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Deciphering the gut–eye axis: evidence from observational and genetic analyses linking inflammatory bowel disease with ocular disorders

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Abstract

Ocular comorbidities in inflammatory bowel disease (IBD) have gained increasing attention, with the gut–eye axis hypothesized as a potential biological bridge. However, the genetic architecture and underlying mechanisms remain underexplored. In this study, we integrated longitudinal cohort data from the UK Biobank with genome-wide summary statistics to systematically decode these associations. Observational analyses revealed that IBD, including the subtypes of Crohn's disease (CD) and ulcerative colitis (UC), significantly elevated the risks of multiple ocular comorbidities, specifically uveitis, cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR). Mediation analyses further demonstrated that these risks were partially explained by systemic inflammatory biomarkers. Genetically, we identified significant global and local genetic correlations between IBD and various ocular comorbidities. A cross-trait meta-analysis pinpointed 49 novel pleiotropic variants within ρ-heritability estimation from summary statistics (HESS) significant regions, highlighting shared pathways in immune regulation. Finally, two-sample Mendelian randomization established robust causal relationships between IBD (or its subtypes) and uveitis and AMD. Our findings elucidated a shared genomic foundation and identified systemic inflammation as a contributing link within the gut–eye axis. These results provided novel insights into the co-pathogenesis of intestinal and ocular comorbidities, suggesting that early ophthalmic screening and targeted immunomodulatory strategies are essential for the comprehensive management of IBD patients.

Keywords: Inflammatory bowel disease, Ocular comorbidity, Systemic inflammation, Shared genetics, Gut-eye axis, Phenotypic association, Genetic correlation

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Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is primarily characterized as a chronic and relapsing gastrointestinal inflammatory disorder. As a burgeoning global health challenge, it imposes a profound socioeconomic burden, affecting over 6 million individuals worldwide[1]. Although it is predominantly localized in the gut, IBD is increasingly conceptualized as a multisystemic disorder accompanied by diverse extraintestinal manifestations (EIMs)[2,3]. According to the European Crohn's and Colitis Organization, over 50% of IBD patients will develop at least one concomitant EIM during the clinical course[4]. These systemic involvements span a broad clinical spectrum, encompassing musculoskeletal, mucocutaneous, cardiovascular, and ophthalmic complications[2]. Of note, ocular comorbidities represent the third most prevalent EIM, with an estimated prevalence ranging from 4% to 12%[5]. Although rarely life-threatening, these ophthalmic conditions might inflict severe damage on the patients' quality of life, possibly culminating in devastating visual impairment or even irreversible blindness.

Despite their clinical significance, the pathophysiology underlying ocular EIMs in IBD remains enigmatic, likely representing a multifaceted interplay of biological drivers. Conventional wisdom has it that ocular comorbidities may either represent an intrinsic manifestation of IBD itself or emerge as an iatrogenic sequela secondary to medications[6]. Against this backdrop, the gut–eye axis has been proposed as a pivotal framework to decipher the distal organ cross-talk between the intestinal environment and ocular homeostasis[7]. This theory posits a bidirectional communication network wherein the gut microbiota (GM) and their metabolites modulate ocular health via integrated immunological, metabolic, and neuronal pathways[8,9]. Although an emerging body of evidence has linked gut dysbiosis to a range of ophthalmic conditions[10,11], such as uveitis, diabetic retinopathy (DR), and age-related macular degeneration (AMD), the fundamental mechanisms remain to be fully elucidated. Building upon the conceptual scaffolding of the gut–eye axis, a shared genetic architecture might underpin the connections between IBD and ocular comorbidities.

However, rigorously quantifying these associations and their causal directions remains an outstanding challenge. Though previous observational studies have underscored the epidemiological link between IBD and ocular disorders, these investigations are often restricted to a single ophthalmic condition and constrained by cross-sectional designs[12,13]. Furthermore, the observed phenotypic

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associations are inherently susceptible to biases, residual confounding, and reverse causality. These limitations, compounded by the scarcity of large-scale cohorts and comprehensive covariate data, also further hinder the precise quantification of effects. Apart from observational evidence, recent Mendelian randomization (MR) analyses have indicated the potential causal links between IBD and some ocular diseases[14,15]. Concurrently, previous genomewide association studies (GWAS) have successfully identified a multitude of genetic risk loci related to IBD and various eye diseases[16,17]. Nevertheless, these advancements in biological insights have yet to be translated into clinically actionable interventions. Crucially, the shared genetic architecture—the intricate landscape of pleiotropy and the common biological pathways—underlying the co-occurrence of IBD and ocular conditions remains largely underexplored.

In this study, we used a multidimensional approach to evaluate the association between IBD and an array of ophthalmic disorders. By integrating observational data with shared genetic architecture and MR analyses, we sought to define the shared etiology and causal links underlying these comorbidities within the gut–eye axis, so as to provide a robust framework for targeted clinical surveillance and management.

Materials and methods

Study design

We first evaluated the longitudinal associations between IBD and a spectrum of ocular disorders within the UK Biobank (UKB) cohort. Subsequently, utilizing summary-level data from large-scale GWAS, we estimated both global and local genetic correlations between IBD and ophthalmic phenotypes to delineate their shared genetic architecture. To identify specific pleiotropic loci, a cross-trait meta-analysis was performed. Finally, two-sample MR analyses were conducted to infer the potential causal effects of a genetic liability for IBD on ocular health.

UK Biobank data

Study population

The UK Biobank is an ongoing, population-based prospective cohort study that recruited over 500,000 subjects in the United Kingdom between 2006 and 2010[18]. Following the provision of informed consent, all participants proceeded to a baseline assessment that involved detailed questionnaires, physical measurements, and biosample collection. The research was executed with ethical approval granted by the North West Multi-Center Research Ethics Committee (11/NW/0382). We excluded individuals with IBD diagnosed after the baseline (n = 3,320) and those with baseline ocular diseases, establishing the final analytical cohort for the longitudinal study (Fig. 1). The UK Biobank application number for this study is 73595.

Ascertainment of exposure

We set IBD and its subtypes as the exposure. Baseline diagnoses of IBD were established by integrating records from self-reports, primary care, and hospital admissions in accordance with the International Classification of Diseases coding system (ICD-9 and ICD-10) (detailed in Supplementary Table S1). When determining the event date, the initial diagnosis was adopted for individuals with multiple

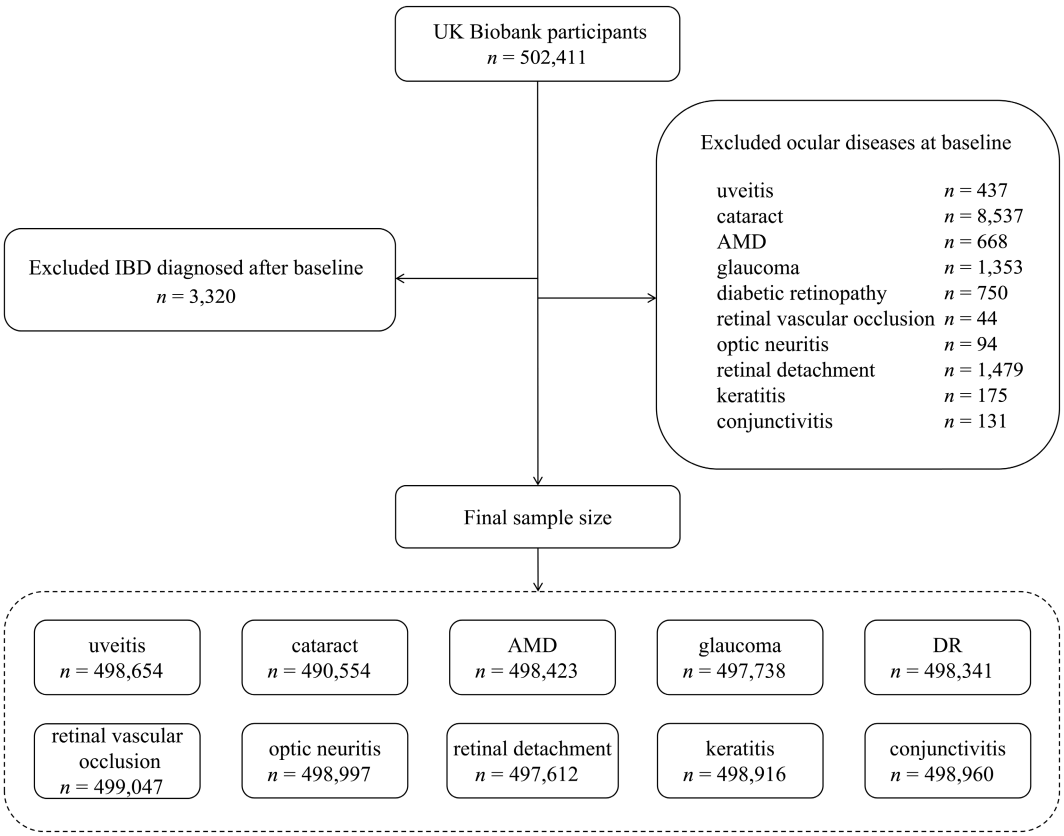

Fig. 1 Study flow charts of the UK Biobank cohort study. IBD, inflammatory bowel disease; AMD, age-related macular degeneration; DR, diabetic retinopathy.

records. For the purpose of subtype confirmation, the latest available diagnosis was utilized to distinguish between CD and UC. Subjects not designated to a specific subtype were retained in the IBD cohort without contributing to subsequent subtype-specific analyses.

