The causal relationship between immune-mediated inflammatory diseases and aortic aneurysm: A bidirectional two-sample Mendelian randomization study

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Abstract

Introduction: Many observational studies have identified aortic aneurysm (AA) as a cardiovascular complication of immune-mediated inflammatory diseases (IMIDs). However, due to the effects of various confounders, it is still uncertainty whether this association holds or whether reverse causality is involved. Here we conducted a two-sample bidirectional MR study to infer the causal relationships between the two diseases. **Method:** We obtained genetic association datasets from public GWAS databases in populations of European ancestry. Abiding by the assumptions of Mendelian randomization (MR), we selected valid instrumental variables from genetic variants. Different statistic methods were performed for MR analysis and sensitivity analysis, and the inverse variance weighted (IVW) method was regarded as the most efficient estimate of the causal effect in this study. **Results:** The IVW method found evidence that genetically predicted AA had a causal effect on rheumatoid arthritis (RA) (OR = 1.06, 95%CI = 1.01-1.12, $p = 0.029$), but not of RA or other IMIDs on AA. Besides, no evidence showed that AA may increase the risk of inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE) and psoriasis (PSO). The sensitivity analysis confirmed the absence of heterogeneity or horizontal pleiotropy effect. **Conclusion:** In summary, our study discovered that genetically predicted AA may increase the risk of RA, while no evidence was found that patients with RA had an increased risk of AA. Furthermore, we confirmed no evidence of association between IBD, CD, UC, SLE, PSO and AA. This is in accordance with other reports that demonstrated the human leukocyte antigen molecule in inflammatory aortic aneurysm was a genetic risk loci. Our study provides directions for future research on genetic susceptibility to inflammatory aortic aneurysm.

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Results: The IVW method found evidence that genetically predicted AA had a causal effect on rheumatoid arthritis (RA) (OR = 1.06, 95%CI = 1.01-1.12, $p = 0.029$), but not of RA or other IMIDs on AA. Besides, no evidence showed that AA may increase the risk of inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE) and psoriasis (PSO). The sensitivity analysis confirmed the absence of heterogeneity or horizontal pleiotropy effect.

Conclusion: In summary, our study discovered that genetically predicted AA may increase the risk of RA, while no evidence was found that patients with RA had an increased risk of AA. Furthermore, we confirmed no evidence of association between IBD, CD, UC, SLE, PSO and AA. This is in accordance with other reports that demonstrated the human leukocyte antigen molecule in inflammatory aortic aneurysm was a genetic risk loci. Our study provides directions for future research on genetic susceptibility to inflammatory aortic aneurysm.

Keywords: aortic aneurysm, immune-mediated inflammatory diseases, Mendelian randomization, inflammatory aortic aneurysm, rheumatoid arthritis.

Introduction

Aortic aneurysm (AA) is a chronic condition of the aorta characterized by localized distension or weakening of its wall, which may lead to rupture and severe internal bleeding resulting in shock(1). With an incidence rate of approximately 3 per 100,000 individuals worldwide(2), AA ranks second only to atherosclerosis in prevalence and represents the most common disease affecting the aorta(3). AA is considered to be a chronic degenerative disease caused by local damage to the aortic wall, mainly related to chronic inflammatory infiltration(4). Ruptured aortic aneurysms can result in immediate fatality. For patients with apparent symptoms or large diameter aortic aneurysms, open surgery or endovascular repair remains the sole treatment option(4, 5).

Immune-mediated inflammatory diseases (IMIDs) are a collection of chronic inflammatory disorders that involve multiple systems and organs, characterized by common mechanisms of inflammation and immune dysregulation(6). IMIDs comprise a spectrum of disorders, and the presence of multiple systemic symptoms impose a significant burden on healthcare resources(7). Individuals with immune-mediated inflammatory diseases (IMIDs) are at a significantly increased risk of cardiovascular complications, due to both the disease itself and certain corticosteroid medications used in its treatment(8, 9). Of note, atherosclerosis(10) and large vessel vasculitis(11), which are prone to the development of dilated aortic aneurysms, are considered to be immune system-mediated processes. This suggests a potential common genetic etiology or pathogenesis between AA and IMIDs. Although observational studies(12-20) have linked IMIDs with cardiovascular disease (CVD), it is still unclear whether patients with AA are at increased risk of IMIDs. Reverse causation may also account for the association, whereby AA increases the risk of IMIDs rather than vice versa(21). Confounding factors can easily distort the interpretation from observational studies, leading to a fallacious inference of causality. Meanwhile, despite being the standard epidemiological design for establishing causal relationships, randomized controlled trials (RCTs) have some limitations. These include the significant investment of time, manpower and financial resources required to conduct them, as well as strict inclusion and exclusion criteria that can limit the representativeness and external validity of research findings. Therefore, more robust methods are required to assess causality using available data.

