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Causal relationship between atherosclerosis and inflammatory bowel disease risk: a two-sample Mendelian randomization study

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Abstract

Objective This study was to evaluate the causal associations of atherosclerosis with the risk of inflammatory bowel disease (IBD), and its subtypes [ulcerative colitis (UC) and Crohn's disease (CD)]: a two-sample Mendelian randomization study.

Materials and methods Single nucleotide polymorphism (SNPs) associated with atherosclerosis including CPAmax, CPSmax, brachial-femoral pulse wave velocity (bfPWV), coronary atherosclerosis, cerebral atherosclerosis, peripheral atherosclerosis, coronary artery disease (CAD) and ischemic stroke (IS) were identified from previous genome-wide association studies (GWAS). SNPs were strictly selected to fulfill the MR assumptions. The causal links between atherosclerosis and IBD were evaluated using inverse-variance weighted (IVW) as the primary method. Leave-one-out analysis was utilized to evaluate whether the outcomes were attributable to any individual SNP correlated to sex hormones. The estimates were subjected to odds ratio (OR) and 95% confidence interval (CI).

Results The results of IVW revealed that coronary atherosclerosis had causal association with increased risk of CD (OR = 1.162, 95%CI: 1.031–1.311). The causal association was also observed in IS with CD (OR = 1.376, 95%CI: 1.011–1.873) and UC (OR = 1.508, 95%CI: 1.153–1.971). Leave-one-out analysis indicated that no single SNP can affect the associations of CAD with IBD, CD, and UC, coronary atherosclerosis with CD, as well as IC with CD and UC.

Conclusions Coronary atherosclerosis was causally related to CD, and IS had causal relationship with CD and UC. The finding might provide evidence for future exploration of the etiology for IBD.

Keywords Crohn's disease, Atherosclerosis, Ulcerative colitis, Inflammatory bowel disease, Mendelian randomization

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Introduction

As a chronic inflammatory disease, inflammatory bowel disease (IBD) is correlated with idiopathic inflammation primarily in the gastrointestinal tract, which has been a global healthcare problem with a sustained increasing incidence [1, 2]. IBD is characterized by a relapsing-remitting pattern and a diverse clinical presentation, encompassing episodes of abdominal pain, chronic diarrhea, rectal bleeding, and weight loss. These symptoms are accompanied by systemic manifestations including fatigue and occasionally fever [3]. IBD included ulcerative colitis (UC) and Crohn's disease (CD) [4]. IBD can result in high morbidity and give rise to complications including strictures, fistulas, infections, and even cancer [5]. Consequently, the disease imposes various healthcare costs and places immense strain on healthcare systems [6]. To identify more reliable biomarkers associated with the occurrence of IBD was of great essential for the management of the disease.

Recent studies suggested that subclinical inflammation may precede the overt diagnosis of IBD [7, 8]. Atherosclerosis is a common and typical inflammatory disease, and plaque deposition activates the innate and adaptive immune system and up-regulate proinflammatory cytokines including interleukin-1β, tumor necrosis factor-α and interleukin-6 [9, 10]. In previous studies, the levels of these cytokines were identified to be significantly increased in patients with IBD at the preclinical stage [11, 12]. Therefore, we hypothesized that atherosclerosis may be related to the development and progression of IBD. Recently, the results of a nationwide case-control study in Sweden showed that atherosclerosis, myocardial infarction, ischemic stroke and other related diseases were related to an increased risk of subsequent IBD [13]. However, observational studies are prone to potential confounding and unmeasured biases, and causality remains unclear.

The method of Mendelian randomization (MR) utilizes genotype as an instrumental variable to infer the causal relationship between phenotype and disease [14]. The usage of MR can mitigate the reverse causality inference and effectively capture the enduring impact of exposure on outcomes [15]. Nevertheless, no MR studies have explored the causal link between atherosclerosis and IBD.

In the present study, we aimed to explore the causal associations of atherosclerosis related biomarkers and diseases with the risk of IBD.

