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Research paper

Genetic association of attention-deficit/hyperactivity disorder with thirteen ocular disorders

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ABSTRACT

Purpose: Although attention deficit hyperactivity disorder (ADHD) is linked to elevated risk of various ocular disorders, their genetic association and causality remain unclear.
Methods: This study performed linkage disequilibrium score regression (LDSC) and pleiotropic analysis under composite null hypothesis (PLACO) to explore genetic associations, and bidirectional mendelian randomization (MR) to assess the causality between ADHD and thirteen ocular disorders.
Results: LDSC showed ADHD genetically correlated with corneal ulcer, keratitis, blepharochalasis, lacrimal system disorders, senile cataract, retinal vascular occlusion, and age-related macular degeneration. MR revealed genetic liability to ADHD increased the risk of corneal ulcer (OR = 1.18, FDR adjusted $P = 0.01$), keratitis (OR = 1.13, $P = 0.007$), blepharochalasis (OR = 1.23, $P = 0.002$), and lacrimal system disorders (OR = 1.09, $P = 0.04$), while decreasing the risk of primary open-angle glaucoma (OR = 0.83, $P = 0.003$), exfoliation glaucoma (OR = 0.71, $P = 0.001$), and normotensive glaucoma (OR = 0.79, $P = 0.02$). Conversely, genetic liability to strabismus increased ADHD risk (OR = 1.09, $P = 0.03$). The identification of pleiotropic loci using PLACO suggested that genetic factors played a role in the associations between ADHD and ocular diseases.
Conclusions: This study revealed genetic associations between ADHD and multiple ocular disorders, identifying causal effects of ADHD on an increased risk of corneal ulcer, keratitis, blepharochalasis, and lacrimal system disorders, while showing a protective effect against glaucoma. Conversely, genetic liability to strabismus increased ADHD risk.

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is neurodevelopmental conditions that typically emerge early in childhood and often persist into adulthood(Faraone and Larsson, 2019). ADHD affects approximately 5 % of children and 3 % of adults, and it is characterized by developmentally inappropriate inattention and/or hyperactivity-impulsiveness(Faraone et al., 2015; Fayyad et al., 2007; Polanczyk et al., 2014). Since ADHD is neurodevelopmental disorder, and the eyes have long been regarded as the window to the nervous system, various ocular disorders have been identified in both children and adults with ADHD. A recent meta-review revealed that individuals with ADHD have a higher risk of astigmatism, strabismus, reduced near point of convergence, and increased lag and variability of the accommodative response(Bellato et al., 2023). Conversely, visual disturbance such as amblyopia and strabismus may lead to attention deficits or increase the hazard ratio of ADHD in long-term observation(Su et al., 2019; Tsai et al., 2021; Wei et al., 2024).

Associations between ADHD and ocular disorders have been studied extensively. Oculomotor deficits, strabismus or amblyopia in patients with ADHD are often contextualized within top-down, executive dysfunction frameworks of ADHD(Feifel et al., 2004; Johnson et al., 2016; Maron et al., 2021; Sowell et al., 2003; Sweeney et al., 2004). Conversely, various vision disorders may lead to the neurocognitive symptoms of ADHD(Cavézian et al., 2013). Impaired vision may influence cognitive function and long-term psychosocial development by diminishing engagement in activities(Dunn, 2001). Therefore, it is speculated that impaired vision from an early age may be partly associated with an increased risk for ADHD, and untreated visual impairment could exacerbate neurocognitive symptoms. Moreover, ocular structures develop from the same embryological tissue as the brain (London et al., 2013) and ADHD is neurodevelopmental disorders characterized by structural brain abnormalities(Ecker, 2017; Hoogman et al., 2017; Kelley and Paşca, 2022). Thus, the development of ocular structures might be affected by the same processes that cause ADHD.

However, the genetic association between ADHD and ocular disorders remains unexplored, and the potential causal relationship between them remains ambiguous. Understanding the genetic association could provide valuable insights into shared genetic pathways and potential comorbidities, ultimately contributing to improved diagnosis and treatment strategies. Establishing their causality could aid in guiding the development of screening and preventive measures. Furthermore, there is currently a lack of associated etiology for both ADHD and various ocular disorders. Based on the aforementioned associations between these conditions, we hypothesize that there may be an underlying reciprocal etiology between them.

Linkage Disequilibrium Score Regression (LDSC) is a statistical method used to estimate the genetic correlation between traits by leveraging the linkage disequilibrium (LD) structure of the genome(Ni et al., 2018). Mendelian randomization (MR) is an innovative statistical method that employs genetic variants [single nucleotide polymorphisms (SNPs)] as instrumental variables (IVs) to establish causal relationships between risk factors (exposures) and diseases (outcomes) (Lawlor et al., 2008). Bidirectional MR, which assesses causality in both directions, can help clarify the causal temporal relationships between two related variables(Zheng et al., 2017). Colocalization analysis aims to identify whether the same genetic variants are associated with both ADHD and ocular disorders within specific genomic regions(Giambartolomei et al., 2014). PLACO (pleiotropic analysis under composite null hypothesis) is a statistical method specifically designed to detect pleiotropic loci between two traits(Ray and Chatterjee, 2020). In this study, we employed LDSC, bidirectional MR, colocalization and PLACO analysis to elucidate the genetic association and causality between ADHD and thirteen ocular disorders.