Ascertainment of outcomes

To select ocular outcomes, we first defined a candidate panel of ocular diseases with potential immune, vascular, or age-related links to systemic inflammation on the basis of clinical knowledge and previous literature, and retained only those with at least five incident cases. We included diverse ocular outcomes in the UK Biobank to seek out their comorbidity relationships with IBD, among which significant associations were observed for uveitis, cataracts, AMD, glaucoma, and diabetic retinopathy. The confirmation of ocular disorders was coded according to ICD-9 and ICD-10 (Supplementary Table S2). The duration of follow-up for each outcome was determined from enrollment in the UK Biobank until the first record of ocular disorders, death, loss to follow-up, or end of follow-up (1 April 2024), whichever came first.

Covariates and mediators

The following were regarded as covariates: Age at recruitment, sex, ethnicity, educational level, Townsend Deprivation Index (TDI), physical activity, smoking status, alcohol consumption, body mass index (BMI), use of IBD-related medications (including nonsteroidal anti-inflammatory drugs, aminosalicylates, corticosteroids, and immunomodulators), diabetes, and hypertension. A touchscreen questionnaire captured self-reported data on age at enrollment, sex, and ethnicity (White or non-White). Educational achievement was dichotomized according to the possession of a university or college degree. Socioeconomic status was evaluated using the TDI, an area-level metric derived from national census data that was linked to participants' residential postcodes. Participants were stratified into low, middle, and high TDI groups according to the tertiles of the index. Smoking and alcohol status were categorized into never, previous, and current. Physical activity data gathered via touchscreen questionnaires were appraised as adequate or inadequate according to the recommendations of the American Heart Association[19]. The adequate threshold was defined as fulfilling any of the following weekly criteria: ≥ 150 min of moderate-intensity activity, ≥ 75 min of vigorous-intensity activity, ≥ 5 d of moderate-intensity activity, or ≥ 1 d of vigorous-intensity activity. BMI was derived using height and weight measurements at the baseline UK Biobank assessment. IBD-associated medication information was acquired from baseline touchscreen questionnaires and verbal interviews. Baseline diabetes and hypertension states were defined using ICD-10 codes. Missing values in continuous covariates were imputed with the median, whereas those in categorical covariates were imputed with the mode. The percentage of missing data for covariates remained below 3%.

Referring to previous literature, we identified 15 parameters associated with potential inflammatory response processes as mediating variables[20], including counts of basophils, eosinophils, lymphocytes, monocytes, white blood cells (WBCs), neutrophils, and platelets; level of C-reactive protein (CRP); neutrophil percentage; lymphocyte percentage; monocyte percentage; neutrophil-to-leukocyte ratio; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; and erythrocyte distribution width (RDW). This panel was chosen because it collectively serves as a robust proxy for the overall systemic immune–inflammatory burden.

More detailed definitions are provided in Supplementary Table S3.

GWAS summary-level data

Comprehensive details regarding the genome-wide association study (GWAS) summary statistics utilized in this work were cataloged in Supplementary Table S4. To investigate the genetic architecture of IBD and its subtypes, we acquired summary-level data for IBD (n = 500,348) and UC (n = 499,380) from the FinnGen Research Project (Release 12; available at https://r12.finngen.fi/). Genetic data for CD were retrieved via the integrative epidemiology unit (IEU) OpenGWAS project[21], encompassing a cohort of 20,883 individuals. The ophthalmic phenotypes examined herein comprised five distinct ocular comorbidities, namely uveitis, cataract, AMD, glaucoma and DR. Summary statistics for uveitis (n = 483,053), cataracts (n = 157,296), and DR (n = 96,429) were similarly sourced from the FinnGen R12 repository. For AMD and glaucoma[22], we extracted summary data from the GWAS Catalog, representing populations of 426,887 and 430,721 participants, respectively. To ensure the integrity of subsequent analyses, all datasets underwent a stringent harmonizing and filtering pipeline. We excluded single-nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) below 1%, as well as variants with missing or ambiguous reference SNP ID number (rsID) identifiers. All genomic coordinates were standardized to (or transformed into) the GRCh37 (hg19) reference assembly. To minimize bias from population stratification, the study was restricted to cohorts of European ancestry, all of whom had previously undergone rigorous quality control protocols.

Statistical analysis

Prospective cohort study

In descriptive analyses, continuous variables are summarized as mean ± standard error or the median and interquartile range, whereas categorical variables are presented as frequencies and percentages. We used the Cox proportional hazard regression model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between IBD and the risk of incident eye diseases. Two separate models were built for adjustment: Model 1 (minimally adjusted) controlled for age and sex; Model 2 (comprehensively adjusted) included all covariates. For the DR analyses, however, baseline diabetes was excluded from the covariates in Model 2 because of its role as a pathway mediator rather than a true confounder. The proportional hazard assumption was examined using Schoenfeld's residuals[23]. In addition, subgroup analyses were performed to assess the interaction effects of sex, age, ethnicity, history of EIMs (including musculoskeletal, mucocutaneous, hepatobiliary, and any nonocular condition), and Vitamin D levels.

Furthermore, we carried out a series of sensitivity analyses to evaluate the robustness of our findings. To mitigate potential reverse causality, we repeated the Cox models by successively excluding individuals who developed eye diseases within the first 2 years and the initial 4 years. To reduce bias caused by potential confounders, we also implemented propensity score matching (PSM) at a 1:2 ratio to match each IBD subject with non-IBD subjects.

Following the identification of significant associations in the primary Cox models, we continued mediation analyses using the 'bruceR' R package via a nonparametric bootstrapping approach to uncover the mediating role of inflammatory status. A preliminary screening phase was conducted using fully adjusted multivariable linear regression models to identify potential biomarkers associated with IBD, UC, or CD status. Only those retaining statistical significance were designated as mediators for the subsequent mediation analyses. Fully adjusted logistic regression models or linear

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regression were applied to estimate associations across pathways. The proportion of mediation was computed as the ratio of the indirect effect to the total effect. The aforementioned analyses were executed using R software (version 4.3.3). A two-sided *p*-value of 0.05 or lower was taken as statistically significant.

Global and local genetic correlation analyses

To investigate the shared genetic underpinnings between IBD and ophthalmic conditions, we then estimated global genetic correlations using linkage disequilibrium score regression (LDSC)[24]. Our analyses leveraged precomputed linkage disequilibrium (LD) scores derived from HapMap3 SNPs, using the European ancestry subset of the 1,000 Genomes Project serving as the reference panel. To ensure the data's integrity and compatibility with the reference panel, we discarded mismatched variants as part of our standard quality control pipeline. By integrating GWAS summary statistics with these population-specific LD scores, the LDSC framework was applied to simultaneously estimate SNP-based heritability (h^2_{SNP}) for individual traits and quantify genetic correlations (r_g) between trait pairs. A conservative Bonferroni-corrected threshold of $p < 3.33 \times 10^{-3}$ (0.05/15) was set for statistical significance, thereby accounting for multiple testing across the 30 distinct trait pairs examined.

Having established the global genetic profiles, we next sought to dissect these relationships at a finer genomic resolution. This was achieved by using heritability estimation from summary statistics (ρ-HESS)[25] to investigate local genetic correlations between IBD and its related ophthalmic conditions. In contrast to the genome-wide perspective of LDSC, heritability estimation from summary statistics (ρ-heritability estimation from summary statistics [HESS]) quantifies trait correlations attributable to genetic variation within discrete, approximately independent LD blocks (derived from the 1,000 Genomes Project's European reference panel, hg19 build). Specifically, the ρ-HESS framework provides methodological rigor by virtue of its capacity to operate exclusively on summary-level data without requiring distributional assumptions for causal variants, while explicitly accounting for LD and sample overlap. This approach estimates local SNP-based heritability and genetic covariance for each predefined region, deriving the local genetic correlation estimates as their standardized ratio. Statistical significance was assessed using Bonferroni correction, with the threshold set at $p < 0.05/n$, where n represents the total number of independent regions tested[25].