Materials and methods

Study design and data sources

MR analysis should be performed before fulfilling three assumptions including relevance assumption (the genetic variants should be strongly correlated with the exposure, independence assumption (independent of the confounding factors of the link between exposure and outcome, and exclusion restriction assumption (only affect the outcome via the exposure). The study design was exhibited as a directed acyclic graph in Fig. 1. The traits related to atherosclerosis included area of the largest plaque detected at any of the six regions (CPAmax),

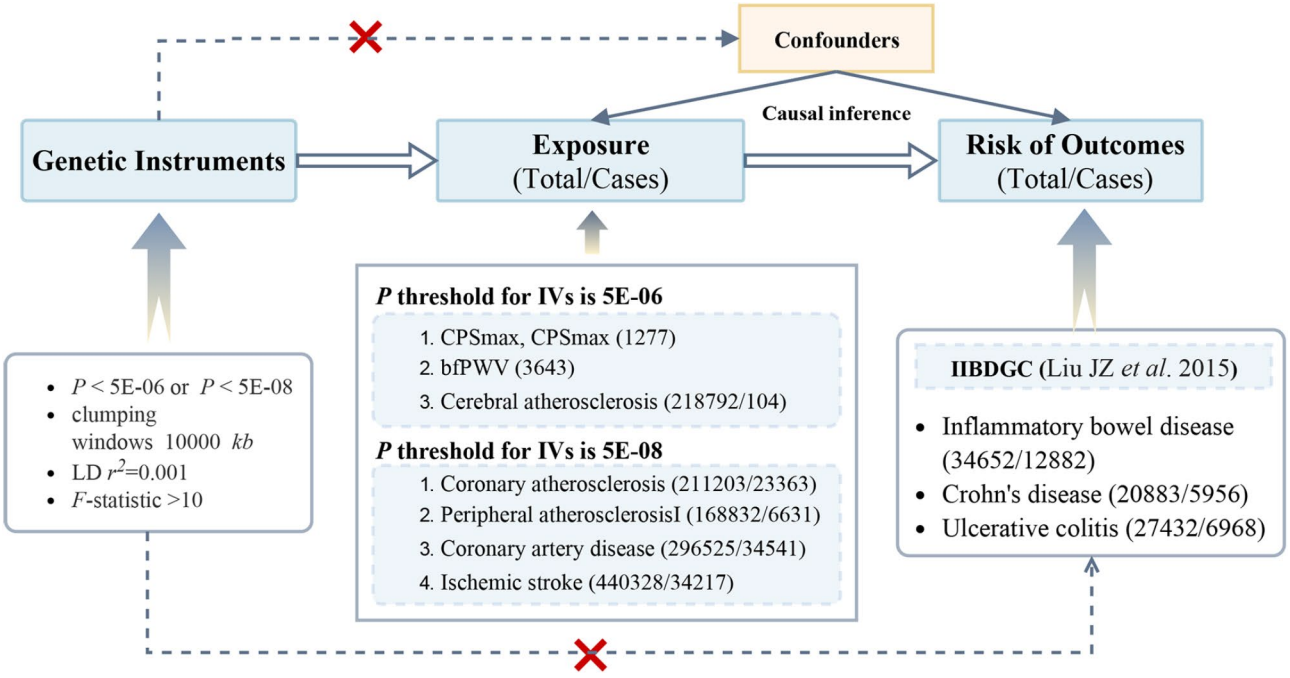

Fig. 1 The directed acyclic graph on the associations of atherosclerosis related biomarkers and diseases with the risk of IBD

maximal degree of stenosis (plaque area/lumen area) at any of the six regions (CPSmax), brachial-femoral PWV (bfPWV), coronary atherosclerosis, cerebral atherosclerosis, peripheral atherosclerosis, coronary artery disease (CAD), and ischemic stroke (IS). CPAmax and CPSmax-associated summary single nucleotide polymorphisms (SNPs) [16], bfPWV-related SNPs [17], CAD-related SNPs [18], IS-associated SNPs [19] were got from published genome-wide association studies (GWASs), SNPs related to coronary atherosclerosis, cerebral atherosclerosis, and peripheral atherosclerosis were identified from FinnGen.