2. Methods and materials

2.1. GWAS data for ADHD and ocular disorders

Genetic data were obtained from genome-wide association study (GWAS), with Caucasians being the predominant ethnicity for both ADHD and ocular disorders. The latest statistics on ADHD were sourced from the Psychiatric Genomics Consortium (PGC), encompassing 38,691 cases (defined by ICD-10 or structured/semi-structured clinical interviews) and 186,843 controls(Demontis et al., 2023). The most recent data on ocular disorders were derived from the FinnGen study, which was launched in Finland in 2017. The FinnGen study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic variation with health data to understand disease (defined by ICD-10) mechanisms and predispositions(Kurki et al., 2023). The project is a collaboration between research organizations and biobanks within Finland and international industry partners. Genome-wide data of FinnGen R12 version were collected for the following thirteen disorders: amblyopia (1568 cases and 475,933 controls), anisometropia (1141 cases and 474,776 controls), strabismus (10,045 cases and 476,776 controls), corneal ulcer (7927 cases and 473,095 controls), keratitis (16,577 cases and 473,095 controls), blepharochalasis (12,170 cases and 453,930 controls), disorders of the lacrimal system (19,195 cases and 453,930 controls), allergic conjunctivitis (29,791 cases and 470,557 controls), glaucoma (26,591 cases and 473,757 controls), senile cataract (83,886 cases and 409,535 controls), retinal vascular occlusion (4560 cases and 455,449 controls), retinal detachments and breaks (15,490 cases and 455,449 controls), age-related macular degeneration (AMD, 12,495 cases and 461,686 controls). Since the GWAS data for ADHD was based on GRCh37, while the GWAS data from FinnGen was based on GRCh38, we converted the former to GRCh38. This harmonized version was then used for all analyses in this study.

2.2. Linkage disequilibrium score regression (LDSC)

LDSC was used to assess the genetic correlations of ADHD and ocular disorders. This analysis employed the European ancestry linkage disequilibrium reference panel from the 1000 Genomes Project (Auton et al., 2015; Bulik-Sullivan et al., 2015). GWAS data for ADHD and ocular disorders were clumped ($r^2 \leq 0.001$ in 10,000 kb windows) to identify approximately LD independent SNPs. R package ldscr was used to conduct LDSC analysis. The *P* values of LDSC were corrected by false discovery rate (FDR) using the Benjamini-Hochberg (BH) procedure.

2.3. Bidirectional Mendelian randomization (MR) analysis

Bidirectional MR was used to determine the effect of the liability for ADHD on ocular disorders and the effect of the liability for ocular disorders on ADHD. The basic principle of MR is that genetic instruments, which could predict the level of a modifiable exposure, should be causally linked to the exposure-related outcome(Evans and Davey Smith, 2015). The robustness of this method relies on the following assumptions: (i) there must be a strong association between the implicated genetic variants and the exposure; (ii) the variants should not be associated with any confounders of the relationship between the exposure and the outcome; and (iii) the variants should influence the outcome solely through the exposure(Haycock et al., 2016).

Significant SNPs of ADHD were extracted at a genome-wide association level of $p < 5\times 10^{-8}$ and F statistic ($beta^2/se^2$) >10. Clumping for linkage disequilibrium ($r^2 \leq 0.001$; window of 10,000 kb) based on data of European ancestry from the 1000 Genomes Project. Additionally, to further eliminate biases related to the outcome, genetic instruments associated with the outcome at a threshold of $p < 1 \times 10^{-5}$ were manually removed. For all the eligible SNPs, search their associated traits using LDlink online suite (https://ldlink.nih.gov/?tab=home),

then SNPs associated with confounding traits with the exposure-outcome relationship been excluded. Here list the confounding traits: "autism spectrum disorder" for amblyopia, anisometropia and strabismus(Hours et al., 2022; Milne et al., 2009; Perna et al., 2023; Reynolds and Culican, 2023; Wang et al., 2018); "allergic" or "C-reactive protein" for corneal ulcer, keratitis, blepharochalasis, lacrimal disorders and allergic conjunctivitis(Wei et al., 2025; Xu et al., 2025); "biological sex" for glaucoma(Vajaranant et al., 2010); "smoking", "alcohol", "glaucoma" or "diabetes" for senile cataract(Alabdulwahhab, 2022; Chua et al., 2021; Osland et al., 2017; Ye et al., 2012; Zare Dehnavi et al., 2024), and "smoking" for AMD(Thornton et al., 2005).

The outcome–exposure SNPs were harmonized to align the alleles and remove palindromic or incompatible alleles, then the remaining eligible SNPs were used to conduct MR analysis. The inverse variance weighted (IVW) method was employed as the primary analysis for MR. By default, fixed-effects IVW was used, while multiplicative random-effects IVW was applied only when heterogeneity was detected. MR-Egger regression was used to detect directional pleiotropy, and MR-Pleiotropy Residual Sum and Outlier (MRPRESSO) test was applied to identify and remove horizontal pleiotropic outliers. Heterogeneity was assessed using the Cochrane Q test, with the presence of significant heterogeneity determined by $p < 0.05$ or $I^2 > 25$ %(Greco et al., 2015). Leave-one-out analyses, which involve removing one variant at a time and re-estimating the causal effect, were performed to evaluate the robustness of the findings(Burgess et al., 2019). Unless otherwise noted, we report IVW effect estimates as the primary result. Statistical analyses and graphical representations were primarily conducted using TwoSampleMR and MRPRESSO package (R version 4.4.1, http://www.r-project.org). MR analysis results were subjected to FDR correction using the BH procedure, applied separately to each analytical method (IVW, MR-Egger, and weighted median).

2.4. Colocalization and PLACO analysis

Colocalization analyses were performed separately for ADHD and each of the thirteen ocular disorders using their original GWAS datasets. In this study, we employed colocalization followed by MR as a test for horizontal pleiotropy, thereby strengthening the validity of MR findings by confirming shared causal variants. The SNPs significantly associated ($p < 5 \times 10^{-8}$) with ADHD and LD-independent ($r^2 > 0.001$; window of 10,000 kb) were selected. For each SNP, a region extending 500,000 base pairs upstream and downstream was defined as the range for colocalization analysis. A SNP was considered to colocalize if the posterior probability that the two traits share a causal SNP (PP·H4) exceeded 85 % using the COLOC package.