Cross-trait meta-analyses

To elucidate shared genetic architectures and identify potential pleiotropic loci between IBD and ocular disorders, we leveraged two cross-trait meta-analyses, including multitrait analysis of GWAS (MTAG) and cross-phenotype association (CPASSOC)[26,27]. First, we performed MTAG to estimate the specific SNP effects for each trait by incorporating information from the correlated phenotypes. A key strength of MTAG is its robustness to sample overlap between GWAS datasets achieved through the incorporation of a bivariate LDSC adjustment[24]. MTAG operates under the assumption that all SNPs share a consistent variance–covariance matrix of effect sizes across traits. To validate the hypothesis of homogeneous SNP heritability and genetic covariance, the maximal false discovery rate (maxFDR) was calculated[28]. Moreover, we took advantage of CPASSOC analysis as a complementary analysis. CPASSOC provided two statistics, namely S_{Hom} and S_{Het}. Given that S_{Hom} suffers a loss of power in the presence of intertrait heterogeneity, we prioritized the S_{Het} statistic. As a robust extension of S_{Hom}, S_{Het} preserved statistical power through adaptively assigning greater weights to larger trait-specific effect sizes. Genome-wide significant SNPs were identified as those surviving the significance threshold of $p < 5 \times 10^{-8}$ in both the MTAG and CPASSOC analyses. Subsequently, independent genomic loci were derived by applying the PLINK clumping algorithm with the following parameters: –clump-p1 5e-8 –clump-p2 1e-5–clump-r2 0.01–clump-kb 500. Finally, to define novel shared SNPs, we retained independent variants absent from LD ($r^2 < 0.01$ within a 1,000-kb window) with any previously reported genome-wide significant loci. In this selection process, we gave priority to SNPs situated within significant genomic regions identified by ρ-HESS if possible.

The ensemble of the variant effect predictor (VEP) and 3DSNP were applied for functional annotation of the identified pleiotropic SNPs.

Enrichment and colocalization analyses

To elucidate the functional implications of the shared loci, we performed pathway enrichment analysis using the clusterProfiler package[29]. Statistical significance was declared with a Benjamini–Hochberg adjusted $p < 0.05$. Furthermore, to explore whether common genetic variations existed among the corresponding gastrointestinal–ocular traits, we accomplished a colocalization analysis based on the Bayesian algorithm using the coloc package[30]. Coloc yielded five posterior probabilities (PPH0–PPH4) for each hypothesis, with a high PPH4 denoting support for a shared variant related to both traits. Specifically, a PPH4 value exceeding 0.90 was interpreted as indicative of a shared causal variant.

Mendelian randomization

We conducted bidirectional two-sample MR analyses to detect the putative causal links between IBD and ocular traits. Instrumental variables (IVs) were extracted from genome-wide significant SNPs ($p < 5 \times 10^{-8}$), followed by LD clumping ($r^2 < 0.001$ within a 10,000-kb window) and filtering for sufficient instrument strength (F-statistics > 10). The inverse-variance-weighted (IVW) served as the chief method, supplemented by a series of sensitivity analyses, including MR-Egger, weighted median, weighted mode, simple mode, generalized summary-data-based Mendelian randomization (GSMR)[31], and MRBEE (a multivariable MR approach that removes weak instrument and sample overlap biases and identifies horizontal pleiotropy simultaneously)[32]. The MR-Egger intercept test and Cochran's Q-statistic were used to assess pleiotropy and heterogeneity, respectively. Horizontally pleiotropic outliers identified by the MR-pleiotropy residual sum and outlier (MR-PRESSO) global test ($p < 0.05$) were subsequently eliminated from the analysis[33]. Additionally, we performed leave-one-out analysis to evaluate the robustness of the causal estimates to individual IVs. Causal effects were deemed to be significant only if they reached the Bonferroni-corrected threshold ($p < 0.05/15$) in the IVW test and exhibited directional consistency across sensitivity analyses.

Results

Baseline characteristics

The baseline demographics and characteristics are depicted in Table 1. After exclusion of subjects with IBD diagnosed after the baseline, the study population yielded 499,089 individuals, constituting 5,990 IBD cases and 493,099 non-IBD controls. The median follow-up time for each eye disease ranged from 5,481 to 5,543 d. By comparison, the IBD group was marginally older and displayed a

modestly lower education status, while also comprising a comparatively greater share of males and White ethnicity. Furthermore, this group was characterized by a greater prevalence of suboptimal lifestyle factors, including a higher rate of inadequate physical activity, and an elevated proportion of former smokers and previous drinkers. Moreover, the IBD group demonstrated a lower median BMI than the non-IBD group, albeit by a narrow margin.

Observational associations between IBD and ocular disorders

Generally, the observational analyses outlined in Table 2 revealed significant associations between IBD and five specific ocular conditions. The results of the Schoenfeld residual tests for the proportional hazard assumption are detailed in Supplementary Table S5. Among all investigated ocular diseases, uveitis emerged as

Table 1. Baseline characteristics of participants with and without IBD.

	Overall (*n* = 499,089)	non-IBD (*n* = 493,099)	IBD (*n* = 5,990)	*p*-value
Age, mean (SD), years	56.53 (8.10)	56.52 (8.10)	57.25 (7.91)	< 0.001
Sex (%)				0.008
Female	271,661 (54.4)	268,502 (54.5)	3,159 (52.7)	
Male	227,428 (45.6)	224,597 (45.5)	2,831 (47.3)	
Ethnicity (%)				< 0.001
White	472,255 (94.6)	466,487 (94.6)	5,768 (96.3)	
Non-White	26,834 (5.4)	26,612 (5.4)	222 (3.7)	
Education (%)				< 0.001
Below college	338,785 (67.9)	334,470 (67.8)	4,315 (72.0)	
College	160,304 (32.1)	158,629 (32.2)	1,675 (28.0)	
TDI level (%)				0.258
Low	166,381 (33.3)	164,435 (33.3)	1,946 (32.5)	
Medium	166,352 (33.3)	164,357 (33.3)	1,995 (33.3)	
High	166,356 (33.3)	164,307 (33.3)	2,049 (34.2)	
PA (%)				< 0.001
Inadequate	105,225 (21.1)	103,777 (21.0)	1,448 (24.2)	
Adequate	393,864 (78.9)	389,322 (79.0)	4,542 (75.8)	
Smoking status (%)				< 0.001
Never	274,996 (55.1)	272,131 (55.2)	2,865 (47.8)	
Previous	171,627 (34.4)	169,085 (34.3)	2,542 (42.4)	
Current	52,466 (10.5)	51,883 (10.5)	583 (9.7)	
Alcohol consumption(%)				< 0.001
Never	22,197 (4.4)	21,892 (4.4)	305 (5.1)	
Previous	17,928 (3.6)	17,615 (3.6)	313 (5.2)	
Current	458,964 (92.0)	453,592 (92.0)	5,372 (89.7)	
BMI, median (IQR)	26.74 (24.16, 29.88)	26.74 (24.16, 29.88)	26.61 (23.97, 29.57)	< 0.001

IBD, inflammatory bowel disease; TDI, townsend deprivation index; BMI, body mass index; SD, standard deviation; PA, physical activity; IQR, interquartile range.

Table 2. Observational associations between IBD and ocular diseases.

Ocular outcomes	Person-years	Cases	IBD				UC				CD			
			Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Uveitis	7,554,323	1,374	2.48 (1.82–3.39)	< 0.001	1.91 (1.37–2.66)	< 0.001	2.33 (1.58–3.43)	< 0.001	1.74 (1.15–2.62)	< 0.001	3.01 (1.81–5.00)	< 0.001	2.23 (1.33–3.74)	< 0.01
Cataract	7,051,549	59,260	1.16 (1.08–1.24)	< 0.001	1.09 (1.02–1.18)	0.01	1.16 (1.07–1.26)	< 0.001	1.1 (1.01–1.20)	0.03	1.17 (1.03–1.32)	0.02	1.09 (0.96–1.23)	0.19
AMD	7,501,978	10,003	1.28 (1.1–1.5)	< 0.01	1.22 (1.04–1.44)	0.02	1.22 (1.01–1.48)	0.04	1.15 (0.94–1.41)	0.17	1.49 (1.14–1.95)	< 0.01	1.40 (1.07–1.84)	0.01
Glaucoma	7,474,110	11,164	1.31 (1.14–1.52)	< 0.001	1.22 (1.05–1.42)	0.01	1.3 (1.09–1.56)	< 0.01	1.2 (1.00–1.45)	0.05	1.25 (0.95–1.65)	0.12	1.15 (0.87–1.52)	0.33
DR	7,534,485	3,734	1.49 (1.18–1.9)	< 0.001	1.39 (1.08–1.79)	0.01	1.52 (1.14–2.02)	< 0.01	1.39 (1.03–1.88)	0.03	1.4 (0.89–2.2)	0.14	1.3 (0.83–2.05)	0.25
Retinal vascular occlusion	7,559,147	2,653	1.05 (0.75–1.47)	0.77	0.92 (0.64–1.32)	0.66	1.05 (0.71–1.58)	0.79	0.91 (0.48–4.93)	0.47	1.04 (0.56–1.93)	0.91	0.95 (0.51–1.87)	0.87
Optic neuritis	7,567,282	184	2.31 (0.95–5.61)	0.07	1.62 (0.64–4.08)	0.3	2.08 (0.67–6.53)	0.21	1.54 (0.63–6.2)	0.24	2.96 (0.73–11.91)	0.13	1.81 (0.43–7.54)	0.41
Retinal detachment	7,522,582	3,099	1.09 (0.8–1.49)	0.57	1.14 (0.83–1.58)	0.42	1.12 (0.77–1.62)	0.56	1.16 (0.78–1.71)	0.45	1.14 (0.66–1.96)	0.64	1.2 (0.69–2.08)	0.52
Keratitis	7,564,144	473	1.74 (0.93–3.26)	0.08	1.05 (0.53–2.06)	0.89	1.56 (0.7–3.49)	0.28	0.91 (0.39–2.15)	0.83	2.3 (0.86–6.15)	0.1	1.41 (0.52–3.82)	0.51
Conjunctivitis	7,563,762	636	1.27 (0.68–2.37)	0.46	1.19 (0.62–2.27)	0.6	1.31 (0.62–2.76)	0.48	1.26 (0.58–2.71)	0.56	0.86 (0.21–3.44)	0.83	0.77 (0.19–3.09)	0.71

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; AMD, age-related macular degeneration; DR, diabetic retinopathy. Model 1: Adjusted for age and sex; Model 2: adjusted for age, sex, ethnicity, educational level, TDI, physical activity, smoking status, alcohol consumption, BMI, IBD-related medications, diabetes (except for diabetic retinopathy), and hypertension.

