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Abstract

Background: Gout and IgA nephropathy (IgAN) are two prevalent extra-intestinal symptoms of inflammatory bowel disease (IBD). However, no randomized controlled experiment has found a link between Crohn's disease (CD) and gout or IBD and IgAN. Thus, the causal relationship between IBD, gout, and IgAN is studied using two-sample Mendelian Randomization and Genome-wide association studies (GWAS) summary statistics.

Methods: Several quality control processes were used to select qualified instrumental SNPs associated with exposure. To ensure the trustworthiness of the conclusion, inverse variance weighted, MR Egger, weighted median, and weighted mode methods were used. To estimate eligible instruments' stability, horizontal pleiotropy, and heterogeneity, leave-one-out analysis, MR-Egger intercept, and Cochran's Q test were used.

Results: At a genetic level, MR analysis revealed that gout was associated with CD (IVW: $P = 0.01$). IBD was also found to increase the probability of IgAN (IVW: $P =$ 4.77e-7).

Conclusions: Gout increased the likelihood of CD, and IBD caused IgAN, according to a Mendelian randomization study. A larger sample size is required to discuss further the causal influence of gout on Crohn's disease.

Keywords: Two-sample Mendelian randomization, Gout, IgA nephropathy, Crohn's disease, Inflammatory bowel disease

Introduction

Gout is caused by hyperuricaemia and the crystallization of monosodium urate and often appears as inflammatory arthritis. Gout affects an estimated 9% of American adults older than 60 years, 1.1% mainland Chinese, and at least 8% indigenous Taiwanese [1]. Genetic factors, chronic renal problems, nutrition, and medications are all risk factors. Urate transporters found in the gut, liver, and kidney have been linked to urate excretion and blood urate levels, according to genome-wide association studies (GWAS) [2]. Studies also reveal that cytokines, especially IL-1β and NLRP3 inflammasome, mediate the autoimmune response [3]. Hence, urate-lowering agents and anti-inflammatory drugs are suggested.

IgA nephropathy (IgAN) is distinguished by the presence of an IgA-dominant or co-dominant immune complex in the glomeruli. Specific IgA and IgG autoantibodies bind to galactose-deficient IgA1 and cause waterfall-like autoimmune reactions that cause glomerular injury. GWAS data demonstrate that IgAN-related genetic loci overlap with intestinal mucosal integrity and the immune network [4]. East Asians have the riskiest alleles, while Africans have the least difficult genetic background. 30-40% of IgAN patients will progress to end-stage renal disease. The diagnosis is aided by hematuria and immunofluorescence microscopy [5]. Glomerular, tubular, and interstitial changes all have prognostic significance in IgAN. There are no specific treatments for IgAN at the moment, but immunosuppressive agents, steroids, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) can help maintain renal function and blood pressure [6]. To improve reproducibility, well-designed prognostic models that fully use histological lesions and clinical features are required.

Inflammatory bowel disease (IBD) refers to a group of nonspecific gastrointestinal disorders that includes ulcerative colitis (UC), Crohn's disease (CD), and IBD unclassified (IBDU). IBD has been a global burden, affecting 0.3% of Europeans and large numbers of people in developing countries [7]. In addition, recurrent gastrointestinal lesions in CD and acute UC flares in the colon reduce the

quality of life for millions of patients. Susceptibility can be attributed to genetic instability, risky environmental elements, damaged mucosa, microbial dysfunction, and immune imbalance [8]. These risk factors have been linked to extra-intestinal manifestations of IBD, such as musculoskeletal, ocular, and urologic symptoms [9]. IBD comorbidities include arthrosis and IgAN. Clinical research has also looked into the link between uric acid stones and CD and IBD and IgA nephrology [10], as well as IBD and IgA nephrology [11]. Gout patients frequently have elevated uric acid levels and arthritis. Although the association between gout and CD and IBD and IgA nephrology has been discussed, a study revealing their genetic basis is still required.

Two-sample using GWAS data, Mendelian randomization is a method for estimating the causal effect of an exposure on an outcome. SNPs (single nucleotide polymorphisms) are frequently used as genetic tools. It must fulfil three requirements. First, the SNPs chosen must be strongly related to the exposure. Second, instruments that are influenced by confounding factors that connect exposure and outcome should be eliminated. Third, the devices cause the disease solely because of our chosen exposure phenotype. In this study, a two-sample MR was used to investigate the relationship between gout and Crohn's disease and IgAN and IBD using the GWAS database.

