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Original article



Polygenic risk scores for pediatric obsessive-compulsive symptoms: Mediating effects in samples clinically diagnosed with mental disorders

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ABSTRACT

Here, we present the first genome-wide association study and polygenic risk score analysis of obsessive-compulsive symptoms in a sample of 661 clinically diagnosed pediatric participants diagnosed with mental illness and healthy controls. Using a psychiatric questionnaire score as a quantitative trait we conducted a large-scale genetic analysis and ran multiple post-association analyses to investigate the mediating role of obsessive-compulsive symptoms in six comorbid mental disorders. Polygenic risk scores were computed for OCS using genome-wide summary statistics from obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, anxiety disorders, depression, autism spectrum disorder, and tic disorders. Across all models, the PRS of OCS explained modest yet significant proportion of shared genetic risk across six mental disorders consistent with effect sizes typically observed in complex psychiatric traits. Furthermore, Mendelian randomization analysis suggested a potential causal pathway in which OCS mediates the genetic risk for anxiety. These findings highlight shared polygenic mechanisms between OCS and a range of neuropsychiatric conditions. We observed a potential causal pathway in which OCS mediates the genetic risk for anxiety, supporting the hypothesis that OCS may serve as a transdiagnostic mediator within the pediatric population. This study underscores the value of examining genetic risk across the symptom spectrum of mental illnesses, rather than relying solely on binary diagnostic categories.

1. Introduction

Obsessive-compulsive (OC) symptoms (OCS), characterized by intrusive thoughts and repetitive intentional behaviors are common in children and youth (Valeni-Basile et al., 1994). These symptoms represent the core features of obsessive-compulsive disorder (OCD), and evidence from large community-based studies of children and youth indicates that OCD and related disorders are associated with higher severity scores on continuously distributed measures of OCS) in the general population (Burton et al., 2021). OCD is impairing, persistent (Murray and Lopez, 1994) and current treatments are insufficiently effective for everyone (Stewart et al., 2004; McGuire et al., 2015). Many studies report that OCD is highly comorbid and occurs with many other mental disorders such as anxiety (ANX), major depressive disorder (MDD), attention deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and tic disorders (TD). OCS are also seen in many of these disorders (particularly ASD, TD, and grooming) even when the individual does not meet full criteria for OCD (Mathews et al., 2014; Gazzellone et al., 2016; Lee et al., 2019; Yang et al., 2021).

Genetics play an important role in OCS where twin-based studies report around 30% heritability in adults and around 47-67% in children (Van Grootheest et al., 2005; Burton et al., 2018; Mahjani et al., 2022; Blanco-Vieira et al., 2023). Genetic etiology of OCD and OCS remains unclear, although recently progress has been made in identifying

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potential genetic risk variants. Numerous candidate gene analyses and genome-wide association studies (GWAS) have been conducted to identify the genetic pathophysiology of OCD and OCS. A number of studies published on candidate gene analysis report mixed findings (Pauls et al., 2014; Burton et al., 2018; Arnold et al., 2023). In comparison to candidate genetic studies which focus on selected single variants, GWAS involves scanning common single nucleotide polymorphisms (SNPs) across genome to identify risk variants.

GWAS have significantly advanced understanding of the genetic architecture of OCD and other mental disorders. Early studies did not identify genome-wide significant variants (Stewart et al., 2013; Mattheisen et al., 2015), although Mattheisen et al. (2015) reported a suggestive association near *PTPRD* ($p = 4.13 \times 10^{-7}$). A subsequent meta-analysis of 2,688 cases and 7,037 controls also failed to detect significant hits (Posthuma, 2018). Later, Burton et al. (2021) performed a GWAS of quantitative obsessive-compulsive symptoms (OCS) using the Toronto Obsessive-Compulsive Scale (TOCS) (Park et al., 2016) in 15, 880 community-based participants, identifying a genome-wide significant SNP in *PTPRD* (rs7856850, $p = 2.48 \times 10^{-8}$). The most recent large-scale GWAS by the OCD/Tourette Syndrome Working Group of the Psychiatric Genomics Consortium analyzed 37,015 cases and 948,616 controls, identifying 15 genome-wide significant loci and approximately 80 associated genes.This study also revealed positive genetic correlations between OCD and several psychiatric traits, including ANX, MDD, TD, anorexia nervosa, neuroticism, and post-traumatic stress disorder (Strom et al., 2025). Population-based GWAS of self-reported OCS have similarly demonstrated a strong polygenic basis and substantial genetic overlap with OCD and related psychiatric disorders (Smit et al., 2020; Strom et al., 2024). To further examine these polygenic relationships, post-GWAS analytic approaches such as polygenic risk score (PRS) and Mendelian randomization (MR) analyses have become increasingly valuable. PRS quantifies the additive effects of multiple genetic variants that contribute to an individual's genetic risk for a given trait using GWAS summary statistics (Choi et al., 2020), while MR may leverage those to high-risk variants to assess potential causal relationships between traits through mediating pathways (Smith and Ebrahim, 2003; Burgess and Thompson, 2015).

