Inflammatory Bowel Disease and Risk of Ocular Inflammation: A Two-sample Mendelian Randomization Study

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Research Article

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Abstract

Purpose: To determine whether there is a causal effect of inflammatory bowel disease (IBD) on ocular inflammation?

Design: Two-sample Mendelian randomization (MR) study.

Methods: IBD-associated genetic instruments were derived from the largest genome-wide association studies published to date for IBD, ulcerative colitis (UC), and Crohn's diseases (CD). FinnGen research project was used to identify genetic risk variants for conjunctivitis, keratitis, iridocyclitis, chorioretinitis, episcleritis, and optic neuritis. All participants were of European ancestry. Inverse-variance–weighted (IVW) was used as the primary outcome, while weighted median (WM) and MR-Egger were used to improve the estimation of IVW.

Results: A nominal causal effect of genetically predicted IBD on risk of conjunctivitis, keratitis, iridocyclitis, and optic neuritis, but not on chorioretinitis or episcleritis. After Bonferroni correction, the results showed that genetically predicted UC was significantly associated with an increased risk of iridocyclitis (IVW: OR, 1.17; 95% CI, 1.10-1.24, $P=2.54\times10^{-7}$), CD was significantly associated with conjunctivitis (IVW: OR, 1.05; 95% CI, 1.03-1.08, $P=3.20\times10^{-5}$), keratitis (IVW: OR, 1.06; 95% CI, 1.02-1.09; $P=1.13\times10^{-3}$), and iridocyclitis (IVW: OR, 1.09; 95% CI, 1.04-1.14; $P=1.43\times10^{-4}$).

Conclusion: This study illustrates that IBD causally poses a risk of inflammation of conjunctival, cornea, iris-ciliary and optic neuritis. Moreover, CD is more closely associated with the eye than UC. These implyed that the relationship of IBD and different parts of the eye structure were different, and provided novel evidence linking based on the association of the gut-eye axis.

Introduction

Since the concept of the "gut-retina" axis was first proposed, the relationship between gut and eye has attracted great interest in recent years[1]. A growing body of research revealed gut dysbiosis may perform a crucial constructive role in the onset and progression of multiple ocular diseases, such as uveitis, diabetic retinopathy[2]. Furthermore, some studies provided perspectives into the presumable pathways forming the gut dysbiosis-ocular surface-lacrimal gland axis[3]. The link between bowel disease and eye disease needs to be gotten attention in more research.

Inflammatory bowel disease (IBD) which typically includes ulcerative colitis (UC) and Crohn's disease (CD), is a recurrent and immune-mediated inflammatory disorder, characterized by chronic diarrhea, abdominal pain, and perianal bleeding[4,5]. In recent years, given the natural increase in Western populations, the number of IBD patients in 2030 is likely to exceed 10 million assuming a 1% prevalence, which would be the largest number of IBD patients ever recorded[6]. In addition, symptoms of IBD occur primarily of but are not limited to the gut, and the quality of life for patients with IBD can be substantially

affected by extraintestinal manifestations (EIM)[7]. The existing epidemiological observational studies suggested the link between IBD and ocular inflammation, which may leave irreversible visual impairment and sequelae[8]. Ocular EIM of conjunctivitis and corneal infiltration were first described in two IBD patients as early as 1925[9]. The reported incidence of ocular complications in IBD rates ranges from 3.5–11.8%, usually of inflammatory nature[10]. Furthermore, published observational study suggests that conjunctivitis and episcleritis are by far the most common ocular EIM of IBD, and the general incidence of ocular fundus manifestations is low, less than 1% in IBD patients, such as chorioretinitis and optic neuritis[11,12]. However, observational studies are non-causality, and susceptible to confounding factors, so it is difficult to determine whether this is really the case. It is hoped that the causal relationship between IBD and ocular inflammation needs to be further clarified to up-grading consciousness of ocular EIM, rather than a simple association in observation.

Mendelian randomization (MR) study is a method of causal inference using genetic variants. It relies on the natural random classification of genetic variation during meiosis, and the difference in results between those who carry the variant and those who can't be attributed to differences in risk factors[13]. Due to the non-causality of observational study and the difficulty of randomized controlled trials study[14], MR has become a popular and convenient technique analysis method mainly applied to the etiological inference of epidemiology in recent years, which can imitate RCT[15,16].

In this study, we performed a two-sample MR analysis to investigate the causal relationship between IBD and ocular inflammation, using the summary statistics from genome-wide association studies (GWAS) of IBD (including UC and CD) and ocular inflammation (conjunctivitis, keratitis, iridocyclitis, chorioretinitis, episcleritis, and optic neuritis), which were common ocular EIM in previous IBD observational studies.