PLACO analyses between ADHD and ocular disorders were conducted separately using GWAS summary statistics. After removing SNPs with allele mismatches between datasets, we harmonized effect alleles across traits to enable joint analysis of *Z*-scores (beta/se) using PLACO (Ray and Chatterjee, 2020). Genome-wide significant pleiotropic SNPs (P of PLACO $<5 \times 10^{-8}$) were subsequently clustered into independent loci ($r^2 > 0.2$; window of 500 kb) via FUMA's SNP2GENE function (Watanabe et al., 2017).

3. Result

3.1. Genetic correlation between ADHD and ocular disorders

Among the thirteen ocular disorders, ADHD showed genetic correlation with corneal ulcer ($r_g = 0.31$, FDR adjusted $P = 1.51 \times 10^{-4}$), keratitis ($r_g = 0.30$, $P = 2.05 \times 10^{-5}$), blepharochalasis ($r_g = 0.20$, $P = 3.84 \times 10^{-6}$), disorders of lacrimal system ($r_g = 0.18$, $P = 2.87 \times 10^{-3}$), senile cataract ($r_g = 0.11$, $P = 1.44 \times 10^{-2}$), retinal vascular occlusion ($r_g = 0.20$, $P = 3.53 \times 10^{-2}$), and AMD ($r_g = 0.10$, $P = 3.53 \times 10^{-2}$) (Table 1, Fig. 1).

Table 1
LDSC results between ADHD and thirteen ocular disorders.

Ocular disorders	rg with ADHD	SE of rg	P value	FDR adjusted P
Amblyopia	0.5466	0.2585	3.45×10^{-2}	5.17×10^{-2}
Anisometropia	0.1639	0.2609	5.30×10^{-1}	5.30×10^{-1}
Strabismus	0.1494	0.0666	2.49×10^{-2}	5.17×10^{-2}
Corneal ulcer	0.3129	0.0799	9.05×10^{-5}	1.51×10^{-4}
Keratitis	0.3003	0.0673	8.21×10^{-6}	2.05×10^{-5}
Blepharochalasis	0.1986	0.0402	7.69×10^{-7}	3.84×10^{-6}
Disorders of lacrimal system	0.1816	0.0597	2.30×10^{-3}	2.87×10^{-3}
Allergic conjunctivitis	−0.0202	0.0401	6.20×10^{-1}	6.20×10^{-1}
Glaucoma	−0.0155	0.0322	6.40×10^{-1}	6.91×10^{-1}
Senile cataract	0.108	0.0362	2.88×10^{-3}	1.44×10^{-2}
Retinal vascular occlusion	0.2038	0.0863	1.82×10^{-2}	3.53×10^{-2}
Retinal detachments and breaks	0.0226	0.0568	6.91×10^{-1}	6.91×10^{-1}
AMD	0.0983	0.0427	2.12×10^{-2}	3.53×10^{-2}

Abbreviations: rg, genetic correlation; ADHD, attention-deficit hyperactivity disorder; AMD, age-related macular degeneration.

3.2. Bidirectional MR between ADHD and ocular disorders

Using 26 SNPs (Table 2) as genetic instruments from ADHD GWAS data, the result showed liability to ADHD increased the risk of corneal ulcer (IVW, OR = 1.18, 95 % CI: 1.05–1.33, FDR adjusted $P = 0.01$), keratitis (IVW, OR = 1.13, 95 % CI: 1.04–1.23, $P = 0.007$), blepharochalasis (IVW, OR = 1.23, 95 % CI: 1.12–1.36, $P = 0.002$), and disorders of lacrimal system (IVW, OR = 1.09, 95 % CI: 1.01–1.18, $P = 0.04$) (Table 3, Figs. 2 & 3). These results were not influenced by heterogeneity (IVW derived Cochran's Q statistic test, $P > 0.05$) or horizontal pleiotropy (MR Egger intercept test, $P > 0.05$), and remained stable in leave-one-out analysis (SFigure 1, Supplementary file 1).

Liability to ADHD was causally associated with a lower risk of glaucoma (IVW, OR = 0.92, 95 % CI: 0.86–0.98, FDR adjusted $P = 0.05$). Specifically, ADHD showed a negative causal relationship with primary open-angle glaucoma (IVW, OR = 0.83, 95 % CI: 0.75–0.94, $P = 0.003$), exfoliation glaucoma (IVW, OR = 0.71, 95 % CI: 0.59–0.85, $P = 0.001$), and normotensive glaucoma (IVW, OR = 0.79, 95 % CI: 0.63–0.97, $P = 0.02$), but not for primary angle-closure glaucoma and unspecified glaucoma (Table 4, Fig. 4). These causalities were robust in the Cochran's Q test ($P > 0.05$), the MR-Egger intercept test ($P > 0.05$), and leave-one-out analyses (SFigure 2, Supplementary file 1).

In the reverse MR analysis, liability to strabismus was causally associated with an increased risk of ADHD (IVW, OR = 1.06, 95 % CI: 1.01–1.13, $P = 0.03$), The causal estimates remained broadly consistent in MR-Egger method (OR = 1.20, 95 % CI: 1.06–1.35, P = 0.01) and weighted median method (OR = 1.09, 95 % CI: 1.00–1.18, P = 0.04). No other significant causality was observed from ocular diseases to ADHD (STable 1, Supplementary file 1).

3.3. Colocalization and PLACO analysis between ADHD and ocular disorders

Colocalization analysis showed no PP·H4 exceeded 85 % between ADHD and any of the thirteen ocular disorders, while near-threshold values were observed: rs9969232 showed PP·H4 of 84.8 % between ADHD and blepharochalasis, and rs17576773 showed PP·H4 of 84.4 % between ADHD and AMD (Supplementary file 2).