Despite substantial progress in illuminating the genetic architecture of OCD, much less is known about the genetic underpinnings of OCS across clinical populations. Most existing GWAS and PRS studies are conducted in community-based or population cohorts, where OCS may not capture the full clinical spectrum observed in individuals with diagnosed comorbid psychiatric conditions. This limits our understanding of how genetic liability to OCD and related disorders manifests dimensionally across clinical presentations. Investigating OCS in clinically-based samples enables the examination of shared and distinct genetic mechanisms contributing to symptom overlap and comorbidity among mental disorders. Moreover, OCD rarely occurs in isolation and has reported high rates of comorbidity with ANX, ADHD, MDD, ASD, and TD suggest partially overlapping genetic etiology (Ivarsson et al. 2008; Gazzellone et al., 2016; Lee et al., 2019). Yet, the extent to which these shared genetic pathophysiology influences through OCS remains unclear. By integrating PRS derived from large-scale GWAS of OCS, OCD, and other major psychiatric disorders with quantitative measures of OCS in a clinically diagnosed pediatric cohort, this study addresses a key gap in understanding the transdiagnostic mediator role of OCS and the overlapping genetic mechanisms contributing to early-onset psychopathology.

While most prior research has focused on population-based or self-reported symptom data, our approach uniquely examines OCS within a clinically ascertained pediatric sample, where symptom expression, comorbidity, and genetic liability are more definite.

Here, we present a unique study on pediatric samples that are clinically diagnosed with one or more mental disorders. We tested if the effect of OCS genetic risk markers on OCD, ANX, ADHD, MDD, ASD and TD is mediated through OCS severity using PRS and MR analysis.

This study provides a novel framework for identifying OCS as a potential transdiagnostic mediator of genetic vulnerability in pediatric mental health.

2. Methods

2.1. Participants

Child and youth participants between the ages of 6-25 were recruited. Every participant had a general medical exam by their primary care physician within the preceding year and met the inclusion/exclusion criteria (Supplementary Material 1.1). In addition to these general criteria, for inclusion in this study we specified that 1) "cases" should be clinically diagnosed with one or more mental health disorders, such as OCD, ANX, ADHD, ASD, MDD and/or TD (Table S4); 2) "healthy controls" should have no lifetime diagnosis of any mental disorder, no history of intrusive thoughts, repetitive behaviors, or mental rituals meeting according to DSM-5 criteria (DSM-5, 2013). More detailed descriptive statistics on samples are in Table S1 and Table S2. Diagnostic specifications of OCD, ANX, ADHD, MDD, ASD, and TD are explained in Table S3.

For genotyping purposes saliva and/or blood samples were collected to extract DNA. The samples were obtained from different sites including: 1) University of Michigan, MI, and 2) Wayne State University, MI, and 3) SickKids Hospital in Toronto, ON. Predominantly 661 European ancestry participants were included, as we had to exclude other ancestries due to the difficulty of controlling heterogenous ancestries. All 661 samples underwent the clinical assessment process. Of this sample, 446 individuals were clinically diagnosed "cases" and 215 were "healthy controls". Four different genome-wide arrays were used for genotyping purposes. Illumina Multi-Ethnic Global-8 kit (MEG) array, Illumina Omni 2.5 – 8 kit, PsychChip Illumina microarray, and Human Core Exome kit arrays were used for genotyping (Supplementary Material 1.2). The markers from different arrays were merged and imputed before running through quality control (QC) analysis.

2.2. Quantitative trait

OCS was measured by Child Behavior Checklist Scale – Obsessive-Compulsive Subscale (CBCL-OCS). CBCL-OCS is one of the best accepted pediatric questionnaires which is shown to be highly effective to screen for OCS in children (Achenbach and Craig, 1983; Hudziak et al., 2004a). Hudziak et al. described 55% heritability in the largest twin study of CBCL-OCS as a quantitative trait. They also reported that the CBCL-OCS has high sensitivity (92%) and moderate specificity (67%) to distinguish clinical OCD cases compared with healthy controls (Hudziak et al., 2004b).

2.3. Genome-wide association analysis

To increase the marker coverage, SNP imputation analysis was carried out on the Michigan Imputation Server (MIS) via Minimac4 software using 1000 Genome project phase 3v5 as the reference (Das et al., 2016). Eagle v2.4 was implemented for phasing. Samples underwent rigorous quality control both prior to and following imputation. The resulting output files were then processed through comprehensive QC filters, as recommended by the MIS team (Das et al., 2016; Schurz et al., 2019). QC analysis before running GWAS was conducted using standard methods with PLINK v2.00 (Purcell et al., 2007). The major QC steps for individuals and genetic variants are explained elsewhere (Turner et al., 2011; Marees et al., 2018). Genotyping call rates >3%, minor allele frequency (MAF) of 1%, INFO (information metric) scores of 0.3, Hardy Weinberg equilibrium $<10^{-6}$, second degree of relatedness were selected as QC thresholds for this study (Supplementary Material 1.3.2).

Population stratification analysis was applied using the multidimensional scaling (MDS) approach (Figure S4) (Price et al., 2010). The

first four components (PC1-PC4) were used as covariates for the study. Additional utilized covariates were age, age^2, and biological sex.