Mendelian randomization (MR) experiments use variants of genetic loci as instrumental variables (IVs) to investigate the association between exposure and health outcomes. Unlike conventional RCTs and observational studies, MR studies are not suffered to confounders. In MR, genetic variants serve as IVs for exposures to help the identification potential causal effect with disease-related outcomes(22, 23). Generally, the IVs must fulfill these three assumptions: (1) the IVs are strongly associated with the exposure; (2) the IVs are independent of other factors that may affect the inference of causal relationship; and (3) the IVs do not affect the outcome except with its potential effect on the exposure(24). Besides, germ-line genotypes are established during conception and precede the observed variables in temporal sequence, thus avoiding issues of reverse causality(25). Here, we obtained public datasets from various genome-wide association studies (GWASs) of IMIDs (including IBD, CD, UC, RA, SLE, and PSO) and AA in populations of European ancestry and performed a two-sample bidirectional MR study to infer the magnitude and direction of causal associations between the two diseases.

Methods

2.1 Data sources and study design

To explore the causal relationship between IMIDs and AA, we utilized summary genetic association datasets of European ancestry for both IMIDs and AA from the IEU OpenGWAS Database Project (https://gwas.mrcieu.ac.uk/). The GWAS summary statistics for AA (GWAS ID: finn-b-I9_AORTANEUR) were obtained from the FinnGen cohorts' Aortic aneurysm GWAS summary statistics, which included 2,825 cases and 206,541 controls with 16,380,417 SNPs (https://r5.finngen.fi/pheno/I9_AORTANEUR). In FinnGen Release 5, the diagnostic criteria for AA are defined in the following link (https://r5.risteys.finngen.fi/phenocode/I9_AORTANEUR). The GWAS datasets for IBD, CD, and UC were established by FinnGen Biobank with the respective GWAS ID numbers of "finn-b-K11_IBD", "finn-b-K11_CROHN" and "finn-b-K11_ULCER". Specifically, the GWAS study related to IBD involved 5,673 cases and 213,119 controls and was further divided into K11_CROHN (2,056 cases and 210,300 controls) and K11_ULCER (4,320 cases and 210,300controls) endpoints. The PSO dataset, identified by the GWAS ID "finn-b-L12_PSORIASIS", was also received from FinnGen Biobank and comprises a sample size of 4,510 cases and 212,242 controls. The GWAS datasets associated with RA and SLE were obtained from European Bioinformatics Institute under the ID numbers "ebi-a-GCST90013534" (14,361 cases and 43,923 controls) (26) and "ebi-a-GCST003156" (5,201 cases and 9,066 controls) (27), respectively. Detailed information of these GWAS datasets are provided in Supplementary Table S1. Based on requirements of STROBE-MR standards(28), we report the design, methods and results analysis of this study. Schematic representation of this MR study is presented in Figure 1A.

2.2 Genetic instrumental variables selection

To obtain robust instrumental variables that are sufficiently correlated with the exposure of interest, SNPs related to IMIDs were chosen with a genome-wide significance threshold of $p < 5e\text{-}08$. Only two potential instrumental variables associated with AA were identified at the threshold of $p < 5e\text{-}08$. Therefore, we modified a more lenient threshold of $p < 5e\text{-}06$ for genome-wide significance to search for additional SNPs. Then, we set parameters related to linkage disequilibrium (r2 = 0.001, distance = 10000 kb) to clump these genetic loci, in which all loci exhibit complete independence in order to avoid double-count the contribution of any particular variants(29). Next, with the help of the online tool PhenoScanner v2 (*http://www.phenoscanner.medschl.cam.ac.uk/*), we checked genotype-phenotype associations between potential IVs and outcome(30), and removed SNPs associated with confounders. Then, SNP harmonization was conducted to correct the orientation of the alleles(31). Finally, we assessed IVs strength by calculating the genetic instruments (R^2) and F-statistic for each instrumental variable. R^2 and F-statistic was calculated as following formula: $R^2=[2\beta^2 \times MAF \times (1\text{-}MAF)] / [2\beta^2 \times MAF \times (1\text{-}MAF)+2\beta^2 \times MAF \times (1\text{-}MAF) \times N \times SE]$, and $F=[R^2 \times (N\text{-}k\text{-}1) /k(1\text{-}R^2)]$ (where β = effect estimate of the SNP in the exposure, MAF = minor allele frequency, N = sample size of the GWAS dataset, k = number of IVs, SE=the standard error of genetic effect) (32). Theoretically, all selected genetic IVs should have F-statistics greater than 10.