Detailed information on the data sources of exposures and outcomes was exhibited in Table 1. The traits including CPAmax and CPSmax were identified in the GWAS performing in LIFE-Adult cohort study. The sizes of plaques in the carotid bulb (Bulb), proximal segments of the internal carotid artery (ICA), and common carotid artery (CCA) were assessed using a selected sample of 1300 specimens [16]. The bfPWV summary statistics were obtained in a 7838 randomly selected samples from a GWAS in the LIFE-Adult study [17]. The coronary atherosclerosis, cerebral atherosclerosis, and peripheral atherosclerosis related data were performed in FinnGen consortium. Coronary atherosclerosis was diagnosed based on ICD-10 codes (I24/Z951/T822/I25), and cerebral atherosclerosis was ICD-10-I672. CAD-related SNPs data were obtained from a total of 34,541 CAD cases and 261,984 controls sourced from the UK Biobank. CAD was defined based on ICD-10 codes (I21-I25) encompassing ischemic heart diseases, as well as OPCS-4 codes (K40-K46, K49, K50, and K75). Additionally, self-reported CAD information including heart attack/myocardial infarction history, coronary angioplasty +/- stent placement procedures, CABG surgeries and triple heart bypasses were also included [18]. The genome-wide association study (GWAS) of ischemic stroke (IS) was conducted within the MEGASTROKE consortium, which comprised 17 studies involving a total of 440,328 participants (including 34217 IS cases and 406111 controls of European descent) [19].

Table 1 The information of and data sources of exposure and outcomes

Phenotype	Total sample size (Case)	GWAS ID	PMID/Consortium	*P* for IVs
Exposure				
CPAmax	1277	GCST010536	32,469,969	5E-06
CPSmax	1277	GCST010541	32,469,969	5E-06
bfPWV	3643	GCST010654	32,790,701	5E-06
Coronary atherosclerosis	211,203 (23363)	I9_CORATHER	FinnGen	5E-08
Cerebral atherosclerosis	218,792 (104)	I9_CERE-BATHER	FinnGen	5E-06
Peripheral atherosclerosis	168,832 (6631)	DM_ PERIPHA-THERO	FinnGen	5E-08
CAD	296,525 (34541)	GCST005194	29,212,778 / UKBB	5E-08
IS	440,328 (34217)	GCST006908	29,531,354	5E-08
Outcome				
IBD	34,652 (12882)	ieu-a-31	26,192,919 / IIBDGC	-
CD	20,883 (5956)	ieu-a-30	26,192,919 / IIBDGC	-
UC	27,432 (6968)	ieu-a-32	26,192,919 / IIBDGC	-

GWAS, genome-wide association studies; bfPWV, brachial-femoral pulse wave velocity; CAD, coronary artery disease; IS, ischemic stroke; IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; UKBB, UK biobank; IIBDGC, International Inflammatory Bowel Disease Genetics Consortium

Selection criteria of instrumental variables

To ensure the SNPs were associated with exposures, a threshold of $P < 5 \times 10^{-6}$ was applied to identify SNPs related to CPAmax, CPSmax, bfPWV, and cerebral atherosclerosis. A threshold of $P < 5 \times 10^{-8}$ was used to identify SNPs related to coronary atherosclerosis, peripheral atherosclerosis, CAD, and IS. SNPs with linkage disequilibrium (clump windows = 10000 *kb*, $r^2 = 0.001$) were excluded. Furthermore, the relative conservative action was used to identify positive strand alleles via allele frequencies for palindromes and SNPs of palindromic with intermediate allele frequencies. The F statistics were computed to evaluate the potential presence of weak instrument bias and sample overlap with F value < 10 indicated potential weak instrument bias. The R^2 statistic represented the proportion of exposure variability that can be attributed to instrument variables.

Horizontal Pleiotropy analysis

MR-Egger regression was employed to test the potential horizontal pleiotropy effect. SNPs directly linked to IBD, UC or CD, not through traits related to atherosclerosis were excluded. *P* value < 0.05 was considered to indicate the possibility of horizontal pleiotropy. MR-Egger and MR Pleiotropy RESidual Sum and Outlier tests (MR-PRESSO) were employed to identify outliers. MR-Egger regression, which employed a weighted linear regression approach, is one the basis of the assumption of instrument strength independent of direct effect. The method allows for the evaluation of pleiotropy existence through the intercept term. However, it should be noted that estimates obtained from MR-Egger generally exhibit low precision and may be influenced by outlying genetic variants [20]. The MR-PRESSO test encompasses the identification of horizontal pleiotropy, correction for such pleiotropy by removing outliers, and determination

of substantial variations in causal effects before and after outlier removal, which was additionally performed to assess the presence of pleiotropy [21].

