
Ever smoker	Suicidal ideation (child)	1.1909 [1.0838, 1.3089]	0.0175	n.s.	0.0077	0.0037
EA	ADHD	0.8799 [0.8207, 0.9431]	0.0177	n.s.	0.0197	0.0174
Ever smoker	Suicidal behaviors (child)	1.1883 [1.0818, 1.3057]	0.0179	n.s.	0.0078	0.0039
Depression	Suicidal ideation (child)	1.1874 [1.0810, 1.3046]	0.0178	n.s.	0.0076	0.0037
Cannabis use	Suicidal ideation (child)	1.1861 [1.0804, 1.3024]	0.0172	n.s.	0.0075	0.0037
Depression	Any psychiatric disorder (parent)	1.1113 [1.0488, 1.1778]	0.0173	n.s.	0.0259	0.0241
Cannabis use	Suicidal behaviors (child)	1.1811 [1.0762, 1.2966]	0.0210	n.s.	0.0076	0.0039
Depression	Suicidal behaviors (child)	1.1820 [1.0765, 1.2982]	0.0203	n.s.	0.0076	0.0039
IQ	ADHD	0.8857 [0.8271, 0.9482]	0.0208	n.s.	0.0195	0.0174
ADHD	Conduct disorder	1.3244 [1.1299, 1.5539]	0.0216	n.s.	0.0210	0.0122
EA	Any depressive disorder (child)	0.7892 [0.6893, 0.9030]	0.0226	n.s.	0.0106	0.0046
BMI	Conduct/Oppositional defiant disorder	1.1301 [1.0534, 1.2126]	0.0248	n.s.	0.0191	0.0168
Depression	Suicidal ideation (parent)	1.1789 [1.0718, 1.2971]	0.0258	n.s.	0.0254	0.0218
Neuroticism	Any anxiety disorder (parent)	1.1476 [1.0593, 1.2435]	0.0267	n.s.	0.0306	0.0279
Depression	Suicidal behaviors (parent)	1.1766 [1.0701, 1.2943]	0.0269	n.s.	0.0250	0.0215
EA	MDD (child)	0.7261 [0.6013, 0.8759]	0.0273	n.s.	0.0135	0.0037
ASP	Social anxiety disorder (parent)	0.8206 [0.7301, 0.9220]	0.0285	n.s.	0.0216	0.0168
ASP	Any anxiety disorder (parent)	0.8738 [0.8062, 0.9468]	0.0312	n.s.	0.0305	0.0279

Ever smoker	Conduct/Oppositional defiant disorder	1.1237 [1.0475, 1.2055]	0.0344	n.s.	0.0189	0.0168
Neuroticism	Any psychiatric disorder (parent)	1.0994 [1.0377, 1.1649]	0.0386	n.s.	0.0256	0.0241
Depression	Sleep problems (child)	1.1250 [1.0465, 1.2096]	0.0410	n.s.	0.0026	0.0005
PTSD	Any depressive disorder (child)	1.2325 [1.0837, 1.4021]	0.0410	n.s.	0.0098	0.0046
ADHD	PTSD	1.3655 [1.1266, 1.6580]	0.0405	n.s.	0.0470	0.0370
Ever smoker	Eating disorder	0.8726 [0.8018, 0.9495]	0.0422	n.s.	0.0029	0.0003
ADHD	Suicidal behaviors (parent)	1.1646 [1.0596, 1.2804]	0.0412	n.s.	0.0246	0.0215
Depression	Conduct/Oppositional defiant disorder	1.1169 [1.0416, 1.1978]	0.0484	n.s.	0.0187	0.0168

Multiple comparison correction for 1,080 tests; Clinical outcomes without reporter are of parent report; OR, odds ratio; ΔR^2 (PGS+FH), the proportion of variance explained by polygenic score and family history of depression; ΔR^2 (FH), the proportion of variance explained by family history of depression; ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; BMI, body mass index; ASP, automobile speed propensity; PTSD, post-traumatic stress disorder; IQ, intelligence quotient; CP, cognitive performance; n.s., not significant

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국문초록

우울증의 가족력과 아동의 정신병리 간 우울 다중유전자점수의 매개효과

정신질환은 세대에 걸친 위험을 지닌다. 특히 우울증의 가족력이 있는 아이들은 정신질환에 걸릴 위험이 높다고 보고되어 왔다. 우울증의 가족력이 아동의 정신건강에 병리적 위험을 증가시키는 메커니즘을 이해하는 것은 정신질환의 고위험군을 초기에 식별하여 적절한 개입이 이루어지도록 하는데에 중요하다. 본 연구에서는 유전적 경향성의 추정치인 다중유전자점수(polygenic score)가 우울증 가족력의 영향에 대한 유전적 메커니즘으로서 역할한다는 가설을 세웠다. 이를 위해 미국 아동청소년 뇌인지발달(Adolescent Brain Cognitive Development, ABCD) 연구의 유럽 계통 인종 6,151명을 포함한 다인종 아동 8,111명의 표현형과 유전체 데이터를 이용하였다. 이전 두 세대(부모와 조부모)에서의 우울증 여부를 포함하는 가족력 변수와 정신질환 및 인지능력과 관련 있는 30가지의 다중유전자점수를 주요 분석에 포함하였다. 로지스틱 회귀 분석은 아동의 정신건강에 영향을 미치는 것으로 알려진 잠재적인 교란 요인을 보정한 이후에도, 우울증에 걸린 세대가 많을 수록 다중유전적 위험도 높다는 결과를 보여주었다. 우울증과 양극성 장애의 다중유전자점수가 우울증 가족력과 유의미한 관련이 있었다. 매개분석 결과, 우울증의 다중유전자점수는 우울증 가족력과 자녀 세대의 정신질환 및 자살경향성의 관계를 유의미하게 매개하는 것으로 나타났다. 본 연구결과는 우울의 다중유전자점수가 우울증의 가족력의 영향에 대한 메커니즘이 될 수 있다는 점을 시사하며, 다중유전자점수와 가족력 위험이 함께 고려되었을 때 아동에게서 정신질환의 고위험군을 정의하는 데 도움이 될 수

있다는 증거를 제공한다.

핵심어: 아동 정신병리, 우울증 가족력, 다중유전자 점수, 정신질환, 자살경향성
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