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the most prominent comorbidity linked to IBD, exhibiting a risk magnitude approximately 1.9 times that of the non-IBD group after adjusting for all covariates (HR = 1.91, 95% CI: 1.37–2.66). Notably, although this association was evident across the IBD spectrum, the susceptibility was more pronounced in CD than in UC (HR = 2.33, 95% CI: 1.33–3.74 vs HR = 1.74, 95% CI: 1.15–2.62). Parallel to this, IBD and UC individuals exhibited a modest but significant 10% increase in the risk of developing a cataract, in contrast to healthy controls. Although IBD and CD demonstrated positive associations with increased AMD risks (HR range: 1.22–1.40, $p < 0.05$), the association for UC did not maintain statistical significance in the fully adjusted model. Furthermore, the elevated hazards for glaucoma and DR were observed only in the UC phenotype instead of CD. Finally, we did not find a discernible association between IBD and the remaining ocular comorbidities.

The results of the subgroup analyses are depicted in Supplementary Figs S1–S5. Specifically, IBD and UC patients who had Vitamin D levels of 50 nmol/L or higher had an increased risk of glaucoma compared with those with levels below this threshold (IBD: HR = 1.57, 95% CI: 1.27–1.95 vs. HR = 1.15, 95% CI: 0.94–1.41, p for interaction = 0.034; UC: HR = 1.67, 95% CI: 1.3–2.15 vs. HR = 1.14, 95% CI: 0.89–1.47, p for interaction = 0.038). Beyond this, no significant interaction effects were detected across other categories between IBD and ocular outcomes. Sensitivity analyses confirmed the stability of most associations (Supplementary Table S6).

Inflammation status mediated the associations between IBD and ocular diseases

Multivariate linear regression results (Supplementary Tables S7–S11) revealed that IBD and UC status showed significant associations with 14 serum biomarkers (excluding monocyte ratio), whereas CD status was significantly associated with 11 biomarkers (excluding monocyte ratio, monocyte count, eosinophil count and basophil count). In conclusion, mediation analyses demonstrated that systemic inflammatory biomarkers partially underpinned the associations between IBD (and its subtypes) and various ocular complications (Supplementary Tables S12–S16). Specifically, neutrophil count, lymphocyte ratio, neutrophil ratio, neutrophil-to-lymphocyte count ratio, and neutrophil-to-leukocyte count ratio were identified as potential mediators for most IBD–ocular links, including uveitis, cataract, AMD, and DR, with proportions of mediation ranging from 1.58% to 11.48%; notably, neutrophil count exerted the most substantial mediating effect (11.48%) on the IBD-related DR pathway. Although CRP mediated the relationship between IBD or its subtypes and uveitis, with estimated proportions between 2.42% and 3.83%, WBC count contributed a modest mediation effect of approximately 0.37% to the associations. RDW emerged as the sole mediator among the relationship between IBD or UC and glaucoma (mediated proportions of 4.46% and 3.79%, respectively). RDW (4.68%–8.16%) and eosinophil count (0.94%–3.48%) were also observed to mediate the associations with cataracts, AMD and DR. Additionally, CRP (3.31%–6.22%) and platelet count (1.81%–3.58%) were found to mediate IBD-associated cataracts and AMD, whereas WBC count consistently mediated the links with cataracts and DR (0.98%–1.98%). Finally, the associations with cataracts were also partially explained by the lymphocyte count (0.56%–1.06%) and the platelet-to-lymphocyte ratio (3.62%–7.59%).

Global and local genetic correlation

Using bivariate LDSC on large-scale GWAS summary statistics, we identified robust genome-wide genetic correlations between IBD ($r_g = 0.4218$, $p = 0.0004$), UC ($r_g = 0.5101$, $p = 2.96 \times 10^{-5}$) and uveitis after Bonferroni correction for multiple testing (Table 3). Moreover, nominally significant genetic correlations were observed for the CD–uveitis ($r_g = 0.2271$, $p = 0.0125$) and CD–AMD ($r_g = 0.0967$, $p = 0.0152$) pairs.

Subsequently, we applied ρ-HESS to determine local genetic correlations across the genome between IBD (including UC and CD) and ophthalmic conditions. At a local level, we identified multiple genomic regions exhibiting significant genetic covariance after Bonferroni correction (Figs 2–4; Supplementary Tables S17–S20). Specifically, the uveitis-related traits demonstrated the most extensive local genetic overlap with IBD and its subtypes. Local genetic overlap between IBD and uveitis was characterized by eight significant regions, primarily spanning chromosomes 6 and 7 and anchored by a highly significant association at 7p22.1 ($p = 9.51 \times 10^{-41}$) (Fig. 2a; Supplementary Table S17). Subtype-specific analyses further revealed four significant regions for UC–uveitis (also anchored by 7p22.1, $p = 6.07 \times 10^{-34}$) (Fig. 2b) and only one prominent region for CD–uveitis at 1p31.3 ($p = 2.78 \times 10^{-8}$) (Fig. 2c). With regard to cataracts, significant local genetic correlations were all localized to chromosome 6. Intriguingly, a shared signal at 6p21.32 was consistently observed across IBD ($p = 2.64 \times 10^{-7}$), UC ($p = 5.01 \times 10^{-10}$), and CD ($p = 2.23 \times 10^{-5}$) for cataracts (Fig. 3a–c; Supplementary Table S18). Moreover, a specific significant region for CD and glaucoma was identified at 16q12.1 ($p = 1.96 \times 10^{-5}$) (Fig. 3d; Supplementary Table S19). Referring to the associations with DR, a highly consistent local genetic architecture was detected between IBD phenotypes and DR on chromosome 6. Precisely, a shared pleiotropic signal at 6p21.33–21.32 was found for IBD–DR ($p = 5.42 \times 10^{-31}$), UC–DR ($p = 2.68 \times 10^{-31}$), and CD–DR ($p = 3.37 \times 10^{-11}$) (Fig. 4; Supplementary Table S20). Conversely, no significant local genetic correlations were detected for IBD (encompassing its subtypes) and AMD, nor for IBD or UC and glaucoma. It is noteworthy that multiple genomic regions identified across multiple IBD–ocular pairs were concentrated within or proximal to the 6p21.3 region (encompassing eight pairs: IBD/UC–uveitis, IBD/UC/CD–cataracts, and IBD/UC/CD–DR), a genomic segment harboring the human leukocyte antigen (HLA) complex known for its central role in modulating immune and inflammatory responses.

Table 3. Genomewide genetic correlations between IBD and ocular diseases.

Trait 1	Trait 2	r_g	SE	p-value for LDSC	Intercept (SE)
IBD	Uveitis	0.4218	0.1192	0.0004	0.0584 (0.0106)
UC		0.5101	0.1221	2.96×10^{-5}	0.0373 (0.009)
CD		0.2271	0.0909	0.0125	0.0078 (0.0047)
IBD	Cataracts	0.0217	0.048	0.6514	0.0208 (0.0067)
UC		0.0239	0.0515	0.6417	0.0137 (0.0061)
CD		0.0676	0.0436	0.1213	−0.0019 (0.0054)
IBD	AMD	0.032	0.0424	0.45	−0.0019 (0.0058)
UC		0.0239	0.0412	0.5615	−0.0023 (0.0057)
CD		0.0967	0.0399	0.0152	−0.0055 (0.0052)
IBD	Glaucoma	−0.0276	0.0335	0.4111	0.0021 (0.0067)
UC		−0.0546	0.0317	0.085	0.0136 (0.007)
CD		−0.0626	0.036	0.0823	0.0129 (0.0067)
IBD	DR	0.0264	0.0899	0.7694	0.0029 (0.0062)
UC		0.048	0.0994	0.6294	0.0029 (0.0061)
CD		−0.0638	0.0918	0.4869	−0.0007 (0.0054)

r_g, genetic correlation; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; AMD, age-related macular degeneration; DR, diabetic retinopathy. Bonferroni-adjusted significance threshold was set at $p < 3.33 \times 10^{-3}$ (0.05/15).