Statistical analysis

The causal links between atherosclerosis related biomarkers and diseases and IBD as well as its subtypes were evaluated via MR analysis with inverse-variance weighted (IVW) as the primary method. The IVW methodology utilizes a meta-analysis approach to incorporate the Wald ratio assessments of the causal association derived from multiple SNPs, thereby yielding a robust evaluation of the causal relationship between the exposure and the outcome [22]. Constrained Maximum Likelihood and Model Averaging (cML-MA), MR-robust adjusted profile score (MR-RAPS), Simple mode, Weighted-median, Weighted mode, MR-PRESSO, and Radial MR were conducted to validate the results of IVW. The cML-MA method is employed to address both correlated and uncorrelated pleiotropic effects, which circumvents the need for assuming Instrument Strength Independent of Direct Effect (InSIDE), distinguishing itself from other MR approaches [23]. The Weighted mode method was utilized to assess the overall causal effect derived from a substantial number of genetic instruments. In various scenarios, this approach demonstrated reduced type-I error rates, mitigated bias, and improved statistical power compared to primary methodologies [24]. The MR-RAPS can address both systematic and idiosyncratic pleiotropy, thereby enhancing its robustness in the presence of these biases, which offers a valuable opportunity to investigate the issue of weak instrument bias and explore potential efficiency gains through the incorporation of multiple weak instrumental variables [25]. Cochran's Q test was conducted to identify whether there was heterogeneity. Leave-one-out was used to measure the robustness of the MR results. MR-CAUSE analysis of the causal association between CAD and IBD with horizontal pleiotropy based on the "CAUSE" package (Version 1.2.0). Multivariate analysis including obesity, Type 2 diabetes mellitus (T2DM), fat intake, polyunsaturated fat intake, saturated fat intake, alcoholic drinks per week, and cigarettes smoked per day was conducted to observe the direct causal effect of atherosclerosis on IBD.

Results

The screen process of instrument variables associated with atherosclerosis related- biomarkers and diseases

A total of 36 CPAmax-related SNPs, 10 CPSmax-related SNPs, 6 bfPWV-related SNPs, and 20 cerebral atherosclerosis-related SNPs were identified according to the threshold of $P < 5 \times 10^{-6}$. In total, 10,054 CAD-related SNPs, 34 coronary atherosclerosis-related SNPs, 8 peripheral atherosclerosis-related SNPs and 302 IS-related SNPs were obtained using the threshold of $P < 5 \times 10^{-8}$. Post excluding SNPs with linkage disequilibrium (clump windows = 10000 *kb*, $r^2 = 0.001$), 4 CPAmax-related SNPs, 7 CPSmax-related SNPs, 4 bfPWV-related SNPs, and 5 cerebral atherosclerosis-related SNPs were identified. In total, 143 CAD-related SNPs, 24 coronary atherosclerosis-related SNPs, 5 peripheral atherosclerosis-related SNPs and 10 IS-related SNPs were included after excluding SNPs with linkage disequilibrium. Then, SNPs of palindromic with intermediate allele frequencies were excluded, we included 4 CPAmax-related SNPs, 7 CPSmax-related SNPs, 4 bfPWV-related SNPs, and 5 cerebral atherosclerosis-related SNPs, 142 CAD-related SNPs, 22 coronary atherosclerosis-related SNPs, 4 peripheral atherosclerosis-related SNPs and 10 IS-related SNPs. The outliers were detected via MR PRESSO and Radial MR, and SNPs with outliers were excluded (Table 2).

Horizontal pleiotropic test, and heterogeneity test of SNPs associated with atherosclerosis-related biomarkers and diseases

According to the data in Table 2, most SNPs showed no horizontal pleiotropy and heterogeneity. There was some heterogeneity in SNPs related to CAD. The heterogeneity was observed in SNPs associated with CAD and CPAmax. The outliers were presented in Supplementary Table 1. The F statistics of all SNPs were > 10, indicated no significant weak instrument bias in the SNPs (Table 2).