2.3 Statistical analysis

We used the "TwoSampleMR" and "MRPRESSO", "mr.raps" packages of the R software (version 4.2.2) to perform MR analysis. Multiple MR approaches were utilized to explore causal relationships between exposure and outcome. Causal effect estimates from the IVW was considered the criterion for establishing a causal relationship between exposure and outcome(33). It is suggested that if the IVs meet the three major assumption of MR and the selected SNPs are all valid IVs, result from IVW model provides an efficient and reliable estimate for the causal effect(34). As an extension to IVW, MR-PRESSO approach attempts to remove outliers based on their contributions to heterogeneity, while other MR Methods were regarded as a supplement and reference(35). After MR analysis, we assessed the quality of the harmonization and whether the variants were difficult to harmonize by performing Cochran's Q test and MR Egger regression analysis, as well as leave-one-out method. The IVW model was applied to the heterogeneity analysis, where Cochran's Q statistic provided evidence for heterogeneity and invalid instruments, with p value greater than 0.05 indicating the absence of heterogeneity(34). The intercept of MR-Egger regression was used to explore and account for the impact of horizontal pleiotropy, and p value greater than 0.05 is evidence for credible instrumental variables(36). To further assess the reliability of the MR results, we evaluated the impact of one single SNP for estimates by performing the leave-one-out method, in which new MR results was recalculated after leaving out each SNP in turn. Finally, we visualized the main results of the MR analysis using scatter plots, forest plots, and funnel plots. Figure 1B shows a detailed flowchart of this MR study.

Results

3.1 The causal effect of IMIDs on AA

A total of 179 independent SNPs associated with IMIDs were collected following the established screening criteria for the MR relevance hypothesis. In order to meet MR independence and exclusion assumption, we conducted a literature review and found smoking(1), high blood pressure(37), obesity(38), and alcohol consumption(39) as established risk factors for AA. After excluding palindromic SNPs and SNPs associated with these confounding variables, 154 independent SNPs remained (10 SNPs for IBD on AA, 6 SNPs for CD on AA, 7 SNPs for UC on AA, 77 SNPs for RA on AA, 39 SNPs for SLE on AA, 15 SNPs for PSO on AA). Most of the F-statistics of these IVs are greater than 10, indicating a low risk of weak instrument bias. Complete information about the IVs is summarized in Supplementary Table S3. In the MR analysis, the result of IVW with fixed effects model indicated that no causal relationship was found between IBD and AA (OR = 0.91, 95%CI = 0.81-1.01, $p = 0.072$), as well as CD and AA (OR = 0.97, 95%CI = 0.88-1.07, $p = 0.544$), UC and AA (OR = 0.95, 95%CI = 0.84-1.07, $p = 0.363$), RA and AA (OR = 0.97, 95%CI = 0.92-1.02, $p = 0.204$), SLE and AA (OR = 0.99, 95%CI = 0.96-1.02, $p = 0.547$), and PSO and AA (OR = 0.96, 95%CI = 0.91-1.03, $p = 0.245$). Meanwhile, the results of other MR methods were also similar to IVW-FE mode (Figure 2). In MR sensitivity analysis, p value of Cochran Q-test revealed no significant heterogeneity was observed (all $p > 0.05$, Table 2). The intercept of MR-Egger regression showed there was no intercept deviated from zero and all p values were greater than 0.05, explaining no impact of horizontal pleiotropy (Table 2). Indeed, these results were also confirmed in the funnel plot with symmetrical distribution (Supplementary Figure S2). Further, the leave-one-out method indicated that no single SNP differed apparently from the overall odds ratio (Supplementary Figure S1).