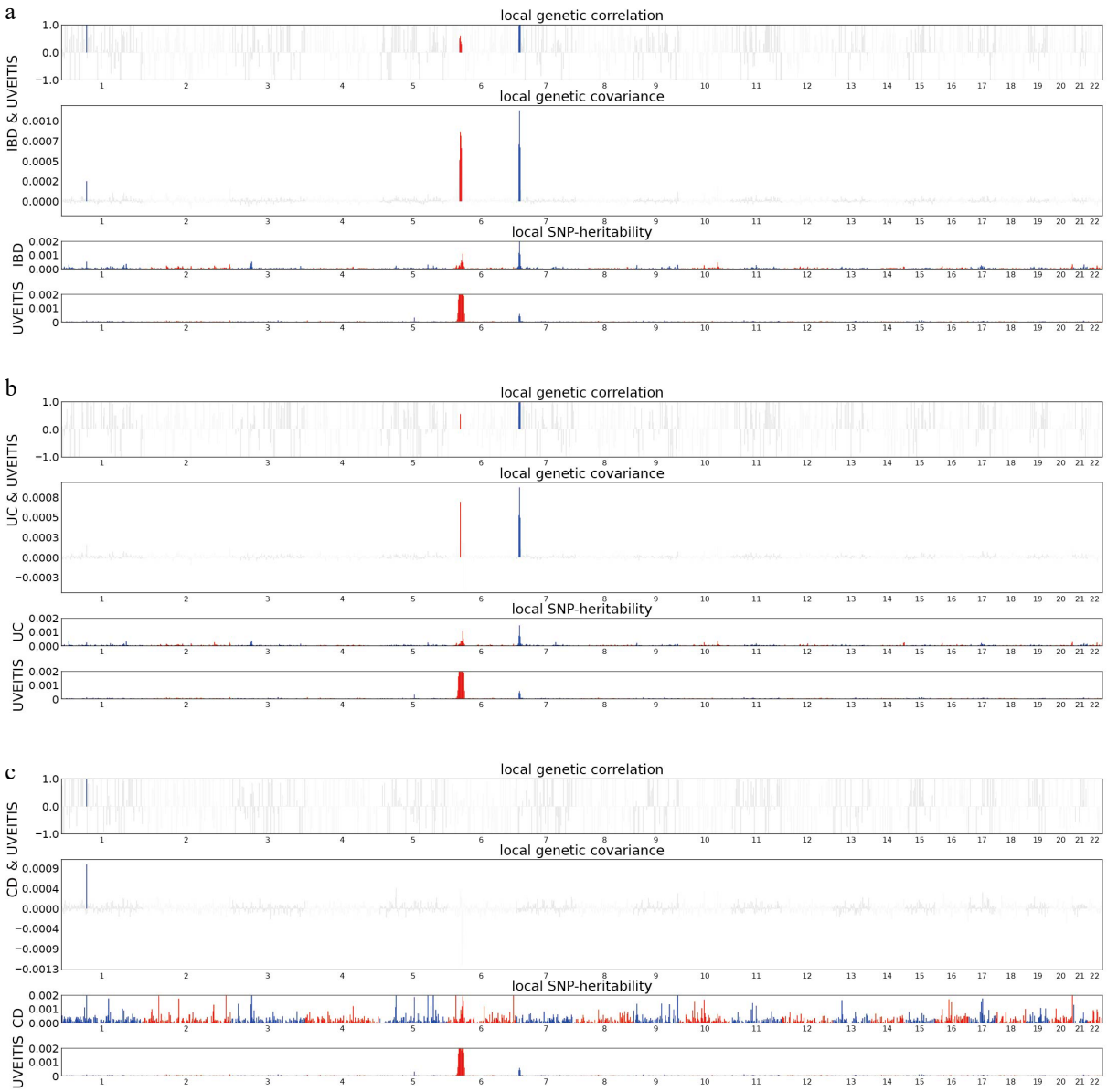

Fig. 2 Local genetic architecture between IBD (including subtypes) and uveitis. Manhattan plots illustrate the distribution of local genetic correlation, local genetic covariance, and trait-specific local SNP heritability across the genome for (a) IBD–uveitis, (b) UC–uveitis, and (c) CD–uveitis. In each subpanel, the top and middle sections display the estimates of local genetic correlation and covariance, respectively. Colored bars (red or blue) highlight specific genomic regions exhibiting significant local genetic overlap after multiple adjustment (p < 5E−08 in both local SNP heritability test, and p < 0.05/1702 in local genetic covariance test). The bottom section represents the regional SNP-based heritability for each individual trait, with colored bars indicating loci reaching statistical significance. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Pleiotropic SNPs from the cross-trait GWAS meta-analysis

Considering the significant genetic overlap between IBD and ocular diseases, we next performed an analysis at the individual variant level to exploit pleiotropic loci. In total, 144 shared independent SNPs reached genome-wide significance across these phenotypes (Supplementary Tables S21–S26). After excluding SNPs that were in LD ($r^2 \geq 0.01$) with any of the previously documented significant single-trait SNPs, we identified 132 novel pleiotropic SNPs (Supplementary Tables S27–S29). Among these, 49 were further validated by their localization within the ρ-HESS significant regions, with 20 exhibiting evidence of colocalization (20/49) posterior probability of hypothesis 4 (PPH4) > 0.9 (Supplementary Table S30).

Overall, we observed that a substantial number of these novel pleiotropic loci for IBD–ocular pairs were predominantly clustered within or near the major histocompatibility complex (MHC) region. These risk-associated variants mapped to a diverse array of genetic elements, including classical HLA genes (such as *HLA-DPA2*, *HLA-DQA1*, and *HLA-C*), protein-coding genes involved in immune signaling (such as *ZBTB12*, *GNL1*, *BTN2A2*, *TAP2*, and *VARS*), and various regulatory noncoding RNAs or pseudogenes (including *HCG23*, *LINC01016*, and *TRIM26BP*). The HLA genes have been implicated in increasing the risk for both IBD[34] and uveitis[35]. Notably, among the top-ranking novel SNPs in the IBD–uveitis analysis, rs9267111, mapping to *HCP5*, stood out as one of the most significant variants ($p_{CPASSOC}$ = 2.51 × 10^{-263}). This gene encodes a regulatory long

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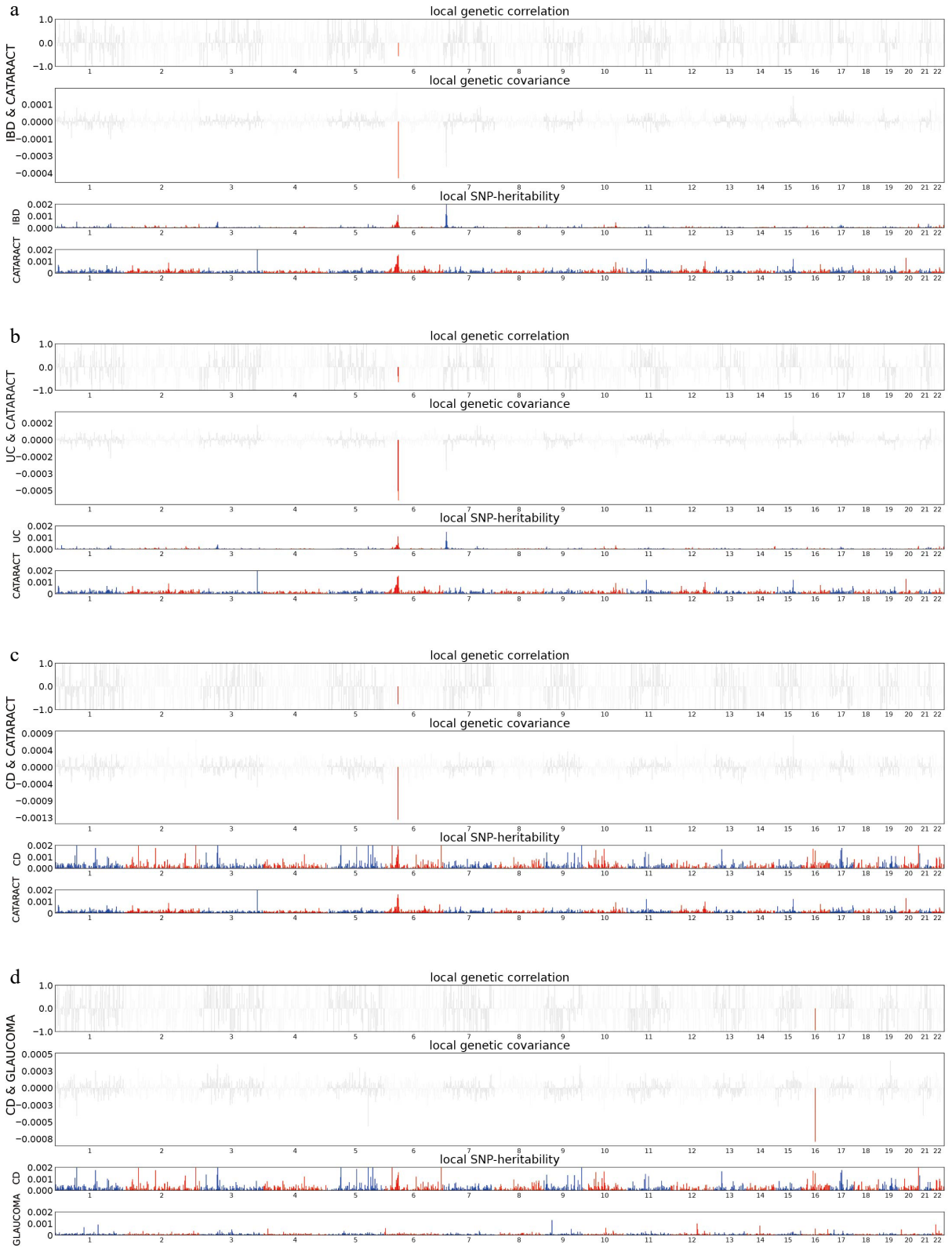