PLACO analysis revealed pleiotropic loci between ADHD and ocular disorders: two loci each for corneal ulcer (lead SNPs rs10933170, rs4636654), keratitis (rs10933170, rs8090577), and blepharochalasis (rs3255501, rs7794413); three loci for lacrimal system disorders (rs7721104, rs7458242, rs1956235); thirteen for glaucoma; and two for strabismus. Pleiotropic loci also identified between ADHD and allergic conjunctivitis, senile cataract, as well as AMD (Supplementary File 2).

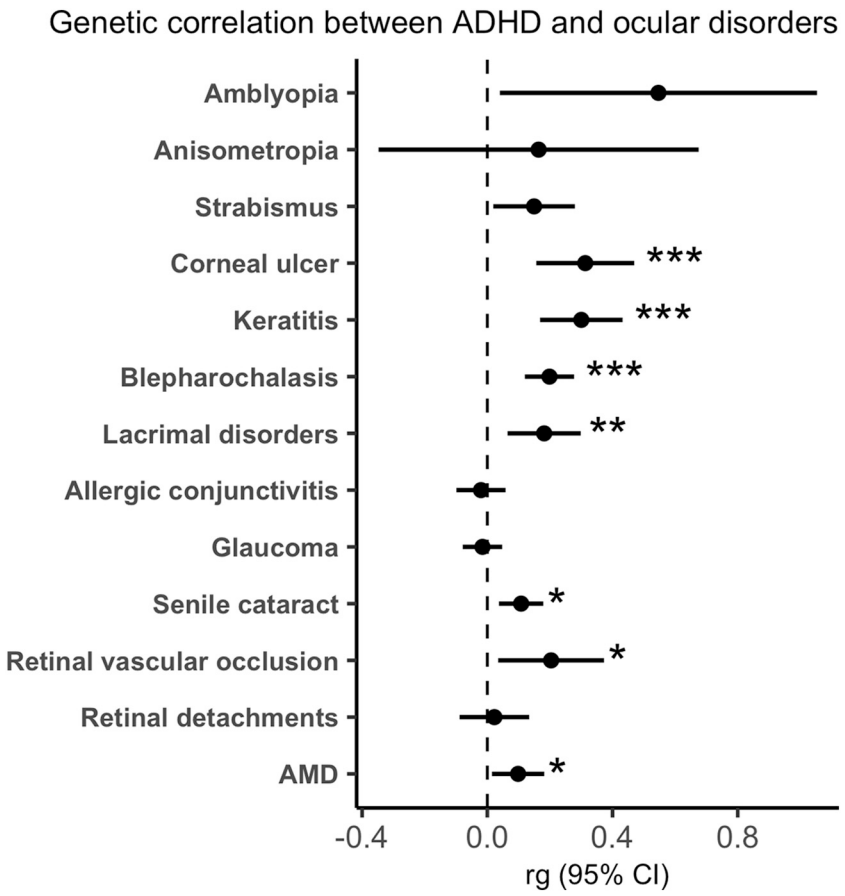

Fig. 1. Genetic correlation between ADHD and corneal disorders.

Table 2
Results for the 26 instrumental variables from ADHD genome-wide association study.

SNP ID	Chr	Position (GRCh38)	Effect allele	Other allele	Effect allele frequency	Beta	SE	P value	F statistic
rs549845	1	43,610,798	G	A	0.33	0.08	0.01	9.03×10^{-15}	60
rs4916723	5	88,558,577	A	C	0.57	−0.09	0.01	9.48×10^{-15}	60
rs2582895	11	28,580,626	C	A	0.62	0.07	0.01	4.09×10^{-14}	57
rs77960	5	104,628,884	G	A	0.68	−0.07	0.01	2.46×10^{-13}	54
rs6082363	20	21,270,205	T	C	0.29	0.07	0.01	4.38×10^{-12}	48
rs9969232	7	114,518,899	G	A	0.38	−0.07	0.01	9.98×10^{-12}	47
rs17576773	4	111,296,367	C	T	0.88	0.10	0.02	1.63×10^{-10}	41
rs114142727	3	86,965,992	C	G	0.99	0.25	0.04	5.13×10^{-10}	39
rs2886697	3	20,682,712	G	A	0.64	0.06	0.01	7.90×10^{-10}	38
rs76284431	14	98,224,586	T	A	0.84	−0.08	0.01	1.19×10^{-9}	37
rs1162202	16	61,932,799	C	T	0.61	0.06	0.01	1.92×10^{-9}	36
rs704061	12	89,378,126	T	C	0.56	−0.06	0.01	2.30×10^{-9}	35
rs17718444	3	71,450,250	C	T	0.67	0.06	0.01	2.87×10^{-9}	35
rs2025286	6	70,148,809	A	C	0.55	−0.05	0.01	4.00×10^{-9}	35
rs1438898	2	144,956,787	A	C	0.77	0.06	0.01	4.88×10^{-9}	34
rs10875612	5	145,095,216	C	T	0.47	−0.05	0.01	5.62×10^{-9}	34
rs9877066	3	43,650,009	G	A	0.95	−0.12	0.02	6.60×10^{-9}	34
rs7844069	8	92,264,859	T	G	0.40	0.06	0.01	6.74×10^{-9}	34
rs4925811	8	144,577,063	T	G	0.53	−0.06	0.01	8.30×10^{-9}	33
rs76857496	18	5,871,801	C	A	0.86	0.08	0.01	1.24×10^{-8}	33
rs7506904	18	53,099,409	G	A	0.37	−0.06	0.01	1.24×10^{-8}	33
rs6537401	4	146,178,502	G	A	0.66	−0.06	0.01	1.40×10^{-8}	32
rs11596214	10	104,694,074	G	A	0.57	0.05	0.01	3.17×10^{-8}	31
rs7613360	3	49,879,277	C	T	0.61	−0.05	0.01	3.18×10^{-8}	30
rs73145587	7	68,220,767	A	T	0.90	0.10	0.02	3.67×10^{-8}	30
rs11255890	10	8,742,810	C	A	0.40	0.05	0.01	4.14×10^{-8}	30

Abbreviations: ADHD, attention-deficit hyperactivity disorders.