Methods

Study Design

According to the three key assumptions of MR: (1) The instrumental variables (IVs) is associated with risk factors; (2) IVs is not associated with confounding factors; (3) IVs affects results only through risk factors[17], SNPs representing IVs after screening were selected. Figure 1 shows the flowchart of the two-sample MR study between IBD and ocular inflammation. A nominal causal effect of genetically ($P < 0.05$) was firstly applied to predict IBD on risk of conjunctivitis, keratitis, iridocyclitis, chorioretinitis and episcleritis. Then through Bonferroni correction, a significantly causal effect of genetically, the relationship of UC and CD on increased risk of ocular inflammation, was obtained. In addition, our findings were reported in accordance with MR-STROBE guidelines.

Data sources

IBD-associated SNPs were derived from the largest GWAS published to date for IBD, UC and CD in the European Genome-phenome Archive[18]. The statistics came from an extended cohort of 86,640 European

individuals and 9,846 non-Europeans. Although studies showed that majority of the genetic risk were shared across diverse populations, a few loci that showed heterogeneous effects between populations were able to detect[18,19]. In older to reducing resulting ethnically related bias, our study population's genetic background was restricted to European ancestry. The summary statistics for IBD (N = 12,882 cases, 21,770 controls), UC (N = 6968 cases, 20,464 controls), and CD (N = 5956 cases, 14,927 controls).

FinnGen research project (https://r5.finngen.fi/) was used to identify genetic risk variants for conjunctivitis, keratitis, iridocyclitis, episcleritis, chorioretinitis, and optic neuritis. The summary statistics for conjunctivitis (N = 13,655 cases, 203,517 controls), keratitis (N = 5,561 cases, 209,287 controls), iridocyclitis (N = 3,622 cases, 209,287 controls), episcleritis (N = 660 cases, 209,287 controls), chorioretinitis (N = 384cases, 203,018 controls), and optic neuritis (N = 582 cases, 217,491 controls).

All participants were of European ancestry.

SNP Selection

Firstly, SNPs closely related to IBD were screened from the GWAS data ($P < 5\times10^{-8}$) at the genome-wide significance level. To further eliminate linkage disequilibrium, we take clump steps with the "TwoSampleMR" package of the R software, the parameter is set to $R^2 < 0.001$, and < 10000 from the index variant[20]. Secondly, the SNPs associated with outcome ($P < 5\times10^{-6}$) were excluded from retrieving each SNP from outcome GWAS. Meanwhile, palindromic SNPs and SNPs with non-concordant alleles were excluded from the process of harmonizing the IBD and outcome datasets[21,22]. Thirdly, MR Pleiotropy REsidual Sum and outlier (MR-PRESSO) is used to get rid of potential outliers before each MR Analysis[23]. Figure 1 shows the selection criteria and process of the above SNPs.

Mendelian randomization estimates

Three methods which included inverse variance weighting (IVW), weighted median (WM), and MR-Egger regression were performed in this study to estimate the causal association of exposures (IBD, UC, and CD) on risk of outcomes (ocular inflammation). IVW takes the inverse variance of each study as the weight to calculate the weighted average of effect sizes, to summarize the effect sizes of multiple independent studies, which can provide the most precise estimated results when all selected SNPs are valid IVs[24]. In this study, IVW was used as the primary outcome, while WM and MR-Egger were used to improve the estimation of IVW as they could provide more reliable, albeit less efficient estimates over a wider set of scenarios[25–28].

Sensitivity analysis

The MR-Egger intercept test was performed to assess the potential pleiotropic effects of the SNPs used as IVs[29]. If the MR-Egger intercept was statistically significant ($P < 0.05$), the MR analysis was considered to be unreliable. Additionally, to identify potentially influential SNPs, we performed a "leave-one-out" sensitivity analysis to where the MR is performed again but leaving out each SNP in turn. Heterogeneity

of IVs was assessed by Cochrane's Q-statistic. A P value of < 0.05 would be regarded as significant heterogeneity. Causal estimates are presented as odds ratios (ORs) with 95% confidence intervals.

Statistical analysis

Before MR analysis, F statistics of these IVs were calculated to determine whether there was a weak IV bias. Respectively, for all IVs, the F > 10, the impact of weak IV bias is small, so the selected SNPs can be further used in MR Studies[30].