Fig. 3 Local genetic architecture between IBD (including subtypes) and cataract, CD and glaucoma. Manhattan plots illustrate the distribution of local genetic correlation, local genetic covariance, and trait-specific local SNP heritability across the genome for (a) IBD–cataract, (b) UC–cataract, (c) CD–cataract, and (d) CD–glaucoma. In each subpanel, the top and middle sections display the estimates of local genetic correlation and covariance, respectively. Colored bars (red or blue) highlight specific genomic regions exhibiting significant local genetic overlap after multiple adjustment ($p <$ 5E−08 in both local SNP heritability test, and $p < 0.05/1702$ in local genetic covariance test). The bottom section represents the regional SNP-based heritability for each individual trait, with colored bars indicating loci reaching statistical significance. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

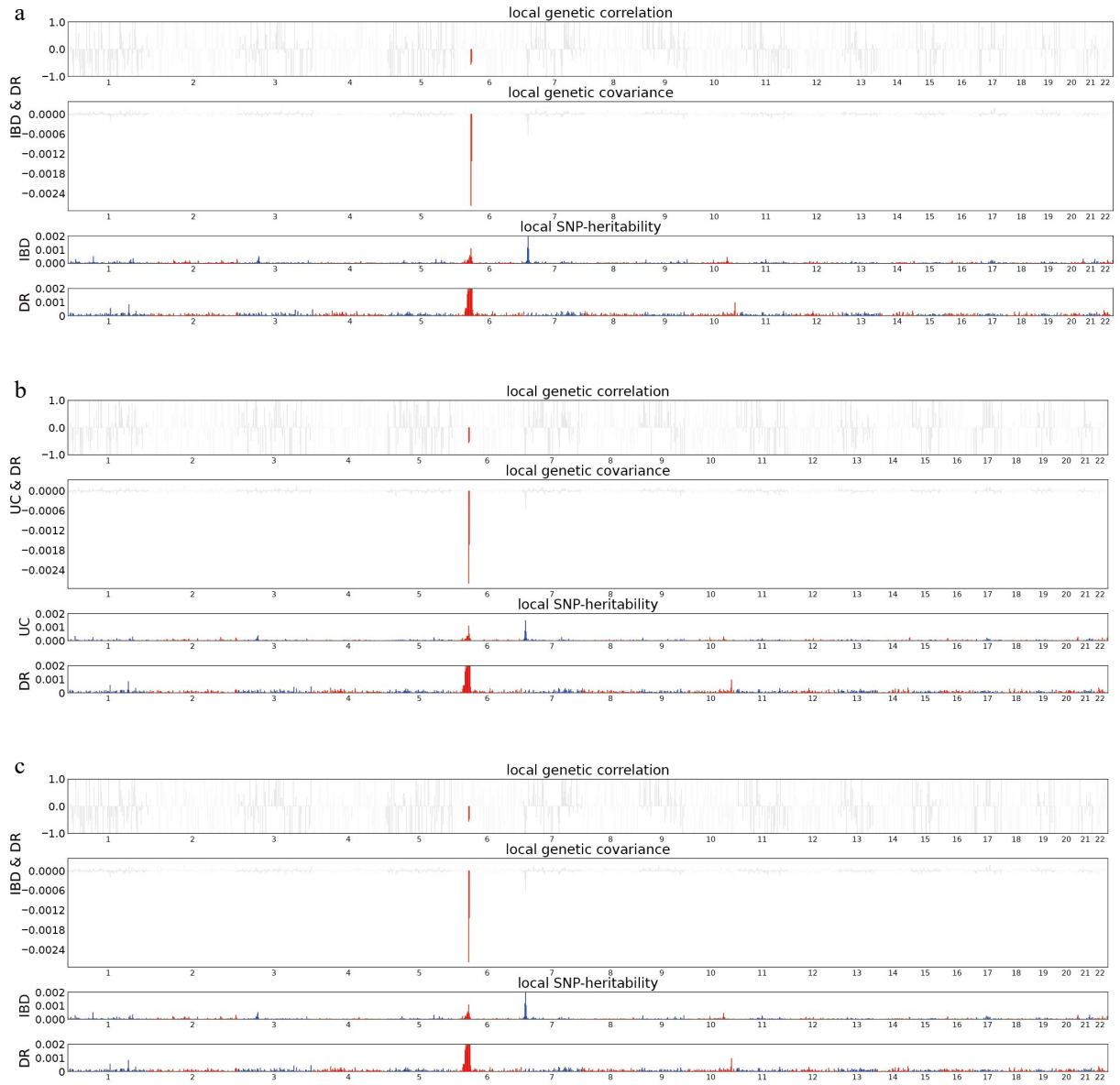

Fig. 4 Local genetic architecture between IBD (including subtypes) and DR. Manhattan plots illustrate the distribution of local genetic correlation, local genetic covariance, and trait-specific local SNP heritability across the genome for (a) IBD–DR, (b) UC–DR, and (c) CD–DR. In each subpanel, the top and middle sections display the estimates of local genetic correlation and covariance, respectively. Colored bars (red or blue) highlight specific genomic regions exhibiting significant local genetic overlap after multiple adjustment (p < 5E−08 in both local SNP heritability test, and p < 0.05/1702 in local genetic covariance test). The bottom section represents the regional SNP-based heritability for each individual trait, with colored bars indicating loci reaching statistical significance. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

noncoding RNA (lncRNA) that plays a critical role in both the adaptive and innate immune responses and has been previously linked to IBD susceptibility[36,37]. In addition, rs62395330 ($p_{CPASSOC}$ = 6.40 × 10^{-21}), another novel locus in the UC–uveitis pair, was mapped to *HCP5*. Furthermore, the missense variant rs9394078 ($p_{CPASSOC}$ = 6.63 × 10^{-255}), was identified as a top novel SNP in the mapping of UC–uveitis to *ZBTB12*, which was characterized as a molecular barrier that ensured the unidirectional transition of metastable stem cells towards the advanced development[38]. The most significant novel shared SNP for IBD or CD and glaucoma was rs17622378 ($p_{CPASSOC}$= 3.65 × 10^{-24} and 3.53 × 10^{-21}, respectively) located near *C5orf56* (also known as *CARINH* or *IRF1-AS1*), a lncRNA that regulates intestinal homeostasis and inflammatory cytokine production via an IRF1 regulation loop in IBD[39,40]. Moreover, 7, 9, and 25 shared novel loci were identified for IBD (including its subtypes) and cataracts, AMD and DR, respectively, mapping to 5, 9, and 18 related genes (Supplementary Tables S28, S29). Furthermore, the enriched pathways were mainly involved in T-cell-mediated immune activity, cell adhesion, and MHC-dependent antigen presentation (Supplementary Table S31). Interestingly, signaling pathways related to synaptic architecture and function were also overrepresented, pointing to a potential neuro-immune interplay between the gastrointestinal and ocular systems.

Causal relationship between IBD and ocular disorders

The *F*-statistics for the selected IVs indicated a negligible risk of weak instrument bias (Supplementary Table S32). Following the

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exclusion of potential outliers identified by the MR-PRESSO global test, bidirectional two-sample MR analyses were executed to evaluate the causal links between IBD (including UC and CD) and five ocular diseases (Supplementary Table S33, Supplementary Figs S6–S10). In the forward MR analyses, IBD and its subtypes demonstrated robust causal links with increased susceptibility to uveitis. Specifically, after Bonferroni correction for multiple testing, IBD (odds ratio [OR] = 1.31, 95% CI: 1.15–1.50), UC (OR = 1.17, 95% CI: 1.10–1.24), and CD (OR = 1.09, 95% CI: 1.05–1.14) were all strongly associated with an elevated risk of uveitis. Similarly, IBD (OR = 1.04, 95% CI: 1.02–1.17) and CD (OR = 1.02, 95% CI: 1.01–1.03) exerted modest but significant causal effects on AMD. Additionally, nominal causal evidence suggested that IBD (OR = 0.90, 95% CI: 0.81–0.99) and CD (OR = 0.96, 95% CI: 0.93–1.00) were associated with a reduced risk of DR, whereas UC exerted nominally deleterious effects on susceptibility to AMD (OR = 1.02, 95% CI: 1.00–1.04). Reverse MR analyses hinted at a reciprocal relationship for certain traits. Evidence of reverse causality was observed from uveitis (OR = 1.13, 95% CI: 1.08–1.18) and DR (OR = 0.80, 95% CI: 0.73–0.87) to IBD. Moreover, nominal significance was noted for the causal influence of uveitis (OR = 1.08, 95% CI: 1.02–1.14) and DR (OR = 0.87, 95% CI: 0.79–0.95) on UC risk. Other investigated associations did not reach statistical significance at the nominal threshold. Heterogeneity was observed in the causal estimates between IBD and ocular comorbidities (some *p*-values for heterogeneity from IVW and MR-Egger were below 0.05). However, the MR-Egger intercept remained nonsignificant for the vast majority of associations (nearly all $p > 0.05$), suggesting an absence of substantial horizontal pleiotropy. Crucially, most causal estimates were directionally concordant across multiple MR models (i.e., IVW, weighted median, MR-Egger, simple mode, weighted mode, GSMR, and MRBEE) (Supplementary Table S33), underscoring the resilience of the primary findings despite the underlying heterogeneity (Supplementary Table S34).