Methods

GWAS summary statistics of IBD, gout and IgA nephropathy

All instruments can be searched in publically available IEU GWAS project (https://gwas.mrcieu.ac.uk/) with ID number or specific trait. It was convenient to use the Twosample MR R package to link this database to RStudio. The summary data of GWAS pipeline using Phesant derived variables from UKBiobank for non-cancer illness code, self-reported: gout by Ben Elsworth et al. (*ID:* ukb-b-13251; *N*=6543 cases, 456390 controls; https://gwas.mrcieu.ac.uk/datasets/ukb-b-13251/) was gained. Summary statistics for Non-cancer illness code self-reported: Crohn's disease by Neale et al. (*ID:* ukb-a-103; *N*=1032 cases, 336127 controls;

https://gwas.mrcieu.ac.uk/datasets/ukb-a-103/) was employed. All subjects are of European origin.

For IBD, a study by Liu et al. included in GWAS was applicable (*ID:* ieu-a-294; *N*=31665 cases, 33977 controls; https://gwas.mrcieu.ac.uk/datasets/ieu-a-294/). We chose the summary GWAS data for IgA nephropathy (*ID:* ieu-a-1081; *N*=977 cases, 4980 controls; https://gwas.mrcieu.ac.uk/datasets/ieu-a-1081/). All subjects are European people.

MR analysis

This estimate used genetic instruments with acceptable significance ($P < 0.05$) to ensure that no potential risk factors were overlooked. The exposure and outcome data were then synchronized. The main method was inverse variance weighted (IVW), with MR Egger, weighted median, and weighted mode as auxiliary indexes. IVW is based on the assumption that all SNPs are eligible and reflects linear causality [12]. MR Egger tolerates invalid SNPs and reflects average pleiotropy [13, 14]. Weighted median allows for 50% invalid instruments and demonstrates the causality of the median result of the weighted empirical density function of SNP-outcome/SNP-exposure ratio [15]. The weighted mode uses a weighted observed density function to calculate SNP-outcome/SNP-exposure ratio [16]. The entire procedure was carried out using TwosampleMR R package (https://github.com/MRCIEU/TwoSampleMR) [17].

Sensitivity analysis

To ensure data conformity, a heterogeneity test was performed [18]. The MR Egger intercept was used to determine whether the results were driven by directional horizontal pleiotropy [19]. To eliminate significant single SNPs that cause bias, leave-one-out analysis was used.

Results

Causal effect of gout on Crohn's disease

Table 1 shows the results of MR analysis that revealed the causality of gout on Crohn's disease (CD) using various methods. **Table 1** results are depicted in **Fig. 1**. Gout was found to cause CD (IVW: *OR*: 1.03, *P* = 0.01; MR Egger: *OR*: 1.04, *P* = 0.04). There was no significant heterogeneity (IVW: *P* = 0.08; MR Egger: *P* = 0.08) and genetic pleiotropy (*P* = 0.37).The absence of pleiotropy was also demonstrated by the intercept being close to zero. The single SNP analysis in **Fig. 2** demonstrated the estimate of each SNP, whereas the forest plot in **Fig. 3** compared the causal effect of methods using single SNPs to methods using all SNPs. In **Fig. 4**, the leave-one-out analysis revealed no significant SNPs that produced biased results. Furthermore, the asymmetrical image of the funnel plot in **Fig. 5** reflected the dependability of the result.

Causal effect of IBD on IgA nephropathy

Table 2 depicts MR analysis of the IBD causality on IgA nephropathy (IgAN) using IVW, weighted median, weighted mode and MR Egger. **Fig. 6** visualizes the results in different methods (IVW: *OR*: 1.71, *P* = 4.77e-7; MR Egger: *OR*: 1.73, *P* = 1.53e-1). These results identified that IBD increased the risk of IgAN. No significant heterogeneity (IVW: *P* = 0.25; MR Egger: *P* = 0.23) and horizontal pleiotropy (*P* = 0.78) were observed. **Figs. 7** and **8** illustrate a single SNP analysis and a forest plot, respectively. No biased SNPs were found in the leave-one-out analysis shown in **Fig. 9**. The funnel plot in **Fig. 10** demonstrated the result's dependability even further.