"TwoSampleMR" was used in all statistical analysis software package (https://github.com/mrcieu/TwoSampleMR) and "MR-presSO" package (statistical computing internal resistance project) 4.2.0 version in R (version 3.6.1) packages. For a global-level test, a nominally significant two-sided P-value was set as 0.05. For region-level analyses, given the 12 MR estimates, a Bonferroni-corrected P-value was set as 0.05/12 (4.17×10^{-3}).

Results

Main Results

After excluding outlier SNPs through the MR-PRESSO global test and PhenoSacnner, we used the selected SNPs to explore the causal effects of genetically predicted IBD on ocular inflammation (Supplementary Table). Using these SNPs, we performed a comprehensive MR study and identified nominal and significant ocular inflammation influenced by IBD (Fig. 2).

Causal effects of IBD on Ocular Inflammation

The results of MR showed that genetically predicted IBD was associated with an increased risk of conjunctivitis (IVW: OR,1.05; 95% CI, 0.98–1.12; P = 1.94×10^{-3}), keratitis (IVW: OR, 1.05; 95% CI, 1.02–1.08; P = 6.42×10^{-3}; MR Egger: OR, 1.05; 95% CI, 0.99–1.12; P = 7.20×10^{-2}; WM: OR, 1.05; 95% CI, 1.02–1.10; P = 9.38×10^{-2}), iridocyclitis (IVW: OR, 1.18; 95% CI, 1.12–1.24; P = 6.83×10^{-11}; MR Egger: OR, 1.19; 95% CI, 1.14–1.45; P = 9.97×10^{-5}; WM: OR, 1.19; 95% CI, 1.11–1.29; P = 5.95×10^{-6}), optic neuritis (IVW: OR, 1.14; 95% CI, 1.02–1.28; P = 2.93×10^{-2}). It can be seen from the scatter plot (Figs. 3A-D) that the causal effect among the three methods is consistent. However, IVW, WM and MR-Egger methods showed no significant association of genetically predicted IBD on episcleritis and chorioretinitis (all P > 0.05). More details are shown in Fig. 4.

Causal effects of UC on Ocular Inflammation

The results of the IVW methods showed that genetically predicted UC was associated with an increased risk of keratitis (IVW: OR, 1.05; 95% CI, 1.01–1.10; P = 1.10×10^{-2}; MR Egger: OR, 1.11; 95% CI, 1.00-1.22; P = 5.95×10^{-6}), iridocyclitis (IVW: OR, 1.17; 95% CI, 1.10–1.24; P = 2.54×10^{-7}; WM: OR, 1.18; 95% CI, 1.08–1.28; P = 2.11×10^{-4}), optic neuritis (IVW: OR, 1.18; 95% CI, 1.04–1.24; P = 9.82×10^{-3}). It can be seen from the scatter plot that the causal effect among the three methods is consistent. It can be seen from the

scatter plot (Figs. 3E-G) that the causal effect among the three methods is consistent. However, IVW, WM and MR-Egger methods showed no significant association of genetically predicted UC on conjunctivitis, episcleritis, or chorioretinitis (all $P > 0.05$). More details are shown in Fig. 4.

Causal effects of CD on Ocular Inflammation

The results of the IVW methods showed that genetically predicted UC was associated with an increased risk of conjunctivitis (IVW: OR, 1.05; 95% CI, 1.03–1.08; $P = 3.20\times10^{-5}$; WM: OR, 1.06; 95% CI, 1.02–1.10; $P = 2.57\times10^{-3}$), keratitis (IVW: OR, 1.06; 95% CI, 1.02–1.09; $P = 1.13\times10^{-3}$), iridocyclitis (IVW: OR, 1.09; 95% CI, 1.04–1.14; $P = 1.43\times10^{-4}$; WM: OR, 1.12; 95% CI, 1.05–1.20; $P = 5.05\times10^{-4}$), optic neuritis (IVW: OR, 1.11; 95% CI, 0.95–1.32; $P = 4.80\times10^{-2}$). It can be seen from the scatter plot that the causal effect among the three methods is consistent. It can be seen from the scatter plot (Figs. 3H-K) that the causal effect among the three methods is consistent. However, IVW, WM and MR-Egger methods showed no significant association of genetically predicted UC on episcleritis, and chorioretinitis (all $P > 0.05$). More details are shown in Fig. 4.

Sensitivity analysis

To further verify the reliability of the above results, we performed pleiotropy, heterogeneity, and sensitivity analysis. No directional pleiotropy was found by MR-Egger regression analysis (Fig. 4). Actually, as we used the random-effects IVW as main result, heterogeneity is acceptable[32]. Furthermore, no outliers were identified with MR-PRESSSO and the leave-one-out plot as well as funnel plots (Supplementary Figure).