All the data cleaning and standardization was performed using R software packages (R Core Team, 2016) and/or IBM SPSS Statistics, Version 26. Post-imputation quantitative association analysis using generalized linear model (GLM) was conducted via PLINK v2.00 (Purcell et al., 2007). Genes that were near the genome-wide significant loci were mapped via LocusZoom (Boughton et al., 2021). We also checked if identified genes are differentially expressed in brain regions using GTExPortal database (Lonsdale et al., 2013). The traits and phenotypes that were previously reported in literature to be associated with identified genes were investigated accessing "Ensembl" public database (Cunningham et al., 2022).

2.4. Gene-based analysis

Gene-based and gene-set analyses were carried out using Functional Mapping and Annotation (FUMA) technique (Watanabe et al., 2017). FUMA SNP2GENE tool was used for identifying genes that have functional consequence. FUMA also runs via the Multi-marker Analysis of GenoMic Annotation (MAGMA) v1.10 tool (De Leeuw et al., 2015). MAGMA uses GWAS summary statistics and is based on a multiple regression model to account for LD between the variants. Gene positional mapping was done via 1000 Genomes phase 3 reference panel. To correct for multiple testing a Bonferroni P-value $< 0.05/n$ threshold was set, where n was the number of annotated genes.

Gene-set analysis was conducted based on the genes identified from the previous step. This was done using MAGMA v1.10 (De Leeuw 2015) and FUMA GENE2FUNC tool (Watanabe et al., 2017). It involves the set of curated gene sets and GO terms obtained from Molecular Signatures Database (MsigDB.v7.5.1) (Liberzon, et al., 2015). To be considered significant gene-sets should pass the Bonferroni correction P-value $< 0.05/n$ threshold, where n is the number of gene-sets.

2.5. OCS as mediator

2.5.1. Heritability estimate

Heritability estimate (h^2) was assessed through LD regression score (LDSC) where genetic heritability is assumed. LDSC was assessed using bigsnpr R package by Privé et al. (2018). Due to the small sample size, LDSC was calculated using reference LD matrix obtained from HamMap3+ which is an extended set of HapMap3. HapMap3+ reference data is well imputed and covers the whole genome.

2.5.2. Polygenic risk score analysis

To generate PRS, we utilized the base dataset consisted of summary statistics from the large-scale cohort provided by the PGC consortium (2009) (Sullivan, 2010) and our clinically based samples as the target dataset. PRS analysis enabled us to test how the genetic disposition to OCS may predict the risk of having one or more of the six mental disorders.

GWAS summary statistics of OCD (Strom et al., 2025), ANX (Otowa et al., 2016), ADHD (Demontis et al., 2023), MDD (Howard et al., 2019), ASD (Grove et al., 2019), and TD (Yu et al., 2019) were accessed from different working groups of the PGC consortium (Supplementary Material 1.4.1).

We used the LDpred2 method that is based on the Bayesian shrinkage model (Prive et al., 2020; Vilhjalmsson et al., 2015). LDpred2 allows the inclusion of an LD matrix that was obtained from the HapMap3+ reference genome. It also accounts for heritability explained by the SNPs (LDSC). LDSC should be bigger than 0.05 to proceed with meaningful PRS analysis (Prive et al., 2020). LDpred2-auto was selected as it automatically estimates sparsity P and LDSC scores, and further validation set is not required. Analysis was conducted using *bigsnpr* R package (Prive et al., 2018) adopting provided script by Privé et al. (2020). To assess the significance of the OCS PRS SNPs contribution to the six disorders, linear regression model was utilized (Supplementary Material 1.4.1).

To run the next step, Mendelian Randomization, we need high-risk SNPs that contribute to high PRS score in a larger OCS sample. LDpred2 is a Bayesian shrinkage method and identifying SNPs that contribute to polygenicity is not applicable. Thus, PRSice2 clumping+-thresholding (C+T) method was applied (Choi and O'Reilly, 2019) using an OCS study by Strom et al.(2024) as base data. The GWAS summary statistics were obtained from the largest OCS GWAS study that included around 34 000 participants (Strom et al., 2024). At this step we were able to identify the best PRS model that identifies high-risk SNPs of OCS.

2.5.3. Mendelian Randomization

The SNPs that contribute to high risk from the PRS C+T method were utilized as instrumental variables (IV) to run a MR analysis to determine if there is any causal interference between identified polygenic risk loci and the disorders where OCS is the exposure (or assumed mediator) (Fig. 1). The choice of IVs from C+T method also assumes that the SNPs are uncorrelated.

Two-sample MR analysis using an inverse-variance weighted (IVW) approach was applied. IVW is the most widely used approach that combines the estimates from multiple genetic instruments into a single estimate of causal effect of an exposure (Bowden et al., 2015; Burgess et al., 2013).