4. Discussion

This study systematically analyzed the genetic association and causality between ADHD and thirteen ocular disorders. LDSC indicated that ADHD is genetically corelated with corneal ulcer, keratitis, blepharochalasis, disorders of lacrimal system, senile cataract, retinal

Table 3
Mendelian randomization results of ADHD on ocular disorders[a].

	No. of SNPs	MR analysis			Heterogeneity test			MR-Egger intercept
		OR (95 % CI)	P	FDR adjusted P	Cochran's Q	I^2	P	P
ADHD on amblyopia								
IVW	20	1.19 (0.92–1.55)	0.18	0.30	13.82	0 %	0.79	–
MR-Egger	20	1.23 (0.50–3.01)	0.65	0.65	13.82	0 %	0.74	0.94
Weighted median	20	1.23 (0.86–1.76)	0.25	0.37	–	–	–	–
ADHD on anisometropia								
IVW	20	1.19 (0.88–1.61)	0.26	0.30	25.24	24.73 %	0.15	–
MR-Egger	20	1.80 (0.52–6.19)	0.36	0.65	24.60	26.84 %	0.14	0.50
Weighted median	20	1.31 (0.83–2.08)	0.24	0.37	–	–	–	–
ADHD on strabismus								
IVW	20	1.05 (0.95–1.17)	0.30	0.30	22.08	13.95 %	0.28	–
MR-Egger	20	1.14 (0.77–1.69)	0.52	0.65	21.88	17.74 %	0.24	0.69
Weighted median	20	1.07 (0.92–1.24)	0.37	0.37	–	–	–	–
ADHD on corneal ulcer								
IVW	20	1.18 (1.05–1.33)	0.006	0.01	11.55	0 %	0.90	–
MR-Egger	20	0.97 (0.64–1.46)	0.88	1.00	10.56	0 %	0.91	0.33
Weighted median	20	1.10 (0.93–1.29)	0.28	0.29	–	–	–	–
ADHD on keratitis								
IVW	20	1.13 (1.04–1.23)	0.003	0.007	15.42	0 %	0.69	–
MR-Egger	20	0.92 (0.69–1.23)	0.58	0.97	13.21	0 %	0.78	0.15
Weighted median	20	1.12 (1.00–1.25)	0.05	0.08	–	–	–	–
ADHD on blepharochalasis								
IVW	20	1.23 (1.12–1.36)	<0.001	0.002	29.07	34.64 %	0.06	–
MR-Egger	20	1.19 (0.77–1.83)	0.44	0.97	29.02	37.98 %	0.05	0.86
Weighted median	20	1.23 (1.06–1.41)	0.005	0.02	–	–	–	–
ADHD on disorders of lacrimal system								
IVW	20	1.09 (1.01–1.18)	0.03	0.04	19.89	4.47 %	0.40	–
MR-Egger	20	1.00 (0.75–1.32)	1.00	1.00	19.46	7.51 %	0.36	0.54
Weighted median	20	1.11 (1.00–1.24)	0.05	0.08	–	–	–	–
ADHD on Allergic conjunctivitis								
IVW	20	1.03 (0.93–1.14)	0.59	0.59	53.11	64.22 %	<0.001	–
MR-Egger	20	1.22 (0.84–1.76)	0.31	0.97	50.63	64.46 %	<0.001	0.36
Weighted median	20	1.06 (0.95–1.18)	0.29	0.29	–	–	–	–
ADHD on glaucoma								
IVW	17	0.90 (0.84–0.98)	0.01	0.05	18.57	13.84 %	0.29	–
MR-Egger	17	0.82 (0.63–1.07)	0.16	0.62	17.82	15.83 %	0.27	0.44
Weighted median	17	0.86 (0.78–0.96)	0.007	0.03	–	–	–	–
ADHD on senile cataract								
IVW	19	1.05 (0.97–1.13)	0.23	0.29	40.95	56.05 %	0.001	–
MR-Egger	19	1.03 (0.79–1.34)	0.85	0.85	40.90	58.43 %	<0.001	0.88
Weighted median	19	1.03 (0.95–1.12)	0.44	0.72	–	–	–	–
ADHD on retinal vascular occlusion								
IVW	24	1.14 (0.99–1.31)	0.07	0.12	15.92	0 %	0.86	–
MR-Egger	24	0.74 (0.44–1.23)	0.25	0.62	12.93	0 %	0.93	0.10
Weighted median	24	1.08 (0.89–1.32)	0.43	0.72	–	–	–	–
ADHD on retinal detachments and breaks								
IVW	24	1.07 (0.99–1.16)	0.07	0.12	35.55	35.30	0.05	–
MR-Egger	24	0.89 (0.62–1.26)	0.51	0.84	33.64	34.61	0.05	0.28
Weighted median	24	1.02 (0.91–1.15)	0.72	0.72	–	–	–	–
ADHD on AMD								
IVW	19	1.02 (0.92–1.13)	0.66	0.66	32.98	45.42 %	0.02	–
MR-Egger	19	1.08 (0.76–1.53)	0.67	0.84	32.79	48.15 %	0.01	0.76
Weighted median	19	1.03 (0.92–1.16)	0.58	0.72	–	–	–	–

Abbreviations: MR, Mendelian Randomization; ADHD, attention-deficit hyperactivity disorder; AMD, age-related macular degeneration; IVW, inverse variance weighted.

[a] Results from two-sample MR analysis, estimated associations reported as odds ratio (OR) of ocular disorders per unit increase in log odds of ADHD.