Discussion

Main Findings

The main finding of our study is that the UC causally increased the risk of iridocyclitis, and CD causally increased the risk of conjunctivitis, keratitis, and iridocyclitis, whose estimate passed Bonferroni correction. In addition, the estimated effect sizes of UC on conjunctivitis, optic neuritis, and CD on optic neuritis were nominally significant. Given that their IVW-derived $P < 0.05$ without passing Bonferroni correction, these estimates be treated cautiously. On the side, UC did not definitely increase keratitis, and IBD (including UC and CD) did not definitely increase episcleritis, or chorioretinitis, implying that the causal effects of IBD on ocular inflammation at different parts of the eye structure were different.

Results in Context with the Published Literature

Up to 50% of IBD patients experience at least one EIM, whose pathogenic mechanisms are not clearly defined, and unraveling the pathogenic pathways has the potential to enhance our understanding of the pathogenesis not only of EIMs but also of IBD overall[31]. Researchers reported most patients already have diagnosed IBD prior to the development of ocular EIM, and in a minority of cases the ocular disorders precede the diagnosis of IBD[11,33]. IBD may be active in a majority of patients when ophthalmic inflammation occurs, whose incidence of ocular EIM rates range from 3.5–11.8%[10,34]. Therefore, the

occurrence of ocular inflammation perhaps becomes the landmark event of the early onset of IBD, contributing to the clinical diagnosis and treatment of IBD and other EIM.

Reports indicate that the ecological dysregulation of gut microbiota (GM) in the human body could trigger the development of inflammatory, metabolic, mental, and immune diseases[35]. Studies have reported a relationship between and eye diseases[36]. Another study suggested that dysbacteriosis or clear changes in the healthy gut microbiome may be the decisive event in the occurrence and development of IBD[37]. In a meta-analysis of IBD that included over 3000 individuals, Mancabelli et al. reported Christensenellaceae as one of five taxa considered a sign of a healthy gut[38]. In Kangcheng et al. 's MR study on GM in diabetic retinopathy, they surmised that Christensenellaceae and Peptococcaceae might reduce inflammatory damage to the retina through the “intestinal-retinal axis”, thereby affecting disease progression in diabetic retinopathy[39]. Indeed, Christensenellaceae were consistently depleted in individuals with CD and ulcerative colitis, the two major sub-types of IBD[40–42].

Defining the causal relationship and pathogenic pathways in EIMs is challenging due to the lack of consistent criteria for diagnosis and the difficulty in distinguishing drug-induced extraintestinal pathologies from EIMs, including ocular inflammation[43]. In this study, we performed MR, which was able to rule out these confounding factors to determine the causal relationships between IBD with ocular inflammation. Furthermore, MR study uses open GWAS data, which can save research cost and time, and the data banks were all from European populations, avoiding population bias[44]. Compared with traditional experimental studies, MR simulates a more real random assignment process, the research design is relatively simple, and the research implementation will not violate ethics[45]. On the other hand, the MR analysis prevents confusion and provides a new approach to investigating the “gut-retina” axis mechanisms. Most importantly, it examines the etiological strength of the causal association between IBD and ocular inflammation risk.

The difference between the anterior and posterior segments of eye?

Summary of previous observational studies shows that: the most common eye EIMs is episcleritis, occurring in up to 29% of patients with IBD, and uveitis is less common with a prevalence of 0.5–5.3%, mainly including anterior uveitis, and very severe forms, such as scleritis, posterior or intermediate uveitis are rarer[46–49]. In our study, we found that IBD (including UC and UD) can cause iridocyclitis (the main inflammation involved in anterior uveitis), but neither can cause chorioretinitis (the main inflammation involved in posterior and intermediate uveitis), which partially supports previous observational studies. However, neither UC nor CD showed a cause-and-effect relationship with episcleritis in our study, which is not consistent with previous observational studies. This difference is first due to the fact that the results of observational epidemiological studies are affected by other relevant factors but not the disease itself, and one of the advantages of MR is that it can exclude such effects. An explanation for EIMs would see them as independent inflammatory events sharing common genetic or environmental risk factors with

IBD[49,50]. This study suggests that episcleritis in the course of IBD may be a parallel etiology that deserves to be investigated. Due to the high incidence of episcleritis in patients with IBD, external scleritis still needs attention, although there is no causal relationship between IBD and external scleritis.