Discussion:

Our MR analysis results provide genetic evidence for the relationship between gout and Crohn's disease, as well as inflammatory bowel disease (IBD) and IgA nephropathy (IgAN).

Arthritis and increased uric acid are common complications of IBD and are also considered typical gout symptoms. Emerging research has also found elevated uric

acid levels in CD patients but not in ulcerative colitis patients (UC). In terms of comprehension, studies have linked gout to CD rather than UC. Two prevalent theories can account for it. One is concerned with anti-oxidative stress. UC is distinguished by damaged mucous, whereas CD destroys submucous. In gout patients, increased purine metabolism is accompanied by active xanthine oxidase in the mucous layer, generating reactive oxygen species (ROS) and causing gut impairing symptoms [20, 21]. However, in CD patients, the mucous has already been compromised, and studies have revealed no significantly elevated xanthine oxidase activity. Another consideration is mucous integrity. Uric acid treatment reduced the expression of E-cadheration, a cell adhesion protein, as well as the zonula occludes protein, such as protein claudin-1 [22]. These changes weaken the intestinal barrier. However, a study contradicted the preceding conclusion. It was found that gout is not significant comorbidity of IBD patients compared to non-IBD patients [23]. The results may be different if volunteers are further divided into UC, CD, and IBDU.

IgAN and IBD share immunological and genetic imbalances. The overactivation of B cells causes the dominance of IgA1. Furthermore, gut microbes are predicted to activate B cells via a T cell-independent pathway. One example is BAFF overexpression in both IBD and IgAN patients. Moreover, some IBD patients have higher levels of miR-133b expression, which inhibits Treg differentiation in IgAN [24]. IgAN loci are genetically linked to IBD risk genes (HLA-DQ and HORMAD2), mucosal integrity, and immune response genes (DEFA and VAV3). Overall, the immune response connects IBD and IgAN [25, 26]. In addition, our MR analysis first reveals their correlations in a cost-effective and time-saving manner.

We must admit that this study could be improved. First, all SNPs are of European origin, implying that we must proceed with caution when applying the conclusion to other populations. Second, the size of SNPs used to investigate the relationship between gout and CD is insufficient. The findings can be scrutinized using a more recent GWAS database.

Conclusion:

By two-sample MR analysis, we initially bridge the connections between gout and Crohn's disease (CD), as well as inflammatory bowel disease (IBD) and IgA nephropathy (IgAN). We found that gout increases the risk of Crohn's disease and that IBD patients are more prone to IgAN. More importantly, we provide genetic evidence for clinical practitioners to prevent risky diseases and search for more effective treatments.

Declarations

Ethics

Publicly available **GWAS summary data** for free use was employed in our study. Since our study didn't include our original data, no ethical approval was needed. Any GWAS data involved was approved by their ethics review committee.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Chuyuan Ye did the main job. Jianhua Lu, Danna Liang and Gongting Zhou helped analyzed the result. Chenxin Yang gave the inspirations. Wei Zhang modified the language. Hao Wu, Xiufeng Huang, Limiao Lin, Yongdong Yi and Weijian Sun gave the suggestions and guidance.

Acknowlegements

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Consent for publication

All the data downloaded are publicly free for use, so consent for publication in this section is not applicable.

Availability of Data and Materials statement

The datasets used during the current study are available in the Genome Wide Association Study (GWAS) repository (https://gwas.mrcieu.ac.uk/). All the data are analyzed in RStudio (see **supplementary**).

Abbreviations

IgAN: IgA nephrology; **IBD**: inflammatory bowel disease; **CD**: Crohn's disease; **UC**: ulcerative colitis; **GWAS**: Genome-wide association studies; **ACEIs**: angiotensin-converting enzyme inhibitors; **ARBs**: angiotensin receptor blockers; **IBDU**: IBD unclassified; **SNPs**: single nucleotide polymorphisms; **ROS**: reactive oxygen species.

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Fig. 1 Scatter plots for MR analysis revealing the causality of gout on Crohn's disease by using IVW, MR Egger, weighted median and weighted mode.