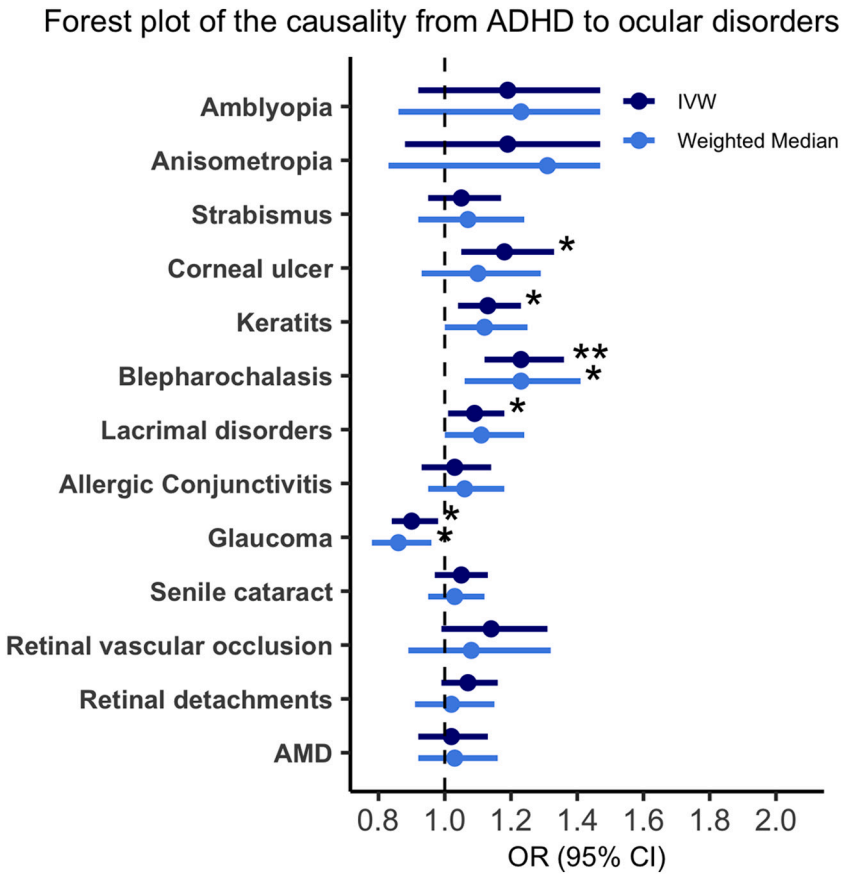

Fig. 2. Forest plot of the causality from ADHD to ocular disorders.

vascular occlusion, and AMD. MR showed the liability to ADHD increases the risk of corneal ulcer, keratitis, blepharochalasis, and disorders of lacrimal system, while lowering the risk of glaucoma. Conversely, the liability to strabismus was causally associated with an increased risk of ADHD. The absence of colocalization further supports the MR results were not confounded by horizontal pleiotropy. While the identification of pleiotropic loci using PLACO suggests that genetic factors play a role in the association between ADHD and ocular diseases.

This study is the first to reveal that ADHD is causally associated with corneal ulcer, keratitis, blepharochalasis, and disorders of lacrimal system. While MR can ascertain the sequence from exposure to outcome, it does not distinguish whether the underlying mechanism is genetic or environmental. Given the significant genetic correlations and pleiotropic loci observed, we hypothesize that part of the causality is derived from genetic pathways. Studies have reported immunological dysregulation in ADHD, prompting interest in the role of atopy and allergic immunopathology(Özyurt et al., 2018; Verlaet et al., 2014; Wang et al., 2022). ADHD has a high comorbidity with both Th1-mediated disorders (stomach aches and ear infections) (Stevens et al., 1995) and Th2-mediated disorders (eczema, asthma, and rhinitis) (Fasmer et al., 2011; Schmitt et al., 2009). Our result of pleiotropic loci between ADHD and allergic conjunctivitis consistent with the above research. Therefore, future studies are needed to elucidate the genetic pathways linking ADHD to corneal disease, blepharochalasis, lacrimal system disorders and allgergic conjunctivitis.

Another interesting finding is that ADHD is causally associated with a reduced risk of glaucoma, including primary open-angle glaucoma, exfoliation glaucoma, and normotensive glaucoma, but not with primary angle-closure glaucoma. Thirteen pleiotropic loci were mapped between ADHD and glaucoma, while no genetic correlation was found in this study. These apparently discordant results are biologically plausible as LDSC captures net genome-wide correlation (which can be neutralized by counterbalancing effects) (Werme et al., 2022), whereas MR and PLACO analysis detect specific causal pathways and localized shared mechanisms respectively. The findings suggest ADHD-related variants may influence glaucoma risk through targeted biological processes rather than overall genetic overlap. Further studies are warranted on this topic. Additionally, we hypothesize environmental factors may play a role in this causality. ADHD is primarily characterized by hyperactivity, which often results in more physical activity compared to the general population. A study of male runners found that rigorous physical activity reduced the risk of glaucoma, particularly for those with faster performance and longer running distances(Williams, 2009). Another study reported that among patients with glaucoma or suspected glaucoma, those who engaged in more physical activity had significantly slower rates of visual field progression(Lee et al., 2019). Given that primary angle-closure glaucoma is due to abnormal structure of anterior chamber, it seems reasonable that hyperactivity traits cannot help.