Ernst el at. reported that the overall incidence of posterior segment manifestations is low, less than 1% in patients with IBD[12]. There was a similar trend in our study, and it was found that IBD (including UC and CD) had a nominal causal relationship with optic neuritis and no causal relationship with chorioretinitis. Faruque et al. thought this low incidence of posterior segment manifestations may be also due to the use of systemic steroids in the treatment of IBD and the rapid resolution of posterior segment manifestations with systemic steroids. Therefore, IBD may be somewhat associated with inflammation of the posterior segment of the eye, but it is weaker than the association with the anterior segment, given the causal relationship of IBD on conjunctivitis, keratitis, and iridocyclitis in this study.

The difference between UC and CD?

Usually, it is difficult to establish whether the diagnosis is UC or CD, and it may be several years before the clinical evolution allows a firm decision to be made, because different diseases UC and CD, share many features, including abdominal pain, diarrhea, and rectal bleeding[11]. Greenstein et al, who recorded a series of 700 patients with IBD, determining the relative incidence and characteristic features of EIM, have shown that ocular EIM is more frequent in CD than UC[51], consistent with other studies[52–54]. In this MR analysis assessing the causal link of IBD (including UC and CD) on ocular inflammation, we determined a significant causal effect of genetically predicted CD on conjunctivitis, keratitis, and iridocyclitis, whereas only got a significant causal effect of UC on iridocyclitis. UC nominally influence conjunctivitis but did not definitely influence keratitis. Therefore, CD may be more closely associated with the eye than UC and is more likely to lead to multiple inflammatory diseases of the eye. CD is a systemic disease with a long course, while UC is a mucosal disease of acute onset, often confined to the distal colon. In addition, CD has important immunological differences compared to UC[54,55]. These differences between the two diseases may be the cause.

Limitations

The study has some limitations. First, it should be noted that the selected GWAS data was all the results of a meta-analysis that had been adjusted for age and sex, and the data for ocular inflammation were all from the Finnish database[56]. Although all the IVs we selected were strong, there is no denying that sample overlap can lead to bias. Secondly, our MR study showed that IBD predicted by genetics had a causal effect on ocular inflammation, but the results of MR Analysis were only genetic evidence. This possible causal relationship and its related mechanisms must be further explored and verified in animal experiments or in population-based observational studies. Thirdly, although the symptoms of ocular inflammation were confined to the eye with subtle or even no effects on gut, we were unable to identify a possible mutual causal relationship between ocular inflammation and IBD due to the lack of an adequate number of IVs for reverse MR analysis.

Conclusions

Our estimates illustrate that IBD causally poses a risk of inflammation of conjunctival, cornea, and iris-ciliary, rather than the posterior segment of eye, which suggests that IBD may have different effects in different eye structures, providing novel evidence linking based on the association of the gut-eye axis. Moreover, IBD showed no cause-and-effect relationship with episcleritis, which is inconsistent with previous observational studies. This difference may be due to the fact that the results of observational epidemiological studies are affected by confounding factors. And CD is more closely associated with the eye than UC, which means UC is more likely to cause multiple inflammation of the eye. Our study is a comprehensive MR analysis that reveals associations between IBD and ocular inflammation and is beneficial to the diagnosis and differentiation of UC and CD. The mechanisms of the association between them should be studied further.

Declarations

Ethics approval and consent to participate

Ethical approval was not sought for this specific project because all data came from the summary statistics of published GWAS, and no individual-level data were used.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available in the https://gwas.mrcieu.ac.uk and https://msk.hugeamp.org.

Competing interests

There are no competing interests for any author.