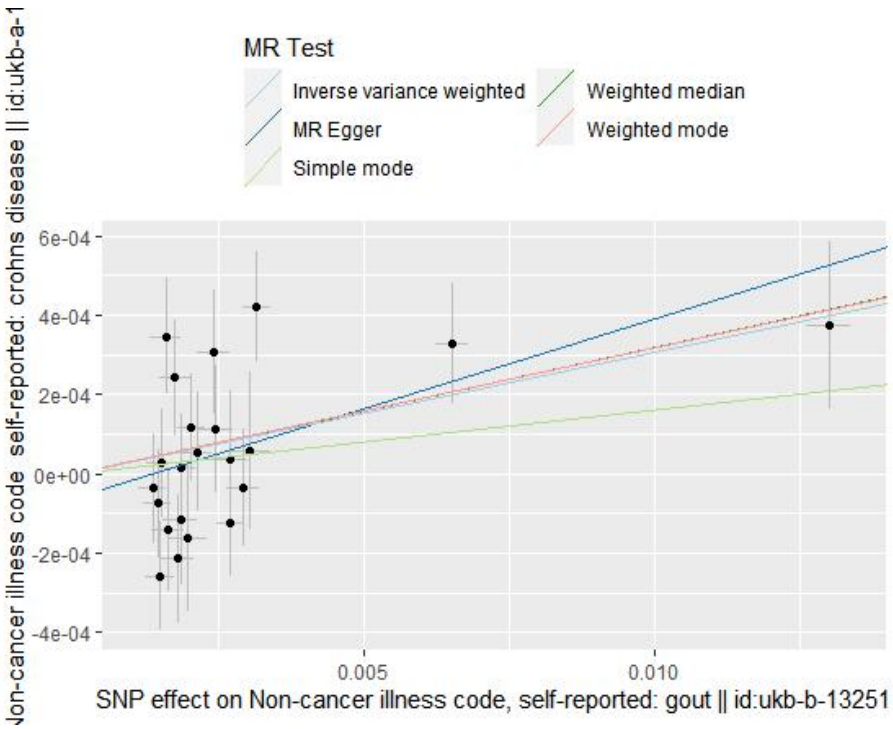


Fig. 2 Single SNP analysis demonstrating each SNP's causal effect by using default IVW and MR Egger methods.

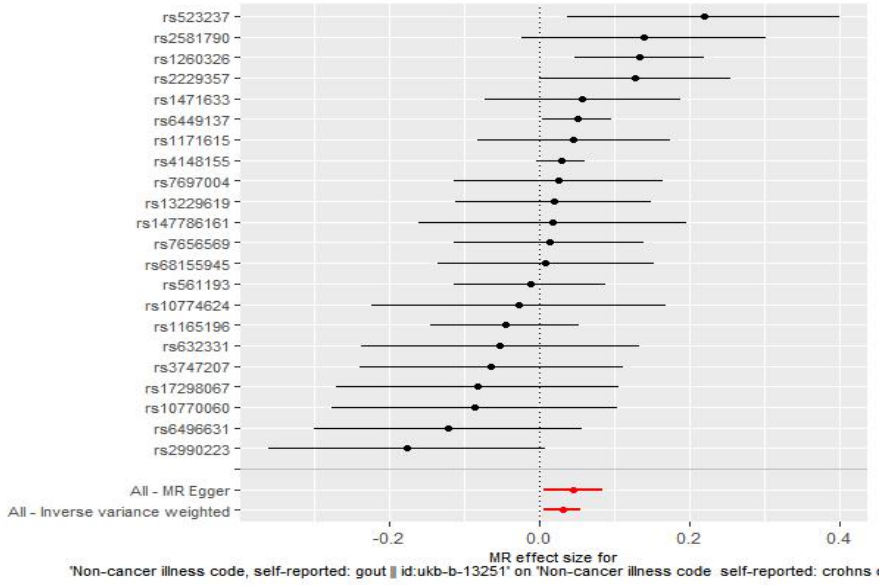


Fig. 3 Forest plot for investigating the causality of gout on Crohn's disease.