MR IVW analysis was carried out using *MendelianRandomization* R package (Yavorska and Burgess, 2017). Next, the most influential observations were detected using Cook's distance and removed via leave-one-out approach (Cook, 1977; Burgess et al., 2017). Additionally, MR-PRESSO was applied to test the validity of MR test and check for horizontal pleiotropy bias (Verbanck, et al., 2018; Hemani et al., 2018). Outliers were removed and we reran IVW MR on the remaining IVs for more reliable results. More detailed methodology can be found in Supplementary Material 1.5.

3. Results

3.1. Samples

GWAS QC analysis was first performed to ensure high quality genotype-phenotype data (Figure S2, S3). A total of 95.7% of variants passed the missingness thresholds. MAF later excluded ~45% of markers that had frequency smaller than 0.01. Next, 99.9% of remaining markers passed HWE threshold. A total of 38 individuals were excluded from the analysis due to high missingness, high heterozygosity rate, relatedness and population stratification filters. Further, another 36 samples have either missing phenotype, or missing covariate information that were excluded as well.

Overall, after data cleaning, standardizing, and QC, high quality genotype-phenotype data included 587 samples and 1 751 493 markers.

During the SNP imputation step around 45 million variants were *imputed* (96% imputation rate) (Figure S2). Only 20% of the imputed SNPs passed the post-imputation QC filters of INFO $>$ 0.3 and MAF$>$0.01 (Figure S3). In total 6 047 748 SNPs remained for further association analysis.

3.2. Genome-wide association analysis

A GWAS of OCS using CBCL-OCS as a quantitative trait was run on 587 samples and included around 6 million markers to test associations. After running the association test, as expected due to the small sample size, no significant variants passed the strict Bonferroni p-value thresholds. SNPs from chromosomes 4, 5, 6, 7, 9, 13, 17, 19, and 22 have suggestive significant association with quantitative OCS as measured using the CBCL-OCS (Fig. 2) (Table S5). The results form gene-based analysis were underpowered too (Fig. 2). Top 10 suggestive significant genes were from 3 loci: 7p22.1 locus with *GRID2IP, CYTH3, C7orf26,*

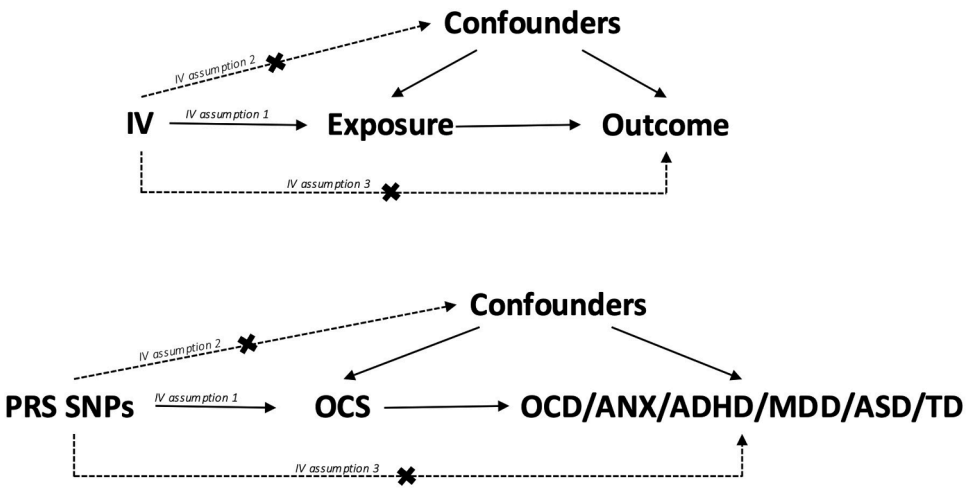


Fig. 1. A general and specific case of Mendelian Randomization (MR).
A) a general case of MR, where it estimates whether the correlation between exposure and outcome is causal in the presence of confounders. B) a specific case of MR adapted to our analysis, where instrumental variables (IVs) are SNPs contributing to polygenic risk score (PRS), OCS is the exposure, and 6 disorders are the outcomes. Confounders are the covariates that were also used in the GWAS and PRS analysis, such as biological sex, ethnicity (PC1-PC4), and age. The *IV assumption 1* is obtained from our target GWAS summary statistics. IV assumption 3 is very crucial and to test that PGC summary statistics from 6 disorders were used.