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Authors' contributions

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Figures

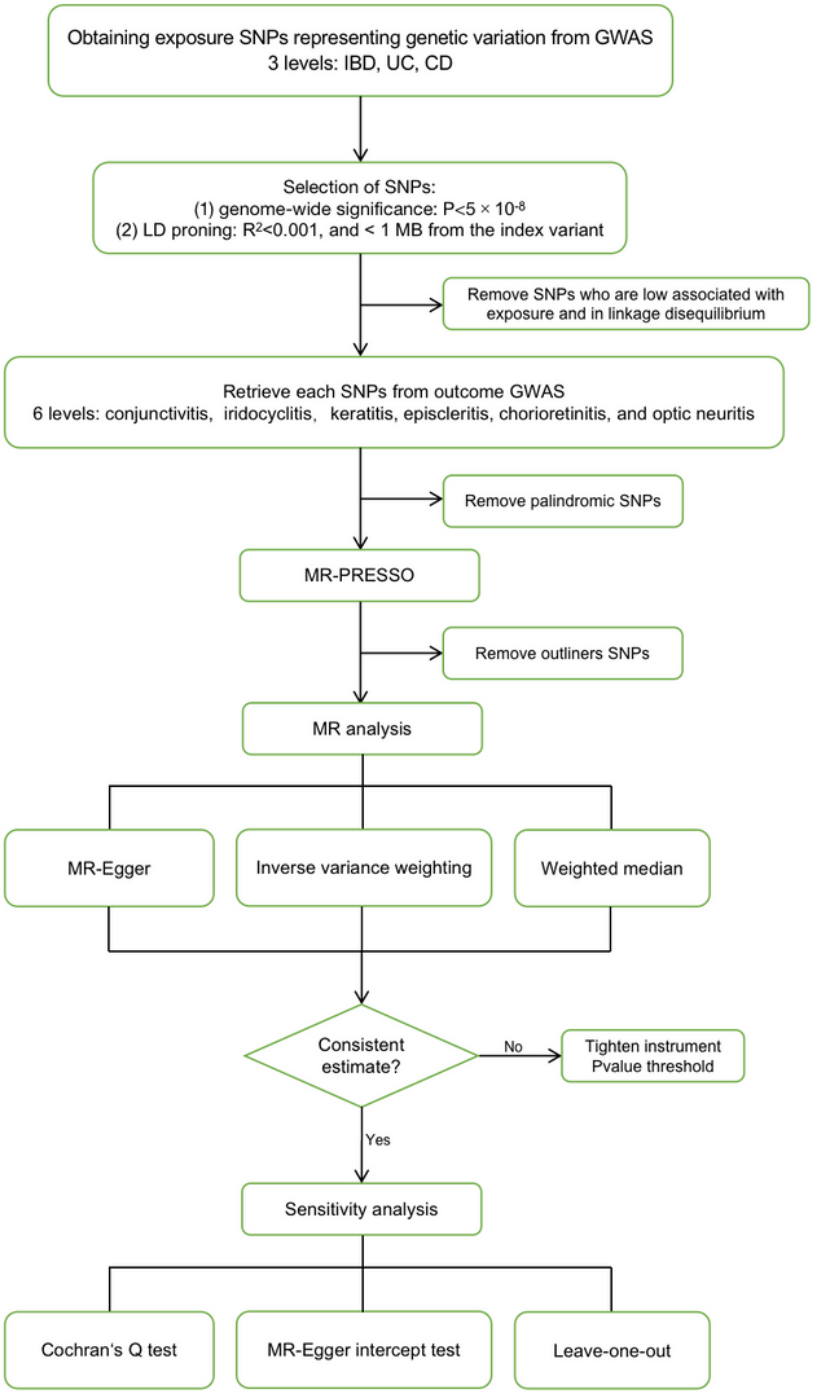

Figure 1

Study flame chart of the MR study revealing the causal relationship of IBD on the risk of ocular inflammation.

SNP, single-nucleotide polymorphisms; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; LD, linkage disequilibrium; MR-PRESSO, MR Pleiotropy

REsidual Sum and outlier.

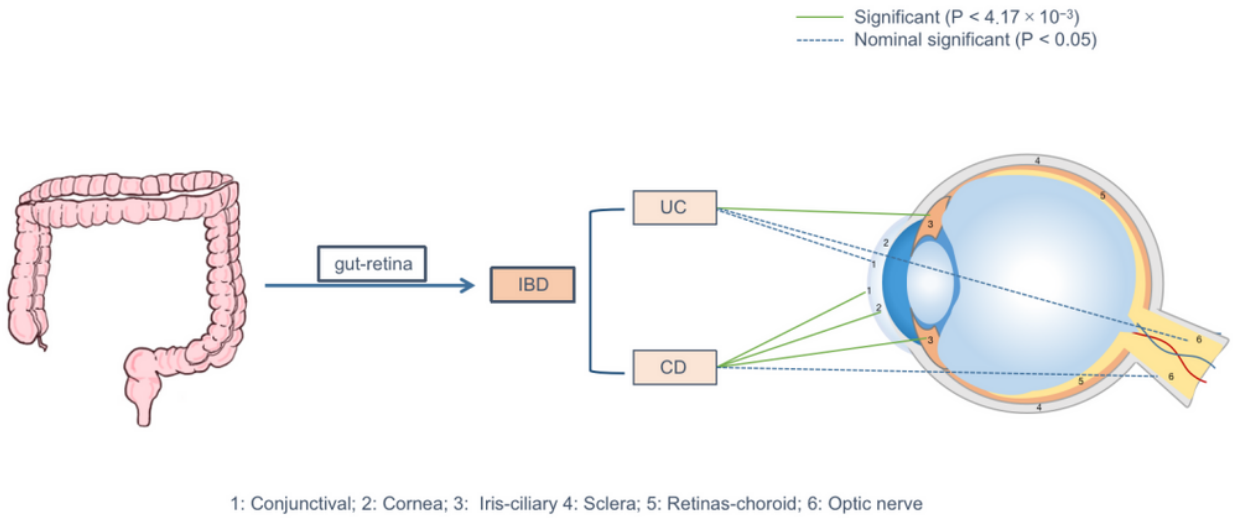

Figure 2

Using two-sample MR framework, we reveal that IBD causally influences ocular inflammation, supporting the existence of eye-brain axis.