3.2 The causal effect of AA on IMIDs

The initial screening identified 138 potentially independent SNPs that meet the inclusion criteria. Genetic variables associated with depression, anxiety, smoking, glucocorticoids and non-steroidal anti-inflammatory drugs use, obesity or malnutrition(12, 40, 41), as known to have causal associations with IMIDs, were removed. After harmonizing the exposure and outcome datasets, a total of 112 SNPs were obtained with most F-statistics greater than 10 (21 SNPs for AA on IBD, 21 SNPs for AA on CD, 21 SNPs for AA on UC, 15 SNPs for AA on RA, 13 SNPs for AA on SLE, 21 SNPs for AA on PSO, Supplementary Table S2). 112 independent SNPs associated with AA were selected as IVs to explore the effect of AA on IMIDs. As shown in Figure 2 and the scatter plot (Supplementary Figure S3), the IVW method indicated that patients with

AA had a 6% increased risk of RA (OR = 1.06, 95%CI = 1.01-1.12,p = 0.029). MR-PRESSO method also presented unanimous evidence of causality between AA and RA (OR = 1.06, 95% CI = 1.01-1.11, p = 0.019). Cochran's Q test showed there was no heterogeneity in IVs related to RA (Q = 11.82, p = 0.621). Moreover, both results of MR-PRESSO (no outlier was found, Table 1) and MR-Egger regression (intercept = -0.01, p = 0.570, Figure 2) provided no evidence of horizontal pleiotropy. However, the effect of genetically predicted AA on IBD, CD, UC, SLE, PSO did not reach statistical significance in either IVW or MR-PRESSO method (Figure 2 and Table 1). Sensitivity analysis of the above MR results suggested that there was no underlying heterogeneity and horizontal pleiotropy (all p value of Cochran's Q and Egger-intercept > 0.05, Table 2).

Discussion

We conducted a two-sample bidirectional MR study to investigate the causal relationship between IMIDs (mainly including IBD, CD, UC, RA, SLE, and PSO) and AA. We found evidence of a causal effect of AA on RA, but not of RA or other IMIDs on AA. Although evidence from previous observational studies supported a causal relationship between some certain types of IMIDs and AA(12-20), causal inference cannot be made with great certainty in these studies for the possibility of residual confounding factors and various bias.

A retrospective case-control study with age- and gender-matched cohort from Israel, which adjust for different factors including socioeconomic and smoking, found that AA is more prevalent in patients with RA compared with controls (OR: 1.406, 95%CI: 1.094-1.789, p = 0.006). It is worth mentioning that the information regarding the treatment of RA patients and assessment of RA severity had not been formally investigated, as well as congenital diseases predisposing for AA(12). Contrary to above findings, a cohort study in England showed no evidence of a link between RA and AA, even after adjusting for age, gender, cardiovascular disease risk factors or anti-inflammatory drugs(13). Nonetheless, these studies lacked detailed information on daily tobacco use and alcohol consumption, family history of AA, as well as the imaging data, which all could bias causal inference towards a positive or negative direction. In addition, selection bias is also a problem that cannot be ignored. The same problems existed in studies of the association between SLE and AA(14, 15). People with SLE may experience a variety of symptoms and receive examination more frequently than people without SLE, therefore, they are more likely to be diagnosed with AA. Similarly, the two cohort studies on psoriasis failed to account for confounders such as body weight, smoking status, detail imaging findings, and assessment of psoriasis severity(16, 17). Moreover, the estimates from these observational studies are subject to substantial uncertainty with a wide confidence interval, indicating causal effects and their magnitude should be viewed with caution. Several isolated case reports have claimed that CD and UC were frequently observed comorbidities in AA patients(18-20), thus, we also conducted an investigation to explore the causal association of these diseases in AA individuals. However, either by forward or backward analysis, we did not fnd causal association between IBD, CD, UC and AA.

Genetic predisposition to AA is present from birth, therefore the MR results of our study would not be affected by the acquired drug treatment or other known or unknown exposure factors of AA patients. However, the exact mechanism by which genetically predisposed AA increases the risk of RA is still not completely understood. A study investigated the incidence of autoimmune diseases in patients with inflammatory aortic aneurysm (IAA). The serologic tests and biopsy findings were analyzed for the presence of autoimmune diseases before surgery in all cases. Autoimmune diseases were shown to be statistically significant in the inflammatory aortic group compared with the non-inflammatory aortic aneurysm group(21). Previous studies have provided evidence that a genetic predisposition to IAA exists and suggested that it may be related to human leukocyte antigen (HLA) molecule in IAA. HLA molecules play a critical role in the immune recognition process of specific antigen-presenting cells, which can be expressed by macrophages and dendritic cells. Amino acid polymorphism of HLA-DR molecule mediates immune responses to different antigens in different individuals and have also been found to be associated with the development of many diseases. A study investigating the genetic risk associated with HLA-DR gene polymorphism in patients with IAA revealed that HLA-DR B1*15 and HLA-DR B1*0404 allele were significantly enriched in these patients compared to control subjects(42). Moreover, observation with B-cell-enriched lymphoid follicles and CD3-positive T cells from the aneurysm wall of IAA patient suggested that a potential shared pathogenesis with IgG4-related