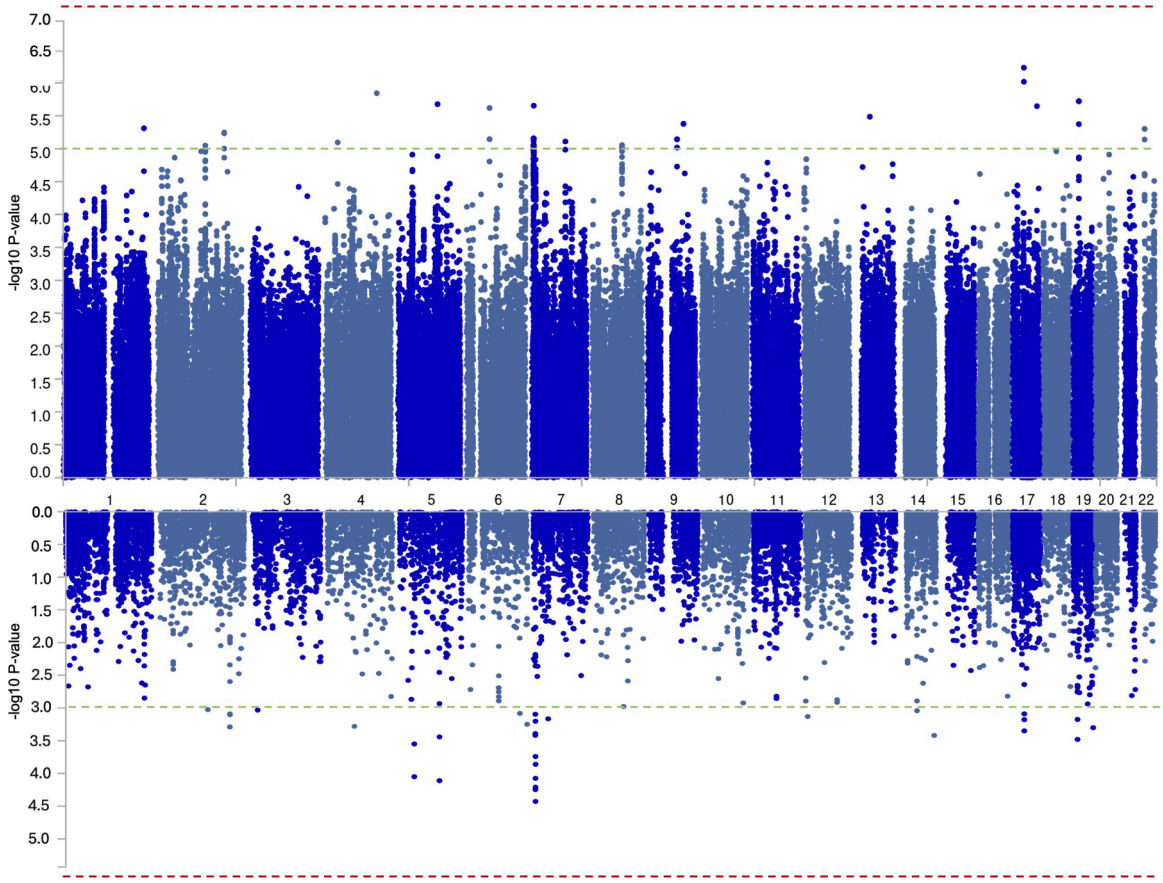


Fig. 2. Miami plot of the GWAS summary statistics.
Miami plot of the GWAS summary statistics of 587 samples using OCS (CBCL-OCS) as quantitative trait. Upper panel is the SNP-based association results and lower panel is gene-based association analysis. Dashed red lines are strict p-value thresholds of 5×10^{-8} (upper panel); and 2.8×10^{-6} (lower panel). Dashed green lines are suggestive significance p-value thresholds of 1×10^{-5} (upper panel); and 1×10^{-3} (lower panel).

DAGLB, ZNF12 and *KDELR2* genes, 5q22.1 locus with *TICAM2* gene, 5p13.1 with *FBXO4* and *C5orf51* genes (Fig. 2). The results of the gene-set analysis are reported in Table S6. Most of the marginal significant genes from SNP-based and gene-based GWAS were strongly expressed in brain according to GTExPortal database (Boughton et al., 2021). Specifically, *AP2B1, GRID2IP, PLPPR1*, and *DAGLB* were more differentially expressed in brain than in other tissues. More results are in Supplementary Material 2.3.

3.3. Polygenic risk score

The estimated SNP heritability of OCS from LDSC was ~6%. The relatedness matrix included ~63% of the genotyped markers. PRS analysis was run using our target OCS data (587 samples) against six disorders: OCD (23 493 cases/1 114 613 controls) (Strom et al., 2025), ANX (18 186 cases/17 310 controls) (Otowa et al., 2016), ADHD (38 691 cases/186 843 controls) (Demontis et al., 2023), MDD (170 756 cases/329 443 controls) (Howard et al., 2019), ASD (18 382 cases/ 27 969 controls) (Grove et al., 2019), and TD (4 819 cases/9 488 controls) (Yu et al., 2019). For all six tests around 1 million SNPs were matched between our target sample, the HapMap3+ dataset, and corresponding summary statistics (Figure S7). Table 1 shows the results of the cross-disorder PRS analysis that were carried out using LDpred2-auto. All six disorders showed significant ($P_{Bonferroni} = 0.05/6 = 0.008$) but limited polygenic variance explained (~2%). The full model of PRS variance explained (Full R^2) was ~2% for each disorder. This includes variance because of OCS, and covariates such as age, sex, and PC1-PC4 compared to PRS variance explained only by OCS (ΔR^2) was only 0.03-0.4% (Fig. 3).

3.4. Mendelian randomization

After running PRSice2 C+T method to identify high-risk SNPs from the best PRS model of OCS, a total of 356 SNPs were obtained (Choi and O'Reilly, 2019). The best model for PRS p-value was 0.05 (Figure S10) and explained 0.6% of only OCS genetic contribution, and 2% for OCS and covariates. To test if OCS may act as a mediator between high-risk SNPs that contribute to OCS severity and six mental disorders as outcomes genetic markers and disorder outcome (Fig. 1B), MR via IVW model was carried out on the selected and pruned 500 IVs. Table 2 shows the results of IVW MR after Cook's distance and MR-PRESSO outlier filtering for all six disorders.