**: P value of IVW estimate <4.17×10^{-3} is set as significant, represented in solid line whereas <0.05 is set as nominal significant, represented in dotted line.

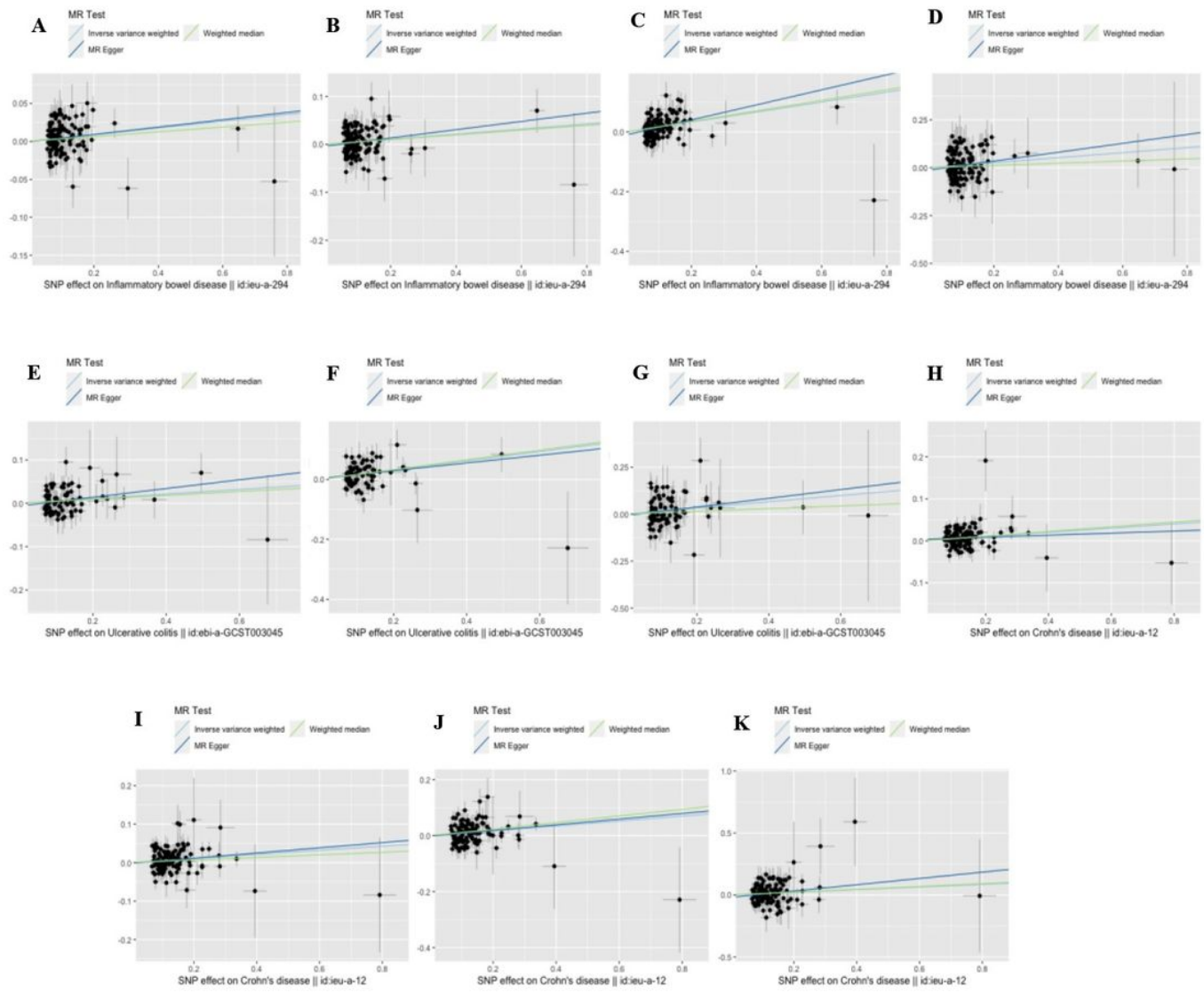

Figure 3

Scatter plots for MR analyses of the causal effect of IBD (including UC and CD) on ocular inflammation.