Causal association between atherosclerosis-related biomarkers and diseases and IBD

The results from IVW indicated that CAD was causally related to IBD (OR = 1.148, 95%CI: 1.065–1.237), CD (OR = 1.216, 95%CI: 1.104–1.339), and UC (OR = 1.142, 95%CI: 1.041–1.254). However, there were potential horizontal pleiotropy and heterogeneity in SNPs related to CAD. Coronary atherosclerosis was identified to have causal effect on the increased risk of CD (OR = 1.162, 95%CI: 1.031–1.311). The causal associations of IS with the elevated risk of CD (OR = 1.376, 95%CI: 1.011–1.873) and UC (OR = 1.508, 95%CI: 1.153–1.971) were observed. The associations of coronary atherosclerosis, peripheral atherosclerosis, and IS on IBD were not significant ($P > 0.05$). No significant associations of CPAmax, CPSmax, bfPWV, and cerebral atherosclerosis on the risk of IBD, CD, and UC was identified ($P > 0.05$) (Table 3). The scatter plot of the causal associations of coronary atherosclerosis with CD as well as IS with CD and UC was exhibited in Fig. 2. A positive association between coronary atherosclerosis and CD was observed. Also, IS was positively related to elevated risk of CD and UC. The Funnel plot symmetry generally indicated no significant genetic heterogeneity or measurement bias (Fig. 3). The

Table 2 The selection of SNPs and pleiotropic and heterogeneity test of instrument variables

Outcome	Exposure	Selected SNP	Omitting LD SNP	Dropping palindromic SNP	Dropping Outlier SNP	Heterogeneity test				Horizontal pleiotropic test				Strength	
						MR Egger Q	*P*	IVW Q	*P*	Egger intercept	*P*	MR-PRESSO Global test	*P*	F-statistic	R^2 (%)
P threshold for IVs is 5E-08															
IBD	CAD	10,054	143	142	137	194.42	6.00E-04	204.65	1.00E-04	0.012	0.009	207.10	< 1e-04	73.06	3.37
	Coronary atherosclerosis	34	24	22	21	30.93	0.041	30.98	0.056	-0.003	0.868	33.78	0.061	49.88	0.50
	Peripheral atherosclerosis	8	5	4	4	0.86	0.649	1.78	0.618	-0.052	0.439	2.59	0.702	47.66	0.11
	Ischemic stroke	302	10	10	7	7.76	0.170	7.77	0.256	-0.005	0.946	10.11	0.310	38.89	0.06
CD	CAD	10,054	143	142	139	184.36	0.004	188.53	0.003	0.010	0.081	190.63	0.004	73.07	3.42
	Coronary atherosclerosis	34	24	22	22	23.17	0.280	23.75	0.305	0.013	0.490	25.96	0.328	49.65	0.52
	Peripheral atherosclerosis	8	5	4	4	2.65	0.266	5.05	0.168	-0.114	0.310	7.99	0.281	47.66	0.11
	Ischemic stroke	302	10	10	9	13.81	0.055	14.12	0.079	0.039	0.702	18.58	0.087	42.59	0.09
UC	CAD	10,054	143	143	140	200.91	4.00E-04	208.3094	1.00E-04	0.012	0.026	211.11	1.00E-04	73.39	3.46
	Coronary atherosclerosis	34	24	22	21	27.80	0.087	27.92	0.111	0.006	0.779	31.01	0.111	50.20	0.50
	Peripheral atherosclerosis	8	5	4	4	0.81	0.666	0.86	0.836	-0.014	0.854	2.19	0.774	47.66	0.11
	Ischemic stroke	302	10	10	9	12.26	0.092	12.74	0.121	0.044	0.617	16.68	0.138	42.82	0.09
P threshold for IVs is 5E-06															
IBD	CPAmax	36	4	4	4	9.55	0.008	9.68	0.022	0.031	0.884	17.13	0.069	24.27	7.47
	CPSmax	10	7	7	7	2.78	0.734	5.95	0.429	0.049	0.135	8.21	0.450	23.08	12.45
	bfPWV	6	4	4	4	0.89	0.641	0.94	0.815	-0.029	0.841	1.79	0.810	25.26	1.31
	Cerebral atherosclerosis	20	5	5	5	3.61	0.306	5.92	0.206	0.020	0.261	11.16	0.334	21.90	0.05
CD	CPAmax	36	4	4	4	5.41	0.067	5.52	0.138	-0.039	0.861	9.71	0.210	24.27	7.47
	CPSmax	10	7	7	7	3.22	0.666	4.50	0.609	0.042	0.309	6.12	0.632	23.08	12.45
	bfPWV	6	4	4	4	1.48	0.477	4.19	0.242	-0.283	0.242	7.58	0.302	25.26	1.31
	Cerebral atherosclerosis	20	5	5	5	3.81	0.283	5.65	0.227	0.026	0.314	10.29	0.339	21.90	0.05
UC	CPAmax	36	4	4	4	6.51	0.039	6.51	0.089	-0.009	0.968	11.52	0.152	24.27	7.47
	CPSmax	10	7	7	7	2.88	0.719	3.92	0.687	0.036	0.354	5.35	0.697	23.08	12.45
	bfPWV	6	4	4	4	0.23	0.892	1.56	0.668	0.183	0.367	2.73	0.695	25.26	1.31
	Cerebral atherosclerosis	20	5	5	5	5.57	0.135	6.41	0.170	0.015	0.548	9.14	0.326	21.90	0.05