Considering studies have reported a higher odds ratio of amblyopia, anisometropia, and strabismus in patients with autism spectrum disorders (ASD) (Milne et al., 2009; Perna et al., 2023; Reynolds and Culican, 2023; Wang et al., 2018), and given the high comorbidity between ASD and ADHD(Hours et al., 2022), any SNPs associated with ASD were excluded from the MR analysis between ADHD and these three ocular disorders. The liability to ADHD was associated with a higher risk of amblyopia, anisometropia, and strabismus, although this did not reach

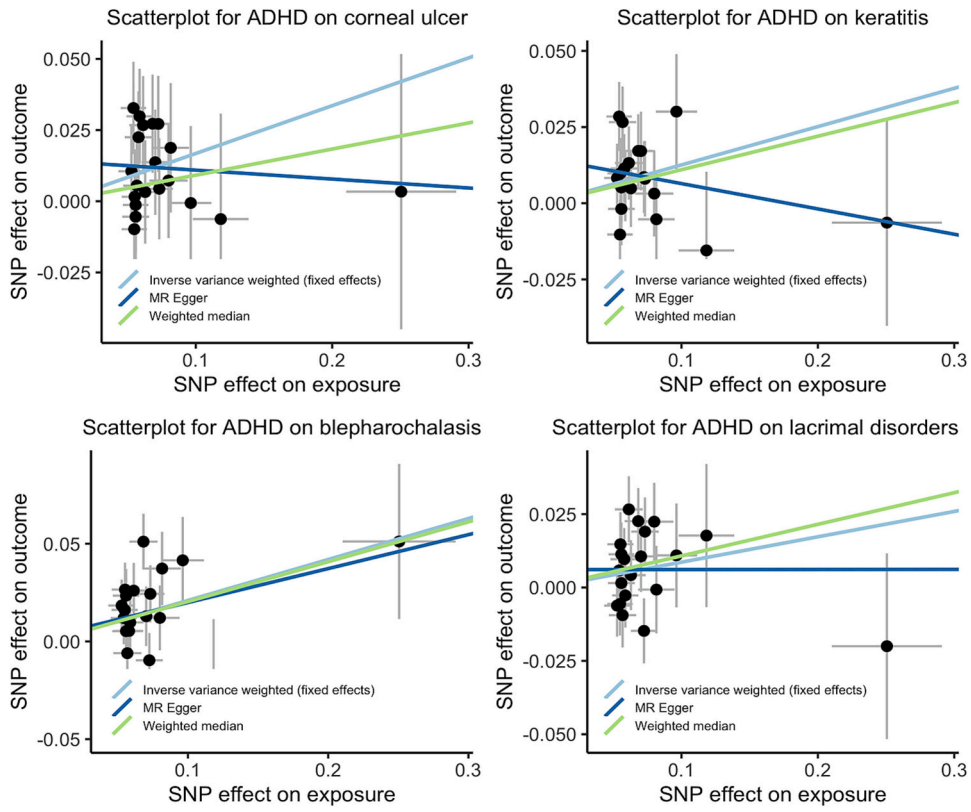

Fig. 3. Scatter plot of MR from ADHD to ocular disorders.

Table 4
Mendelian randomization results of ADHD on the subtypes of glaucoma[a].

	No. of SNPs	MR analysis			Heterogeneity test			MR-Egger intercept
		OR (95%CI)	P	FDR adjusted P	Cochran's Q	I^2	P	P
ADHD on primary open-angle glaucoma								
IVW	17	0.84 (0.75–0.94)	0.002	0.003	14.44	0 %	0.56	–
MR-Egger	17	0.78 (0.54–1.14)	0.23	0.54	14.32	0 %	0.50	0.72
Weighted median	17	0.79 (0.67–0.93)	0.002	0.006	–	–	–	–
ADHD on exfoliation glaucoma								
IVW	17	0.71 (0.60–0.85)	<0.001	0.001	15.25	0 %	0.51	–
MR-Egger	17	1.21 (0.66–2.19)	0.54	0.54	11.96	0 %	0.68	0.09
Weighted median	17	0.70 (0.54–0.90)	0.005	0.007	–	–	–	–
ADHD on normotensive glaucoma								
IVW	17	0.78 (0.63–0.97)	0.02	0.02	21.59	25.89 %	0.16	–
MR-Egger	17	0.76 (0.33–1.78)	0.54	0.54	21.58	30.50 %	0.12	0.95
Weighted median	17	0.76 (0.56–1.03)	0.08	0.08	–	–	–	–
ADHD on primary angle-closure glaucoma								
IVW	17	0.95 (0.71–1.27)	0.75	0.75	10.45	0 %	0.84	–
MR-Egger	17	0.83 (0.32–2.17)	0.71	0.71	10.36	0 %	0.80	0.77
Weighted median	17	0.82 (0.55–1.22)	0.33	0.33	–	–	–	–
ADHD on other and unspecified glaucoma								
IVW	17	0.98 (0.78–1.23)	0.84	0.84	12.37	0 %	0.72	–
MR-Egger	17	0.88 (0.41–1.88)	0.75	0.75	12.29	0 %	0.66	0.78
Weighted median	17	0.98 (0.71–1.36)	0.92	0.92	–	–	–	–

[a] Results from two-sample MR analysis, estimated associations reported as odds ratio (OR) of ocular disorders per unit increase in log odds of ADHD.

the criteria for significance. In the reverse MR, the liability of strabismus was linked to higher risk of ADHD. Previous studies reported a higher risk of amblyopia and visual disturbances in ADHD patients(Grönlund et al., 2007; Ho et al., 2020) and a higher risk of ADHD in children with amblyopia(Kim et al., 2022; Su et al., 2019). These ocular disorders are often contextualized within the top-down and executive dysfunction frameworks of ADHD(Feifel et al., 2004; Maron et al., 2021; Sowell et al., 2003). Additionally, since attentional and ocular motor networks