diseases(43). The etiology of RA remains elusive, and several studies have consistently demonstrated its association with genetic factors. As early as 1976, Stastny(44) reported a correlation between RA and the HLA-DR4 allele of the human leukocyte antigen class II. Many studies have confirmed the association between RA and HLA-DR4 in a various of different ethnic groups, but the subtypes of HLA-DR4 and other types of HLA-DR vary widely among ethnic groups (45-48). Given the limited sample size and racial difference in previous studies, more large-scale research should focus on investigating the genetic contribution of HLA risk loci in IAA patients worldwide. Furthermore, the investigation of the genetic determinants and their role in the pathogenesis of RA necessitates further explore. Hopefully, the efficacy of autoantigen immunoregulation in treating RA has been demonstrated in animal studies. Clinical trials of autologous modified dendritic cells exposed to citrulline peptide by percutaneous injection are currently underway (49).

Unlike previous observational studies examining the association between IMIDs and AA, we used MR method to deal with known and unknown confounding factors such as smoking, alcohol or fallacies caused by reverse causation. Thus, our results overcome the limitations of observational studies to reflect causal associations and effects of IMIDs and AA. Our work also had some limitations. While we concluded that exposure to genetically predisposed AA increased the lifetime risk of RA, this does not mean that this conclusion can be used directly to infer the possible impact of interventions targeting genetically predisposed AA patients on RA risk. Besides, owing to constraints within the GWAS database, we did not distinguish the anatomic site of the aortic aneurysm. Although the thoracic aorta and the abdominal aorta share certain anatomical features, these two disease subtypes exhibit marked differences with respect to their pathophysiological mechanisms. Finally, our study was dependent on data from European population, which limits generalizability to other racial populations.

Conclusion

In summary, our study has showed genetically predicted AA may increase the risk of RA, while there was no evidence that RA had an increased risk of AA. Furthermore, we found no evidence of association between IBD, CD, UC, SLE, PSO and AA. This finding is in line with other research that demonstrated the genetic risk determinants are linked to HLA molecules in IAA patients. IAA may be a separate entity with similar pathogenesis with IgG4-related disease. Our study provides directions for future research on genetic susceptibility to IAA. The antigen binding role of IAA risk genes in the disease origin of RA needs additional investigation.

Ethics approval and consent to participate

No extra ethical approval or informed consent is required.

Consent for publication

All authors contributed to this article and approved the submitted version.

Availability of data and materials

The summary genetic association datasets for IMIDs and AA are accessible through the IEU OpenGWAS Database Project (https://gwas.mrcieu.ac.uk/) or the published article and its supplementary files. For further inquiries, please contact the corresponding author.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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No financial support was received for this study.

Authors' contributions

XF guided and funded this study. SS designed, conducted the MR analysis and draft of the manuscript. JH, GW, YZ, ST provided insightful feedback on both the study and manuscript. MS assisted in organizing the tables and figures. SS, MS and JH shared equal contribution of this article.

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Figure legends

Figure 1. (A) Schematic view of this MR study for the association between IMIDs and AA. IMIDs, Immune-mediated inflammatory diseases, including inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and psoriasis (PSO). AA, aortic aneurysm. **(B) Detailed flowchart of the study design.** IVs, instrumental variables.

Figures 2. Main result of estimates from MR analysis with forward and reverse direction. (A) (B), forward analysis. (C) (D), reverse analysis. IBD, inflammatory bowel disease, CD, Crohn's disease, UC, ulcerative colitis, RA, rheumatoid arthritis, SLE, systemic lupus erythematosus, and PSO, psoriasis. CI, confidence interval.

Supplementary Figure S1 Leave-one-out sensitivity analysis. (A) IBD and AA, (B) CD and AA, (C) UC and AA, (D) RA and AA, (E) SLE and AA, (F) PSO and AA, (G) AA and IBD, (H) AA and CD, (I) AA and UC, (J) AA and RA, (K) AA and SLE, (L) AA and PSO.