(A) IBD-conjunctivitis (B) IBD-keratitis (C) IBD-iridocyclitis (D) IBD-optic neuritis

(E) UC-keratitis (F) UC-iridocyclitis (G) UC-optic neuritis (H) CD-conjunctivitis

(I) CD-keratitis (J) CD-iridocyclitis (K) CD-optic neuritis

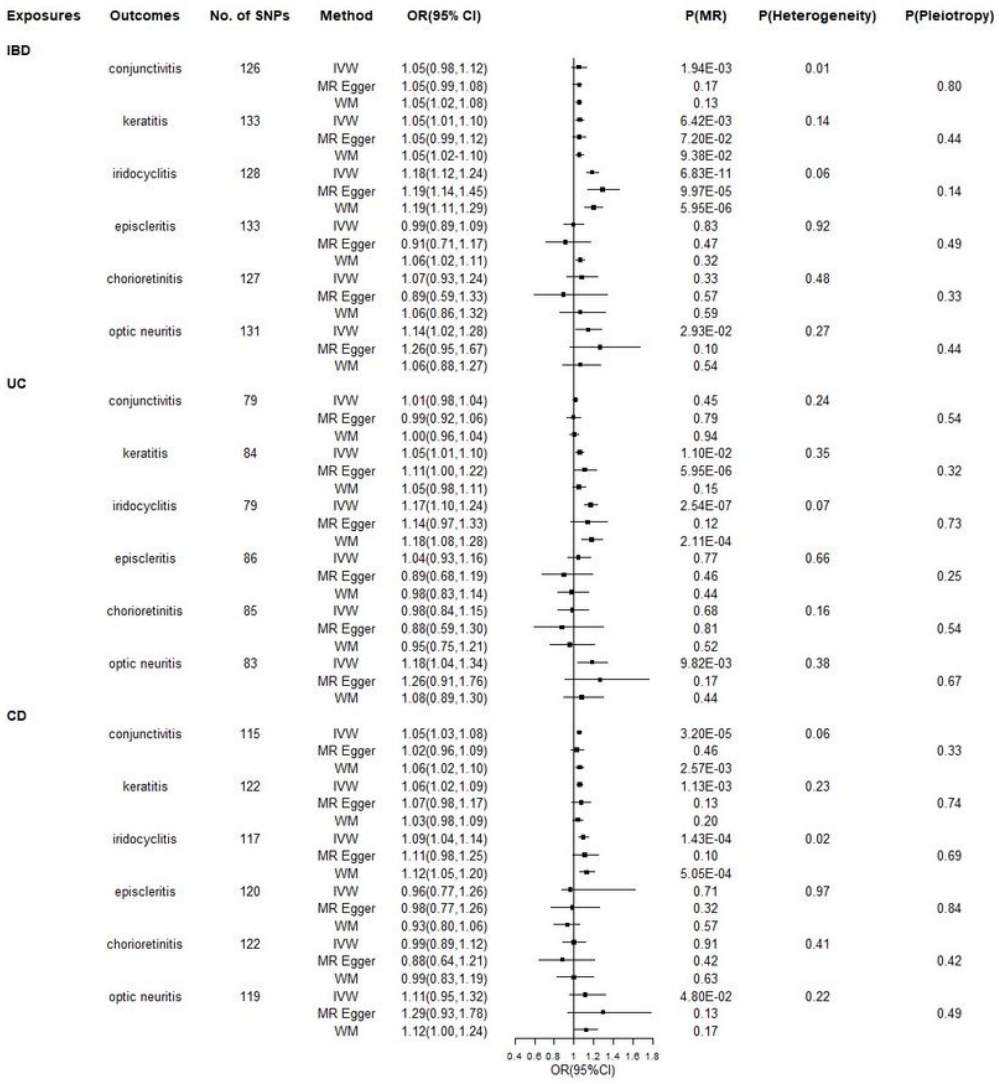

Figure 4

Association of IBD (including UC and CD) on ocular inflammation risk using MR.

SNP, single-nucleotide polymorphism; OR = odds ratio; CI, confidence interval; MR, Mendelian randomization; P(Heterogeneity) , P value for heterogeneity using Cochran Q test; P(Pleiotropy), P value for MR-Egger intercept; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure.docx
- SupplementaryTable.xlsx