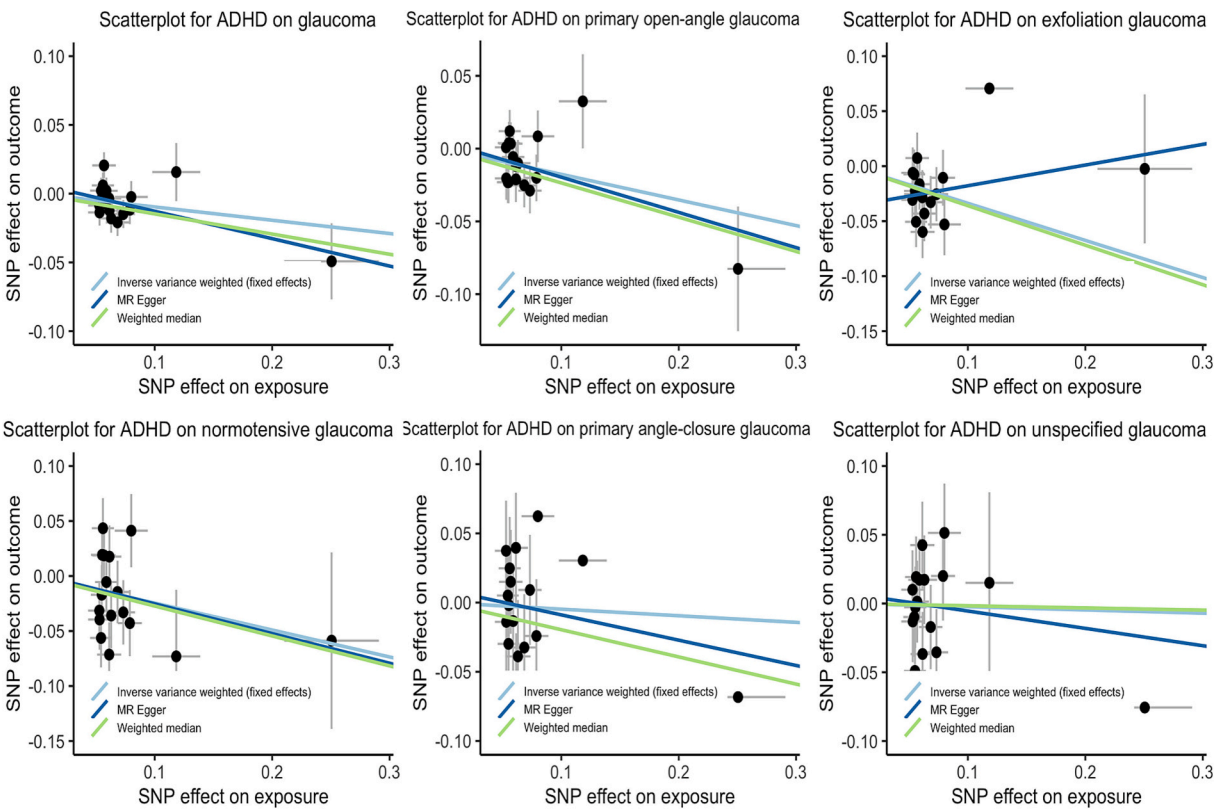

Fig. 4. Scatter plot of MR from ADHD to glaucoma and its subtypes.

in the brain are closely linked(Beauchamp et al., 2001; Nobre et al., 2000), dysfunctions in saccadic control might be associated with visual attentional deficits, directly connecting to anisometropia and amblyopia (Black et al., 2021).

The strength of this study lies in its pioneering exploration of the genetic associations and causal relationships between ADHD and thirteen ocular disorders that have a higher prevalence among adults. There are several limitations to this study. Firstly, the GWAS data used primarily comprise adults, with a notable lack of data on children and adolescents. Given the high prevalence rates of ADHD in paediatric populations, future research should prioritize these groups. Secondly, the high rate of comorbidity between ADHD and other psychiatric disorders forms an intricate network, making it challenging to isolate and interpret the causality between a single psychiatric condition and ocular disturbances. Thirdly, it is important to acknowledge that all current MR methods are approximations when applied to binary outcomes. While our data showed no evidence of effect, this does not necessarily indicate the absence of a causal effect. Lastly, the analyses were conducted using GWAS data from individuals of European descent, which may limit the generalizability of our findings to other populations.

In conclusion, this study reported the liability to ADHD increases the risk of developing corneal ulcer, keratitis, blepharochalasis and disorders of lacrimal system, while it appears to lower the risk of glaucoma. Conversely, the liability to strabismus is causally associated with an increased risk of ADHD. Pleiotropic loci were identified between ADHD and the aforementioned ocular diseases. These findings offer valuable insights into the underlying mechanisms and reciprocal etiology between ADHD and ocular disorders, potentially guiding the development of improved diagnostic and treatment measures for these conditions.

CRediT authorship contribution statement

Xiu Nian Chen: Writing – original draft, Methodology, Conceptualization. **Yuzhou Zhang:** Methodology, Data curation. **Ka Wai Kam:** Writing – review & editing, Conceptualization. **Sunny Chi Lik Au:** Writing – review & editing, Conceptualization. **Xiu Juan Zhang:** Writing – review & editing, Conceptualization. **Mandy P.H. Ng:** Writing – review & editing, Conceptualization. **Wilson W. Yip:** Writing – review & editing, Methodology. **Patrick Ip:** Writing – review & editing, Methodology. **Ian C.K. Wong:** Writing – review & editing, Methodology. **Alvin L. Young:** Writing – review & editing, Methodology. **Chi Pui Pang:** Supervision. **Clement C. Tham:** Supervision. **Li Jia Chen:** Writing – review & editing, Funding acquisition, Supervision. **Jason C. Yam:** Writing – review & editing, Supervision, Funding acquisition.

Consent to publish

Not applicable.

Ethics approval and consent to participate

GWAS data used in this study were derived from PGC and FinnGen. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol (HUS/990/2017). The PGC is committed to an open source philosophy while keeping within the limits of national laws and ethical review restrictions.

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Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

NA

Data available

No data is publicly available from other sources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119422.

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