The causal estimate for ANX was statistically significant ($p = 0.04$). Cochran's Q statistics indicated no evidence of heterogeneity among the instrumental variables for ANX ($Q = 275$, $df = 279$), ASD ($Q = 439$, $df = 464$), or TD ($Q = 425$, $df = 459$) (Table S7). Global tests from MR-PRESSO revealed evidence of horizontal pleiotropy only for obsessive-compulsive disorder (OCD; $p < 0.001$) and major depressive disorder (MDD; $p = 0.006$) (Table S7). As shown in Fig. 4, MR analyses demonstrated a positive causal effect of OCS on ANX, suggesting that genetic variants associated with OCS may influence anxiety through this mediating pathway.

4. Discussion

This study aimed to investigate the genetic basis of OCS and their shared genetic architecture with related mental disorders using a clinically characterized pediatric cohort. To our knowledge, this is the first genome-wide study to employ CBCL-OCS as OCS quantitative trait in "cases": patients with clinically diagnosed OCD, ANX, ADHD, MDD, ASD, and TD, and "healthy controls" free of mental illness. By integrating association studies, PRS, and MR analyses, we examined whether genetic liability to these six mental disorders contributes to OCS and whether OCS may serve as a mediator of shared genetic risk. The PRS analyses revealed significant associations across all six disorders, each explaining ~2% of the variance in OCS, indicating substantial degree of polygenic overlap. Furthermore, MR analyses provided preliminary evidence for a causal pathway in which OCS may mediate the genetic risk for ANX. Collectively, these findings highlight OCS as a potential transdiagnostic phenotype that captures shared genetic liability across multiple pediatric mental disorders where OCS might be prevalent.

Multiple analytical approaches have been developed to perform PRS analyses, including LDpred2 (Prive et al., 2020), PRSice2 (Choi and O'Reilly, 2019), PRS-CSx (Ruan et al., 2022), Lassosum (Mak et al., 2017). We utilized both LDpred2 Bayesian shrinkage framework (Prive et al., 2020; Vilhjalmsson, 2015) and PRSice2 C+T method (Choi and O'Reilly, 2019). LDpred2 was applied to estimate the polygenic liability of OCS across OCD, ANX, ADHD, ASD, MDD, and TD. Given that PRS assumes independent variants with normally distributed effect sizes, multiple testing and potential overfitting remain common challenges (Choi et al., 2020). To minimize these issues, we implemented the LDpred2-auto model, which automatically estimates the sparsity parameter (P) and has demonstrated improved predictive performance in single-ancestry datasets such as ours (Prive et al., 2020). The LDpred2-auto results revealed modest but significant correlations (1-2%) between the PRS of OCS and each disorder, consistent with the limited variance typically explained by PRS in complex psychiatric phenotypes reflecting the higher polygenicity of these disorders (Bogdan et al., 2018; Neumann et al., 2022). This modest effect size likely reflects the heterogeneous genetic architecture underlying DSM-5 defined disorders. Such effect size suggests the cumulative influence of thousands of common genetic variants, each with very small individual effects. Importantly, even modest proportions of explained variance can be informative for elucidating shared genetic architecture and transdiagnostic pathways, particularly in pediatric samples where early-emerging symptom dimensions may capture broad liability across multiple disorders. (Schlag et al., 2022; Murray et al., 2021; Hanna, 1995; Halvorsen et al., 2021).

In parallel, PRSice2 was used to estimate polygenic liability of OCS in an independent sample and to identify specific SNPs contributing to OCS severity. Unlike LDpred2, which models all variants simultaneously through continuous shrinkage, PRSice2 applies a clumping and thresholding approach that enables identification of individual SNPs associated with elevated OCS risk. These significant variants were subsequently used as instrumental variables in MR analyses (Smith and Ebrahim, 2003; Burgess and Thompson 2015) to test potential causal pathways, providing additional insight into how OCS may mediate shared genetic risk across disorders.

MR analysis was conducted to further examine potential causal pathways linking OCS with related mental disorders. MR provides a framework to infer causality by using genetic variants as IVs, allowing us to test whether genetic liability to one trait influences another through a mediating pathway. This approach, however, relies on several critical assumptions, including that the selected IVs are strongly associated with the exposure, are independent of confounding factors, and influence the outcome only through the exposure itself (Smith and Ebrahim, 2003; Burgess and Thompson 2015). To ensure valid instruments, we applied LD clumping and pruning to remove correlated SNPs and minimize bias. We also tested for violations of MR assumptions using sensitivity analyses. Specifically, Cochran's Q statistic was used to detect heterogeneity among IVs, while the MR-PRESSO Global Test assessed horizontal pleiotropy. No heterogeneity bias was observed for the ANX, ASD, or TD analyses (Table S7). However, evidence of horizontal pleiotropy was

Table 1
Results after LDpred2-auto: polygenic risk scores (PRS) of OCS on six disorders (outcomes).