Supplementary Figure S2 Funnel plot for IVW and MR-Egger method. (A) IBD and AA, (B) CD and AA, (C) UC and AA, (D) RA and AA, (E) SLE and AA, (F) PSO and AA, (G) AA and IBD, (H) AA and CD, (I) AA and UC, (J) AA and RA, (K) AA and SLE, (L) AA and PSO.

Supplementary Figure S3 Scatter plot with all IVs. (A) IBD and AA, (B) CD and AA, (C) UC and AA, (D) RA and AA, (E) SLE and AA, (F) PSO and AA, (G) AA and IBD, (H) AA and CD, (I) AA and UC, (J) AA and RA, (K) AA and SLE, (L) AA and PSO.

Tables

Table 1. Results of supplemented MR methods

Exposure	**Outcome**	**MR Methods**	**MR Beta**	**MR OR (95%CI)**	**MR *P* value**
IBD	AA	MR PRESSO	-0.06	0.94(0.88,1.00)	0.100
		Mr raps	-0.06	0.94(0.83,1.06)	0.320
CD	AA	MR PRESSO	-0.03	0.97(0.90,1.05)	0.488
		Mr raps	/	/	/
UC	AA	MR PRESSO	-0.06	0.94(0.88,1.01)	0.139
		Mr raps	-0.06	0.94(0.83,1.06)	0.336
RA	AA	MR PRESSO	-0.04	0.96(0.92,1.01)	0.146
		Mr raps	-0.04	0.96(0.91,1.01)	0.117
SLE	AA	MR PRESSO	-0.01	0.99(0.96,1.02)	0.593
		Mr raps	-0.01	0.99(0.96,1.03)	0.691
PSO	AA	MR PRESSO	-0.01	0.99(0.94,1.04)	0.678
		Mr raps	0.00	1.00(0.94,1.05)	0.870
AA	IBD	MR PRESSO	0.04	1.04(0.99,1.09)	0.154
		Mr raps	0.04	1.04(0.97,1.11)	0.273
AA	CD	MR PRESSO	0.06	1.06(0.97,1.16)	0.207
		Mr raps	0.06	1.06(0.95,1.18)	0.290

AA	UC	MR PRESSO	0.02	1.02(0.96,1.08)	0.529
		Mr raps	0.02	1.02(0.95,1.10)	0.613
AA	RA	MR PRESSO	0.06	1.06(1.01,1.11)	0.019
		Mr raps	0.06	1.06(1.00,1.12)	0.034
AA	SLE	MR PRESSO	-0.03	0.97(0.88,1.07)	0.561
		Mr raps	-0.04	0.96(0.87,1.07)	0.453
AA	PSO	MR PRESSO	0.01	1.01(0.95,1.08)	0.691
		Mr raps	0.01	1.01(0.94,1.09)	0.791

Table 2. Heterogeneity and pleiotropy analysis

Exposure	**Outcome**	**Heterogeneity Methods**	**Heterogeneity Cochran's Q**	**Heterogeneity** *P* **value**	**Pleiotropy Egger-intercept(95%CI)**	**Pleiotrop** *P* **value**
IBD	AA	IVW	2.88	0.969	-0.02(-0.06,0.03)	0.491
CD	AA	IVW	3.28	0.656	0.00(-0.06,0.06)	0.929
UC	AA	IVW	2.48	0.871	0.00(-0.05,0.06)	0.911
RA	AA	IVW	72.14	0.604	0.01(-0.01,0.02)	0.353
SLE	AA	IVW	30.16	0.810	0.02(-0.01,0.05)	0.157
PSO	AA	IVW	11.51	0.645	0.00(-0.04,0.03)	0.897
AA	IBD	IVW	12.72	0.889	0.01(-0.02,0.05)	0.405
AA	CD	IVW	16.40	0.691	0.03(-0.03,0.08)	0.353
AA	UC	IVW	13.22	0.868	0.01(-0.03,0.05)	0.596
AA	RA	IVW	11.82	0.621	-0.01(-0.04,0.02)	0.570
AA	SLE	IVW	7.44	0.827	0.03(-0.05,0.10)	0.507
AA	PSO	IVW	18.99	0.522	0.01(-0.03,0.04)	0.772

Supplementary tables

Supplementary table S1. Characteristics of GWAS datasets in the study

Supplementary table S2. Instrumental variables related to aortic aneurysm

Supplementary table S3. Instrumental variables related to Immune-mediated inflammatory diseases

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