Discussion

This study provides a multifaceted framework of epidemiological and genetic evidence to systematically delineate the phenotypic associations and shared genomic architecture between IBD and a spectrum of ocular disorders. First, from a phenotypic standpoint, our longitudinal analyses confirmed positive associations, indicating that IBD and its clinical subtypes significantly elevate the risks of uveitis, cataracts, AMD, glaucoma and DR. Second, mediation analyses revealed the mediating circulating inflammation biomarkers mediated the relationships across these gut–eye conditions. Last but not least, in view of genetic underpinnings, our study elucidated the profound biological cross-talk underlying these complex traits, stressing on genetic correlations and pleiotropy. This work advanced our understanding of the relationship between intestinal diseases and ocular comorbidities, offering a biological blueprint for early screening and interventions targeting shared inflammatory pathways, and the interpretation of the gut–eye axis (Fig. 5).

To our knowledge, this research was the first large-scale prospective cohort investigation utilizing the UK Biobank to systematically evaluate the risks of IBD and its comprehensive ocular comorbidities. Our observational findings delineated a robust association between IBD and various ophthalmic disorders, aligning with existing cross-sectional evidence[41]. Consistent with previous studies, we shed light on a prominent link between IBD and uveitis, further consolidating the status of uveitis as one of the most classic EIMs of IBD. Our study also provided the first prospective evidence identifying longitudinal clinical links between IBD and cataracts,

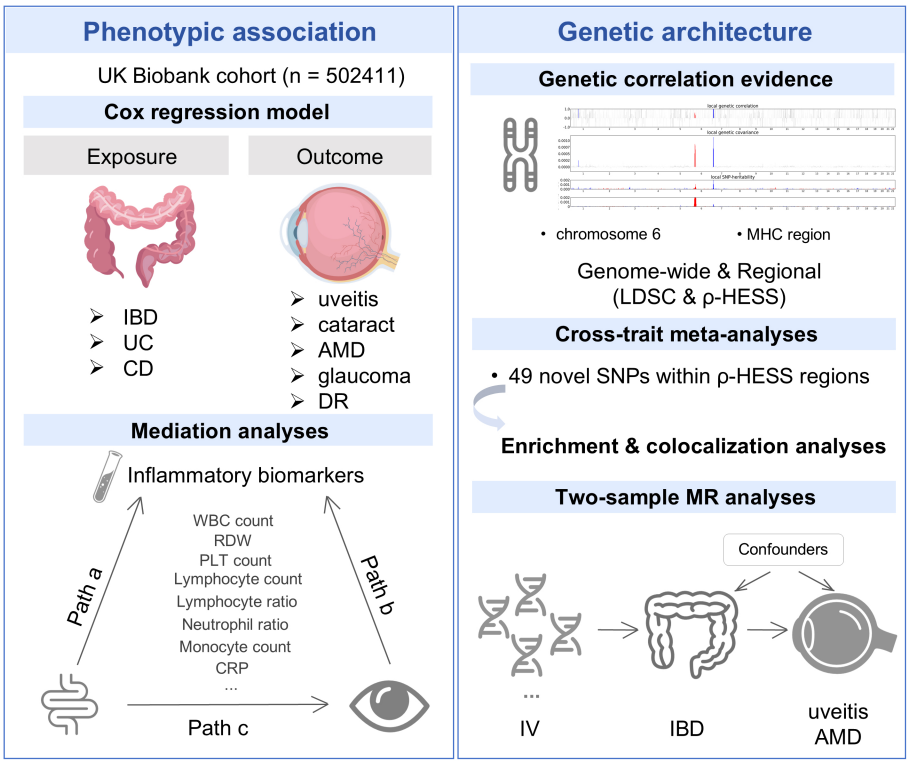

Fig. 5 Graphical summary of the study. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; AMD, age-related macular degeneration; DR, diabetic retinopathy; WBC, white blood cell; RDW, red cell distribution width; PLT, platelet; CRP, C-reactive protein; MHC, major histocompatibility complex; LDSC, linkage disequilibrium score regression; IV, instrumental variable; MR, Mendelian randomization.

AMD, glaucoma, and DR. The links between IBD subtypes and some ocular diseases (such as CD and cataracts) attenuated to nonsignificance after full adjustment, which aligns with previous reports of steroid-induced cataracts in IBD patients[6]. Given the varying incident risks of ocular comorbidities, stratified ophthalmic management and multidisciplinary care are crucial for IBD patients. For example, routine slit-lamp biomicroscopy should be prioritized for the screening of uveitis upon a diagnosis of IBD. Additionally, fundus photography and optical coherence tomography (OCT) are essential for detecting early posterior segment and optic nerve lesions (e.g., DR, AMD, and glaucoma). Furthermore, regular monitoring of lens opacity is recommended for early cataract detection, especially considering long-term corticosteroid use.

Most associations in our observational study remained robust after multiple sensitivity analyses. Although a systematic review that included many cross-sectional studies suggested a protective role of Vitamin D against glaucoma[42], our subgroup analyses noted that the risk of glaucoma was more pronounced among IBD patients with higher baseline serum Vitamin D levels (≥ 50 nmol/L). It is well-recognized that Vitamin D levels are closely linked to the circulating calcium concentration. Prior cross-sectional research has identified excessive calcium intake as a risk factor for glaucoma[43], and the associations between calcium overload and damage to retinal ganglion cells and the trabecular meshwork (TM) have been previously documented. Previous studies indicate that TM cells with defective mitochondrial function exhibit abnormal vulnerability to calcium dysregulation, which contributes to the inability to control intraocular pressure (IOP)[44]. Concurrently, calcium dyshomeostasis is linked to neurodegeneration, as evidenced by the loss of the endoplasmic reticulum Ca^{2+}-ATPase2 pump (SERCA2/ATP2A2) in injured retinal neurons of patients and mice with glaucoma[45]. Integrating these insights with our findings, we hypothesize that Vitamin D and calcium may exert a complex, multifaceted influence on the pathogenesis of glaucoma in the context of IBD. Further mechanistic research is needed to disentangle the multifaceted roles of micronutrients in gut–eye diseases.

The current mediation analysis supported the hypothesis that IBD-associated systemic inflammation may contribute to the adverse ocular outcomes. However, the assessed biomarkers mediated merely 0.37% to 11.48% for these associations, implying that additional biological mechanisms of the gut–eye axis are likely at play. Previous literature indicates that in IBD, the release of proinflammatory cytokines (like interleukin [IL]-1β, IL-22 and tumor necrosis factor alpha [TNF-α]) and chemokines (like CCL8) activates peripheral neutrophils and recruits them to the inflamed intestine, compromising the intestinal barrier by exacerbating the inflammation driven by high concentrations of reactive oxygen species (ROS), proteases, and proinflammatory cytokines like IL-8[46]. Notably, neutrophil-related mediators exhibited important mediating effects across most associations and exerted the strongest mediation (11.48%) on the IBD–DR pathway. This may suggest that the neutrophil-mediated oxidative stress, which breached the intestinal barrier, may similarly facilitate the breakdown of the blood–eye or blood–retinal barrier (BRB). Studies have shown that elevated peripheral neutrophils and their aberrant function are associated with increased retinal vascular permeability and DR risks[47,48]. Long-term hyperglycemia enables peripheral neutrophils to cross the BRB more easily, leading to the formation of neutrophil extracellular traps (NETs) under the action of oxidative stress and deposition in the vitreous body and retina[49]. Neutrophil stasis releasing NETs may further disrupt the retinal vasculature. A recent experiment used anti-Ly6G antibodies to deplete neutrophils in oxygen-induced retinopathy. The results indicated that early neutrophil reduction decreased retinal myeloperoxidase (MPO), inflammation, neovascularization, and vascular leakage, providing evidence that circulating neutrophils may be mediators of retinal injury[50]. Modest mediating effects of the lymphocyte ratio align with recent studies suggesting that gut-derived immune cells may aberrantly migrate to the ocular tissues. Noninfectious uveitis involves the activation and differentiation of CD4+ T cells, causing migration to retina and the recruitment of other immune cells like neutrophils[51]. Likewise, IBD is also characterized by the infiltration of intestinal tissue by inflammatory CD4+ T cells[52], but recent studies suggest that these cells are not confined to the gut, such as the migration of lymphocytes to the eye in uveitis driven by short-chain fatty acids (SCFAs)[53], and recruitment of β7+ CD4+ T cells leading to ganglion cell in glaucoma[54]. Of interest, red cell distribution width (RDW) was the exclusive mediator for the IBD–glaucoma link. Elevated RDW has been reported as a biomarker for chronic systemic inflammatory diseases, like IBD[55] and chronic kidney disease[56]. Thus, it may mediate the persistent inflammatory burden, creating a permissive environment for chronic optic nerve neurodegeneration. Moreover, classical inflammatory biomarkers (like CRP and WBC) also exhibited significant but minor mediation effects. The single baseline measurement of these biomarkers might not fully reflect the actual long-term inflammatory fluctuations. Collectively, although these findings could provide supplementary value in understanding the IBD-related ocular link, the modest mediating roles suggest they are likely part of a broader pathophysiological network, rather than standalone targets for immunotherapies centered on the gut–eye axis.