ROIs	Full R^2 (%)	PRS R^2 (%)	LDSC (%)	P-value
OCD	1.5	0.1	18	0.0039*
ANX	1.8	0.4	9	0.0046*
ADHD	1.8	0.4	24	0.0039*
ASD	1.4	0.05	33	0.0043*
MDD	1.8	0.4	30	0.0027*
TD	1.4	0.03	58	0.0041*

Full R^2 shows the variance explained by all predictors that includes covariates (age, sex PC1-PC4) and PRS; PRS R^2 is the incremental ΔR^2 that represents variance uniquely explained by PRS; LDSC score corresponds to heritability estimate in the analysis calculated using HapMap3+ reference data, P-value is the significance, P-value significance (*) is the multiple testing Bonferroni correction p-value equal to 0.05/6 tests=0.008 .

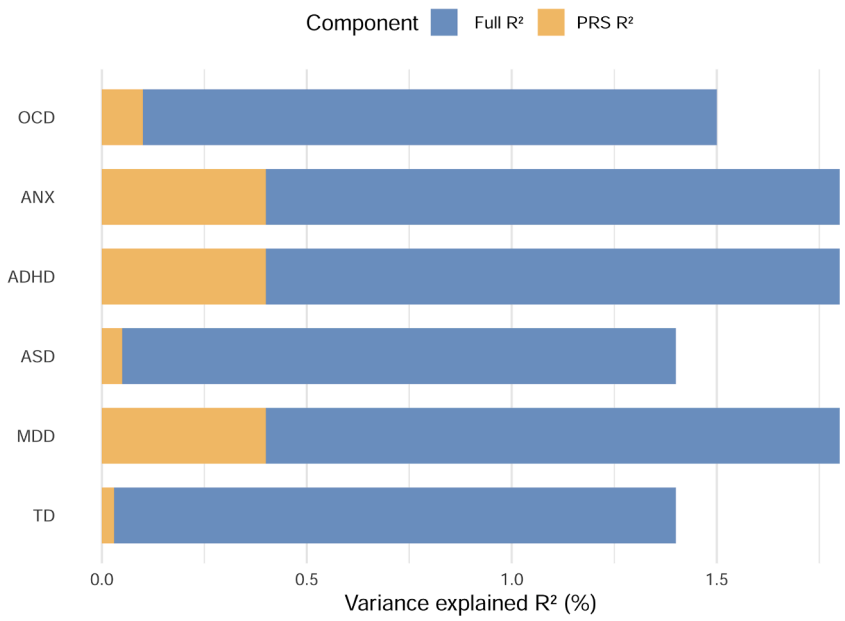


Fig. 3. Results after LDpred2-auto: PRS of OCS on six disorders (outcomes).
The visual representation of the LDpred2-auto results reported in Table 1 where blue bars show the variance explained by all factors (covariates and PRS), orange bars represent the variance only explained by PRS. The six disorders are OCD – obsessive-compulsive disorder, ANX – anxiety disorders, ADHD – attention deficit/hyperactivity disorder, ASD – Autism spectrum disorders, MDD – depression, TD – tic disorders.

Table 2
Results of MR IVW analysis.

Outcomes	MR Estimate (SE)	P_{IVW}	$P_{Cook's\ dist}$	P_{PRESSO}	N of IVs
OCD	0.004 (0.002)	0.14	0.09	0.09	466
ANX	0.02 (0.01)	0.1	0.038*	0.037*	280
ADHD	-0.002 (0.002)	0.45	0.93	0.93	447
ASD	0.003 (0.003)	0.25	0.43	0.41	465
MDD	0.002 (0.002)	0.33	0.3	0.3	416
TS	-0.002 (0.005)	0.3	0.26	0.23	460

Three p-values are reported where P_{IVW} represent the p-value after running first round of IVW; $P_{Cook's\ dist}$ is the p-value of IVW after removing the influential outliers based on Cook's distance; $P_{MR\text{-}PRESSO}$ represents the last round of IVW P-value where outliers are removed after MR-PRESSO tests.

detected for OCD and MDD (Table S7), suggesting that while OCS may act as a potential mediator of genetic risk for these disorders, additional biological or environmental pathways likely contribute to their manifestation. Among the six disorders examined, our MR analysis identified a significant causal pleiotropic relationship between OCS-associated SNPs and ANX, with no detectable biases. This suggests that the polygenic risk variants contributing to OCS exert a positive causal effect on ANX, with OCS acting as a mediator of this relationship. No causal associations were observed for OCD or the other disorders. This outcome may, in part, reflect the nature of the OCS phenotype as measured by the CBCL-OCS questionnaire, which encompasses eight items assessing both obsessive-compulsive and anxiety-related behaviors (Hudziak et al., 2004a; Hanna; 1995). Consequently, the CBCL-OCS may capture overlapping symptom domains shared between OCD and ANX, potentially diluting disorder-specific effects. Furthermore, given that over 30% of the sample was clinically diagnosed with ANX, this high comorbidity may have amplified the observed genetic relationship. While preliminary, these findings highlight the potential mediating role of OCS in the expression of anxiety symptoms. The use of alternative, more specific measures of OCS such as the TOCS (Park et al., 2016) could help disentangle these effects in future studies; however, such data were not available for the majority of our participants.