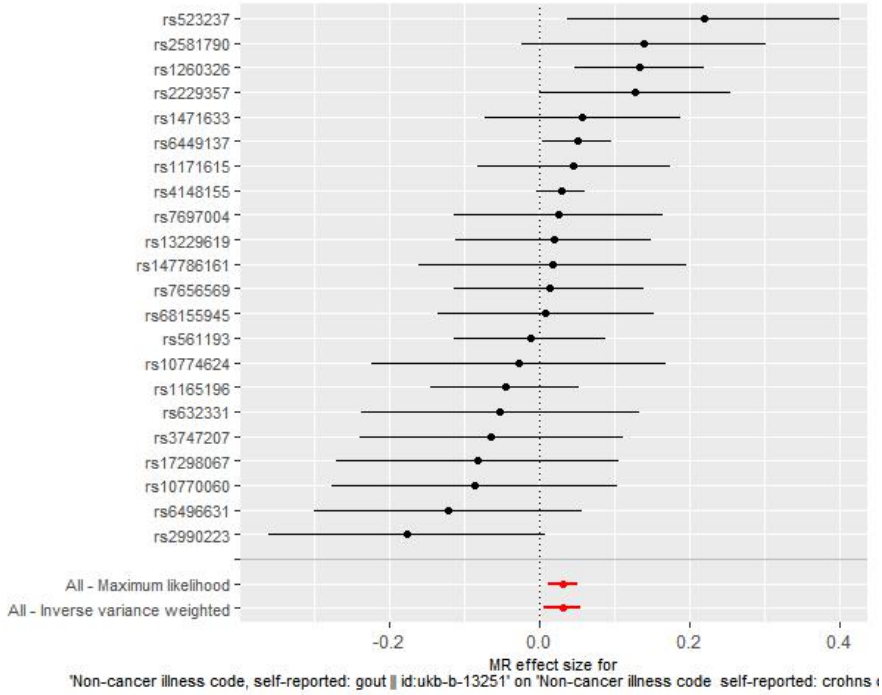


Fig.4 Leave-one-out analysis for probing the causal effect of gout on Crohn's disease.

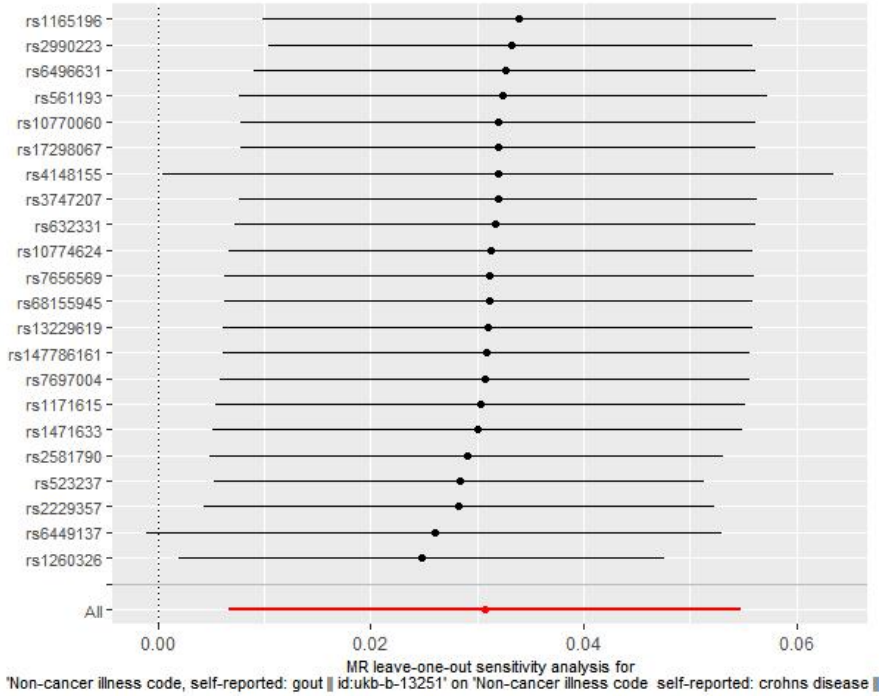


Fig.5 Funnel plot for the causality of gout on Crohn's disease.