Genetically, our study demonstrated significant genomewide genetic correlations and pleiotropic overlaps between IBD and multiple ocular phenotypes, aligning with the overall positive associations observed in our epidemiological studies. These findings reinforced the pivotal role of the gut–eye axis in the shared genetic etiology underlying these conditions. On the basis of a local genetic correlation analysis, we identified 11 independent genomic regions mediating the associations between IBD and different ocular diseases. Notably, the MHC region located on the short arm of chromosome 6 (chr6: 28,477,797–33,448,354, namely 6p22.1–p21.32) exhibited the most prominent and extensive local genetic correlations across IBD and ocular comorbidities. This strongly suggests that HLA-related genes possess functional relevance in the progression of IBD-associated ocular manifestations. It has been reported that specific HLA genotypes increase the susceptibility to EIMs in IBD[2]. For instance, HLA alleles, represented by HLA-B27 and HLA-A29, have been shown to influence the development of uveitis by modulating the composition of the gut microbiota[10]. Furthermore, two-sample MR analyses implied potential causal associations between IBD and both uveitis and AMD, whereas the causal links with other ocular comorbidities remain inconclusive. The identified causal pathway between IBD and uveitis is consistent with our clinical and genetic evidence, as these two conditions share inflammatory signaling pathways[57]. However, our reverse MR analyses revealed that some communications between the gut and eye may be bidirectional, as supported by various pieces of evidence. One retrospective cohort study reported that patients with uveitis are at greater risk of developing IBD than those without uveitis[58]. An increase in Th17 cells in the PBMC has been reported in patients with uveitis[59]. Likewise, under immune dysregulation, the abnormal proliferation of Th17 cells can induce abnormal inflammatory immune responses and mediate the development of IBD[60]. Thus,

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uveitis may not only be a secondary manifestation but could also contribute to the systemic inflammatory burden that predisposes individuals to IBD.

We identified multiple pleiotropic loci. Here, we focused on novel SNPs that were localized within significant ρ-HESS regions and demonstrated robust evidence of colocalization, all of which were found in the shared genetic architecture of IBD (including its subtypes) and uveitis. Specifically, rs62443225, mapping to *FBXL18*, emerged as a top-ranking novel association and was harbored within the most significant local genetic region for IBD, UC, and uveitis at 7p22.1. This gene regulates cellular homeostasis by mediating the ubiquitin-dependent proteasomal degradation of the proapoptotic protein FBXL7[61], thereby potentially limiting aberrant apoptosis and mitotic arrest in both intestinal and ocular tissues. Elevated serum levels of ubiquitin and proteasome 20S subunits have been clinically observed during acute autoimmune uveitis attacks and correlate with disease severity, further supporting the biological involvement of the ubiquitin–proteasome system in ocular inflammation[62]. Another noteworthy novel locus was also identified at the 7p22.1 region for IBD, UC, and uveitis, mapping to *TNRC18* (rs6966019 and rs34693947). *TNRC18* modulates the expression of inflammatory genes, such as IL-1β, by regulating H3K27ac levels in their respective regulatory regions[63]. Disruptions in this TNRC18-mediated epigenetic landscape may drive the systemic autoinflammatory responses characteristic of the gut–eye axis. IL-1β is essential for the development of Th17 cells, which are key effector cells responsible for autoimmune uveitis, and treatment with anti-IL-1β antibodies has shown clinical efficacy[64]. Moreover, rs11209026, harboring *IL23R* at 1p31.3, was identified as the only novel SNP fulfilling the aforementioned criteria for the CD–uveitis trait. *IL23R* encodes a subunit of the proinflammatory cytokine IL-23 receptor, which is strongly associated with CD susceptibility[65]. This variant likely drives the shared pathogenesis of CD and uveitis by modulating the IL-23 signaling pathway, which promotes Th17 cells' expansion and subsequent disruption of both the intestinal and ocular barriers[66]. Ustekinumab, a monoclonal antibody targeting IL-23, has already been established as an effective medication for CD, further underscoring the potential of targeting the IL-23 axis in managing multisystemic inflammatory conditions[67].

Notably, some gut–eye associations observed in our cohort were not corroborated by our genetic analyses. These discrepancies likely stem from two main factors. First, observational data capture cumulative lifetime exposures and environmental factors. For instance, as shown in our analyses, long-term corticosteroid use in IBD may affect the risks of cataracts and glaucoma, an acquired iatrogenic factor undetectable by MR, which relies solely on germline genetics. Second, MR is constrained by the limited phenotypic variance explained by the IVs, potentially yielding false negative results. Thus, these nonsignificant genetic findings do not negate the observed clinical co-occurrence; rather, they suggest that certain gut–eye associations are primarily driven by environmental or therapeutic pathways instead of direct genetic causality.

Our study integrated observational and genetic approaches, providing a multidimensional angle that reinforced the gut–eye axis theory by leveraging the large sample size and abundant phenotypic data of the UK Biobank and GWAS samples. However, several limitations warrant acknowledgement. First, our findings were derived from populations of European ancestry, which might limit generalizability to other ethnic groups. Second, the exclusion of sex chromosomes potentially left X-linked associations undetected. Third, although multiple covariates were adjusted in models, residual confounding like temporal or genetic factors, lifestyle factors, and IBD disease severity, remains possible, which may influence the observed associations to some extent. Fourth, partial sample overlap exists in our MR analyses. We utilized strong IVs (*F*-statistics > 10) and the MRBEE method in an attempt to minimize the impact on the causal estimates. However, it is impossible to ensure that sample overlap bias has been completely eliminated. MR evaluates the lifetime cumulative effect of genetic susceptibility on disease risk, which differs intrinsically from short-term alterations in exposure or medical interventions in clinical settings. Therefore, these MR findings should be regarded as exploratory rather than definitive, and future replication in entirely independent, large-scale cohorts remains necessary. Lastly, patients with unspecified IBD subtypes were excluded from the subtype analyses to maintain phenotypic purity, as incorporating these indeterminate cases would likely introduce misclassification bias and dilute the distinct subtype-specific ocular signals we observed. Future research should prioritize cross-ancestry studies and experimental validation to further elucidate the biological mechanisms of gut–eye comorbidities.

Conclusions

Taken together, this study harmonizes observational and genetic evidence to characterize the complicated interplay between IBD and ocular disorders. Our findings establish that IBD confers a heightened risk for ophthalmic complications, an association likely mediated by the synergistic effects of systemic immune–inflammatory cascades and a shared pleiotropic genetic landscape. Beyond reinforcing the theoretical framework of the gut–eye axis, these results underscore the clinical necessity for integrated ophthalmic screening in IBD populations and provide novel insights for personalized therapeutic strategies aimed at mitigating the dual burden of intestinal and ocular inflammation.

Ethical statements

This research was approved by the North West Haydock Research Ethics Committee (reference 21/NW/0157; approval date: 29 June 2021). All participants provided written informed consent prior to data collection, and the study was conducted in accordance with the Declaration of Helsinki.

Author contributions

The authors confirm their contributions to the paper as follows: conceptualization, data curation, formal analysis, methodology, writing – original draft, review and editing: Zhang Y; data curation, formal analysis, methodology, writing – review and editing: Sun J; funding acquisition, writing – review and editing: Song H; writing – review: Chen J, Liu M, Yao J; supervision, writing – review and editing: Jiang H; data curation, writing – review and editing: Hu L; conceptualization, methodology, supervision, and writing – review and editing: Li X; conceptualization, supervision, funding acquisition, project administration: Wu W. All authors reviewed the results and approved the final version of the manuscript.

Data availability

UK Biobank data are available upon application (Application No. 73595; www.ukbiobank.ac.uk/). Summary statistics were retrieved from publicly available GWASs.

Acknowledgments

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Conflict of interest

The authors declared no conflicts of interest.

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