The findings of this study should be interpreted in light of several limitations. First, our sample was predominantly of European ancestry, which constrains the generalizability of results to other populations. Ongoing efforts to include ancestrally diverse cohorts will be crucial to improving the global applicability of psychiatric genetic findings. Second, association studies such as ours primarily capture common genetic variants, leaving the contribution of rare variants underexplored. Future research employing next-generation sequencing methods, including whole-exome and whole-genome sequencing (Murray et al., 2021), will help clarify the role of rare variation in OCS and related disorders. Our group is currently conducting whole-genome sequencing on an overlapping subset of current study's participants to address this limitation. An additional consideration relates to the choice of OCS as the primary mediating phenotype. OCS represents a broader transdiagnostic phenotype that captures shared genetic liability across both neurodevelopmental and internalizing disorders, whereas for example usage of tic-related traits may reflect a more circumscribed expression of genetic risk. Future studies investigating dimensional tic phenotypes as mediators rather than categorical tic disorder diagnoses would be valuable for understanding shared genetic risk scores of OC related disorders.

Despite these constraints, we identified a weak but significant causal relationship between OCS and ANX. Although these findings require replication in larger and more diverse samples, they provide preliminary evidence that OCS may mediate shared genetic liability between anxiety and other psychiatric disorders. Overall, this study emphasizes the importance of examining the genetic architecture of symptom dimensions rather than relying solely on categorical diagnoses, offering a more nuanced understanding of the shared genetic underpinnings across early-onset psychopathology.

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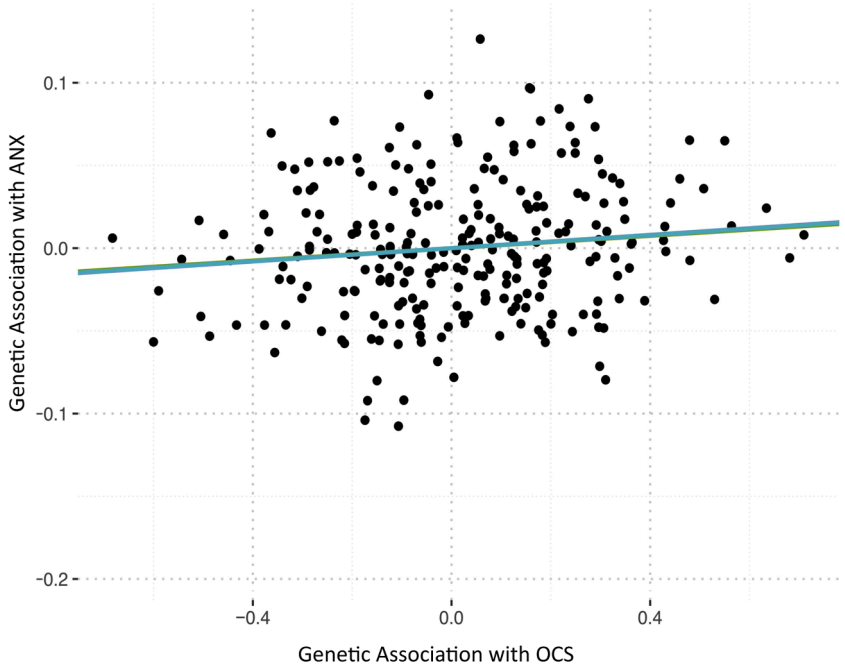


Fig. 4. IVW MR estimate for ANX diagnosis.
The causal relationship between the genetic association with ANX and genetic association with OCS is positive. This means that in our clinical sample OCS severity is a mediator for ANX diagnosis.

CRediT authorship contribution statement

Lilit Antonyan: Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **S-M Shaheen:** Investigation. **Christie L. Burton:** Writing – review & editing, Validation, Conceptualization. **William J. Gehring:** Investigation. **Noam Soreni:** Investigation. **Pamela Falzarano Szura:** Investigation. **Julia Bellamy:** Investigation. **Usha Rajan:** Investigation. **David Rosenberg:** Investigation, Conceptualization. **Gregory L. Hanna:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Paul D. Arnold:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Paul D. Arnold reports financial support was provided by National Institutes of Health. Paul D. Arnold reports financial support was provided by Alberta Innovates Translational Health Chair in Child and Youth Mental Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors contributed as follows: L.A., P.D.A. contributed to the study design, interpretation of results, conceptualization, project administration; L.A. data curation, formal analysis, drafted manuscript; P.D.A, G.L.H. contributed to funding acquisition, supervision, project administration; L.A., P.D.A., G.L.H., C.L.B. methodology, review and editing; S.M.S. genetic data extraction; G.L.H, D.R., W.J.G., N.S., P.F.S., J.B., and U.R. participant recruiting, screening, assessing, and scheduling research participants. All authors read and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2026.116977.

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