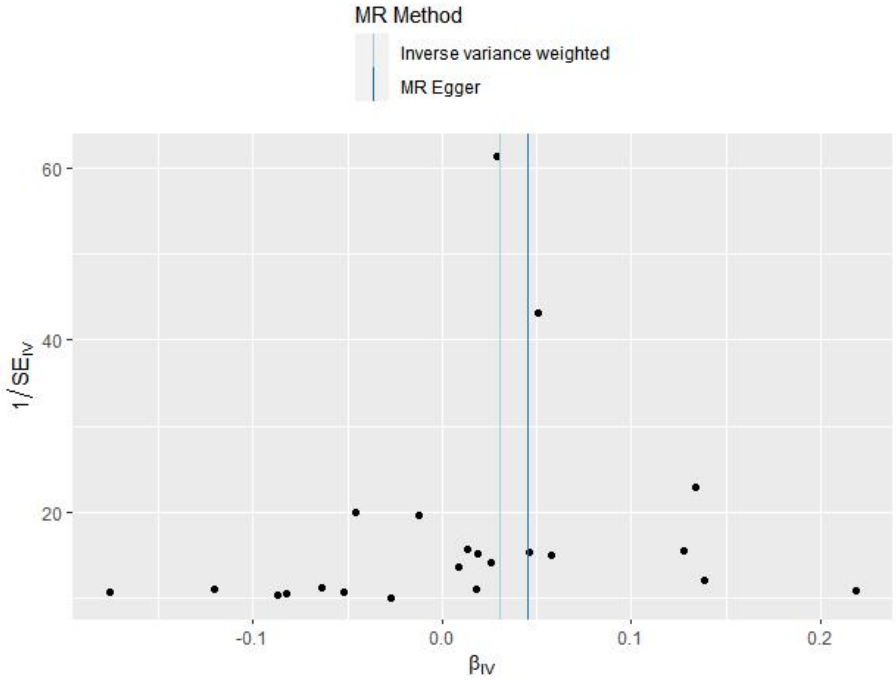


Fig. 6 Scatter plots of MR analysis for the causality of IBD on IgA nephropathy by using IVW, MR Egger, weighted median and weighted mode.

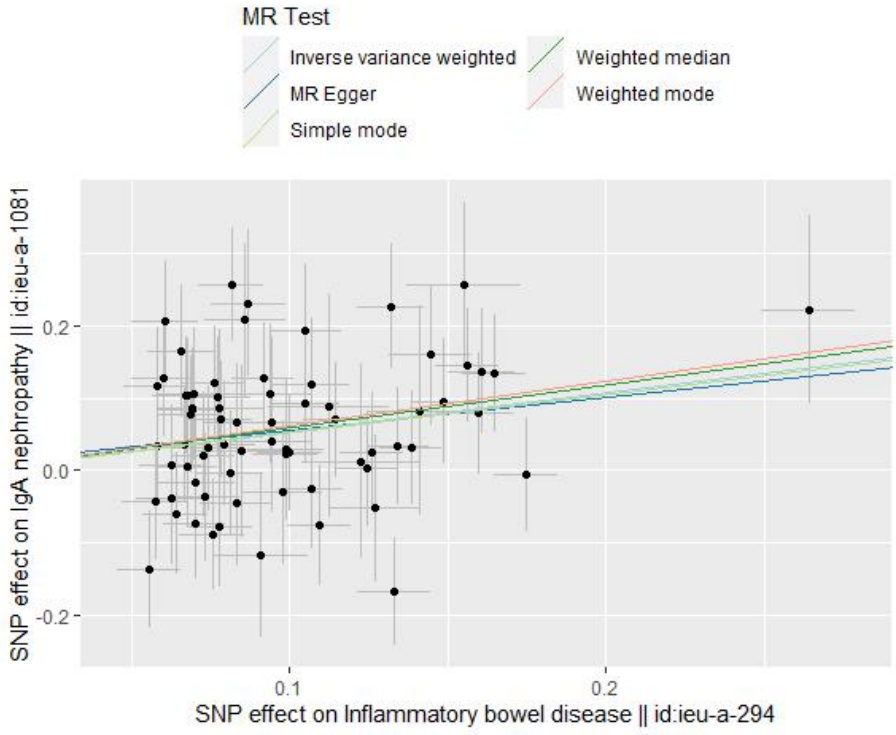


Fig. 7 Single SNP analysis demonstrating each SNP's causal effect by using default IVW and MR Egger methods.