bfPVW, brachial-femoral pulse wave velocity; CAD, coronary artery disease; IS, ischemic stroke (any ischemic stroke); IBD, inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; MR, Mendelian randomization; IVW, inverse variance weighted; LD, linkage disequilibrium; SNP, single nucleotide polymorphism

Table 3 The causal association between exposure and outcome using IVW method

Outcome	Exposure	IVW		
		nSNPs	OR (95%CI)	*P*
P threshold for IVs is 5E-08				
IBD	CAD	137	1.148 (1.065–1.237)	3.20E-04
	Coronary atherosclerosis	21	1.060 (0.953–1.179)	0.281
	Peripheral atherosclerosis	4	0.987 (0.902–1.079)	0.766
	Ischemic stroke	7	1.168 (0.928–1.470)	0.185
CD	CAD	139	1.216 (1.104–1.339)	7.25E-05
	Coronary atherosclerosis	22	1.162 (1.031–1.311)	0.014
	Peripheral atherosclerosis	4	1.010 (0.824–1.238)	0.921
	Ischemic stroke	9	1.376 (1.011–1.873)	0.042
UC	CAD	140	1.142 (1.041–1.254)	0.005
	Coronary atherosclerosis	21	1.082 (0.953–1.227)	0.223
	Peripheral atherosclerosis	4	1.004 (0.929–1.085)	0.921
	Ischemic stroke	9	1.508 (1.153–1.971)	0.003
P threshold for IVs is 5E-06				
IBD	CPAmax	4	1.076 (0.859–1.350)	0.523
	CPSmax	7	0.973 (0.881–1.074)	0.585
	bfPWV	4	0.958 (0.738–1.245)	0.750
	Cerebral atherosclerosis	5	1.018 (0.997–1.040)	0.087
CD	CPAmax	4	1.132 (0.896–1.429)	0.298
	CPSmax	7	0.941 (0.836–1.057)	0.305
	bfPWV	4	1.049 (0.494–2.227)	0.900
	Cerebral atherosclerosis	5	1.024 (0.995–1.053)	0.108
UC	CPAmax	4	1.026 (0.813–1.295)	0.829
	CPSmax	7	1.011 (0.913–1.119)	0.834
	bfPWV	4	0.886 (0.581–1.352)	0.575
	Cerebral atherosclerosis	5	1.016 (0.989–1.044)	0.237

GWAS, genome-wide association studies; bfPWV, brachial-femoral pulse wave velocity; CAD, coronary artery disease; IS, ischemic stroke (any ischemic stroke); IBD, inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization

Radial plot demonstrated the associations of coronary atherosclerosis with CD as well as IS with CD and UC (Fig. 4). The results of the other MR methods revealed similar findings with IVW (Supplementary Table 2). We found that the MR-CAUSE model was better than Sharing Model [Delta of expected log pointwise posterior density (ELPD) < 0]. The results from MR-CAUSE analysis indicated that the causal associations of CAD with CD (Supplementary Fig. 1, Supplementary Table 3) and UC (Supplementary Fig. 2, Supplementary Table 3) was not statistically significant. CAD was causally associated with increased risk of IBD even in the presence of horizontal pleiotropy (OR = 1.127, 95%CI: 1.003–1.266) (Supplementary Fig. 3, Supplementary Table 3).