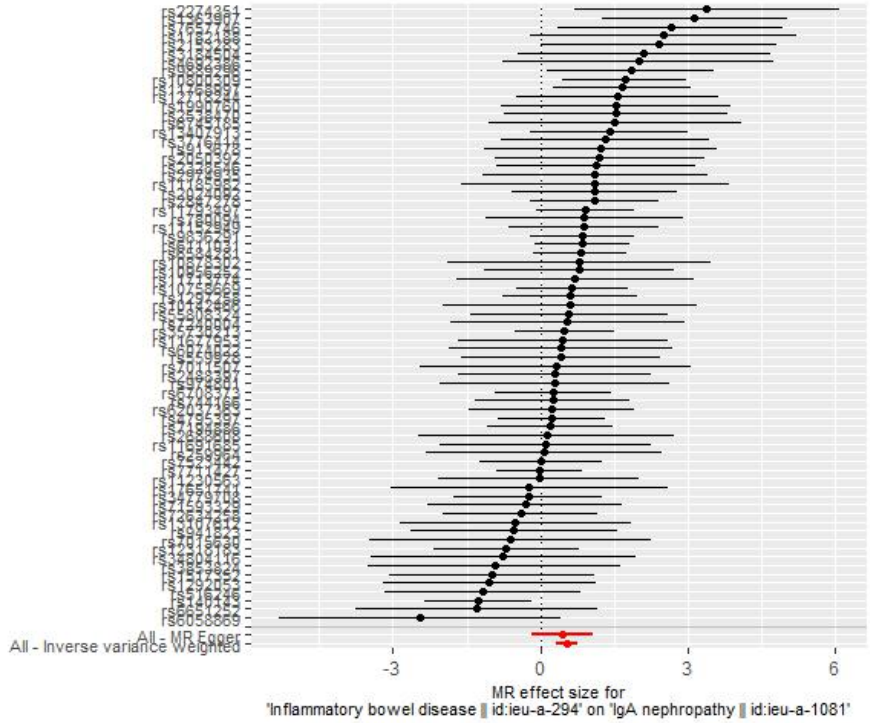


Fig. 8 Forest plot for identifying the causality of IBD on IgA nephropathy.

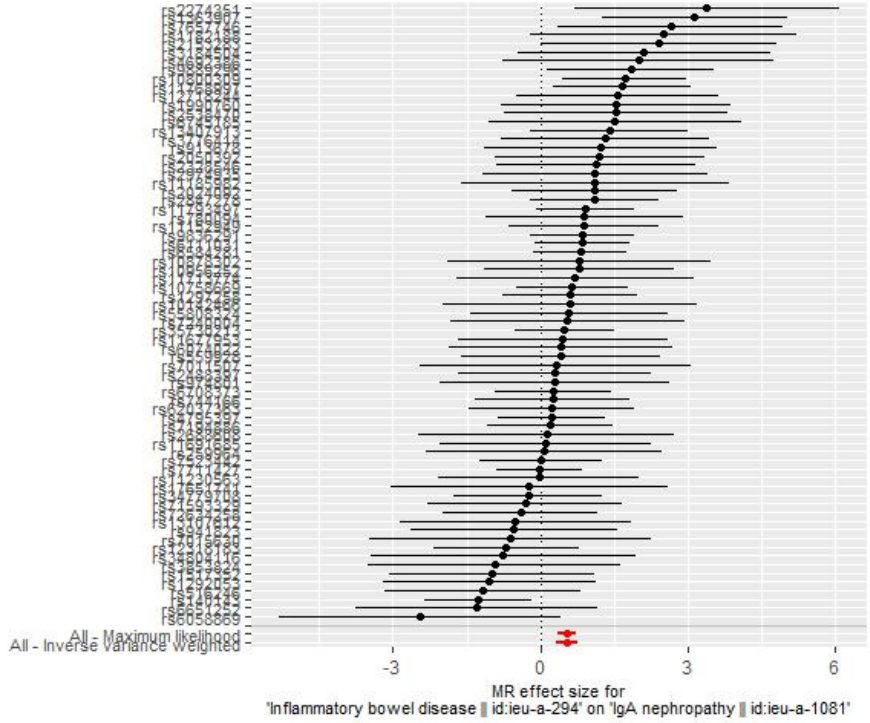


Fig.9 Leave-one-out analysis of the causal effect of IBD on IgA nephropathy.

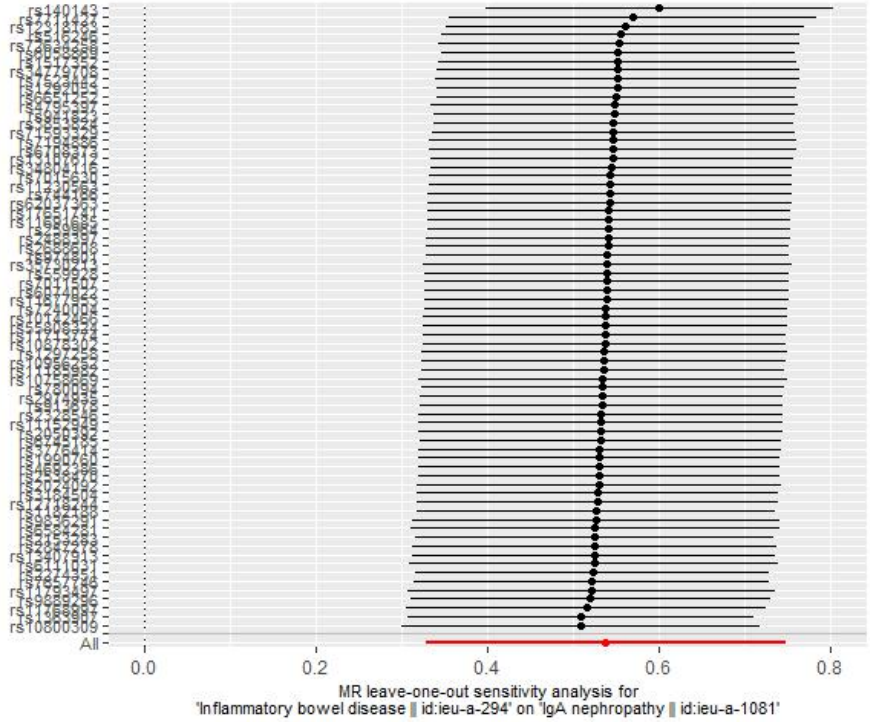
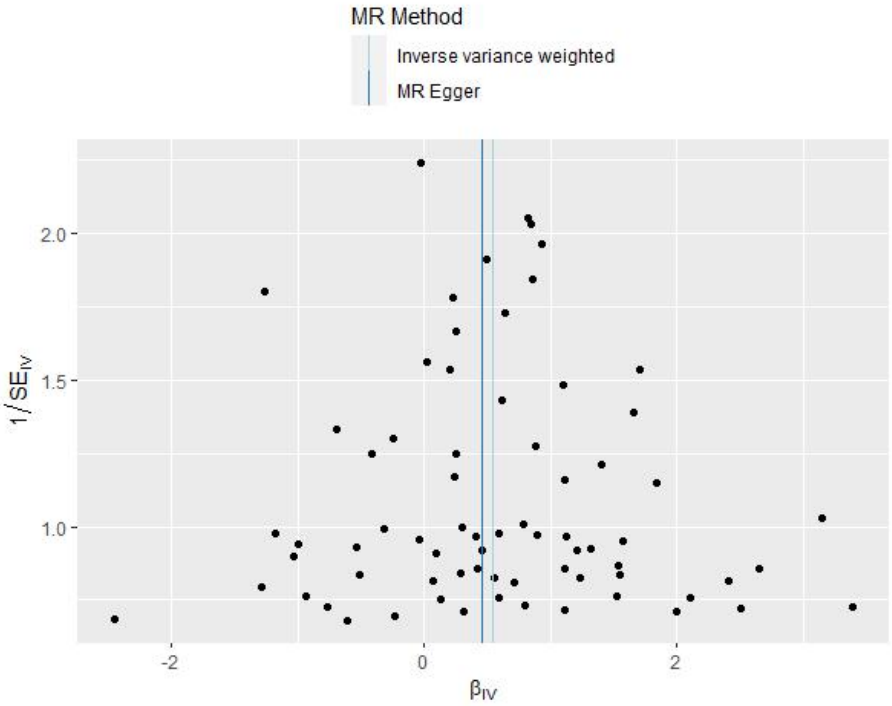


Fig.10 Funnel plot for the causal link of IBD on IgA nephropathy.



Supplementary Files

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- table.pdf
- IBDIgA.png
- 5.png