Sensitivity analysis

Leave-one-out analysis showed no single SNPs could affect the associations of coronary atherosclerosis with CD as well as IS with CD and UC, which suggested that the causal relationship was robustness (Fig. 5).

Multivaraible MR analysis on the causal association between atherosclerosis-related biomarkers and diseases and IBD

The data source information of obesity, T2DM, fat intake, polyunsaturated fat intake, saturated fat intake, alcoholic drinks per week, and cigarettes smoked per day as presented in Supplementary Table 4. The results from multivariable MR analysis indicated that there was a causal effect between coronary atherosclerosis and the increased risk of CD after adjusting for obesity, T2DM and cigarettes smoked per day, respectively. However, after adjusting for fat intake and alcoholic drinks per week, the causal association between coronary atherosclerosis and CD was not statistically significant, suggesting that fat intake and alcoholic drinks may play a mediating role in the causal association between coronary atherosclerosis and CD. After adjusting separately for obesity, fat intake, cigarettes smoked per day, and alcoholic drinks per week, the causal effect between IS and UC was still significant. After adjusting for obesity, T2DM, fat intake, cigarettes smoked per day, and alcoholic drinks per week, CAD was causally associated with an increased risk of IBD (Supplementary Table 5).

Discussion

In our study, the causal associations of atherosclerosis related biomarkers and diseases with IBD risk were analyzed using MR analysis. The results indicated that coronary atherosclerosis and IS had causal associations with CD. In addition, IS was causally related to the risk of UC. The findings might provide references for exploring the mechanisms of IBD, and offer insights for early identification of patients who are at high risk of IBD

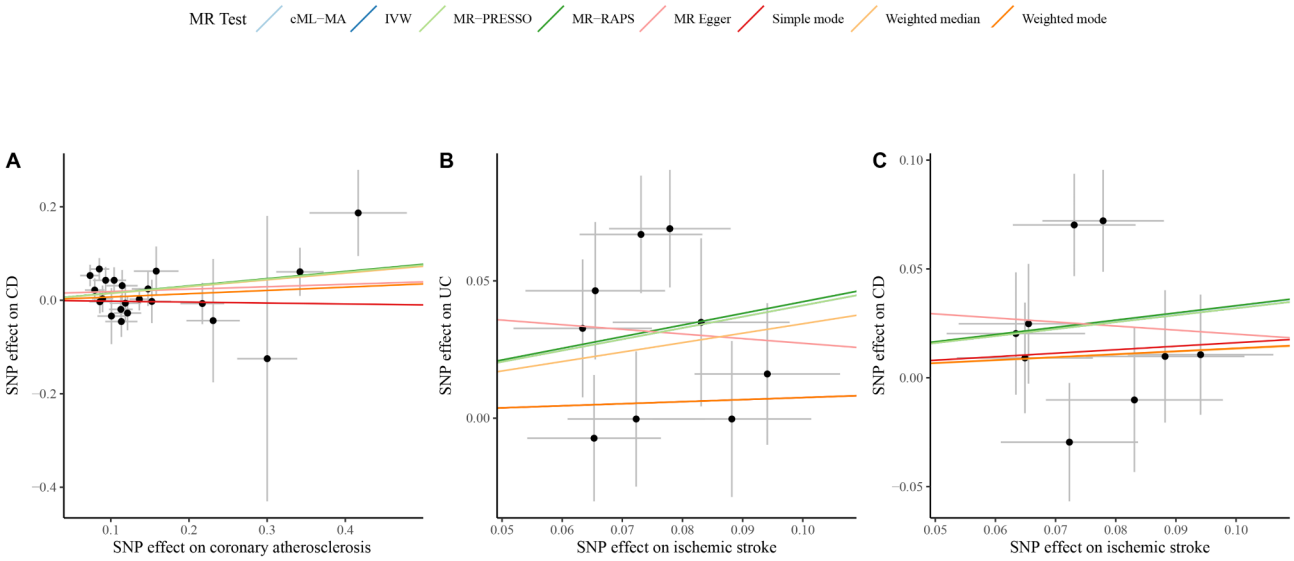

Fig. 2 The scatter plot of the causal associations of coronary atherosclerosis with CD (**A**), IS with CD (**B**), IS with UC (**C**)

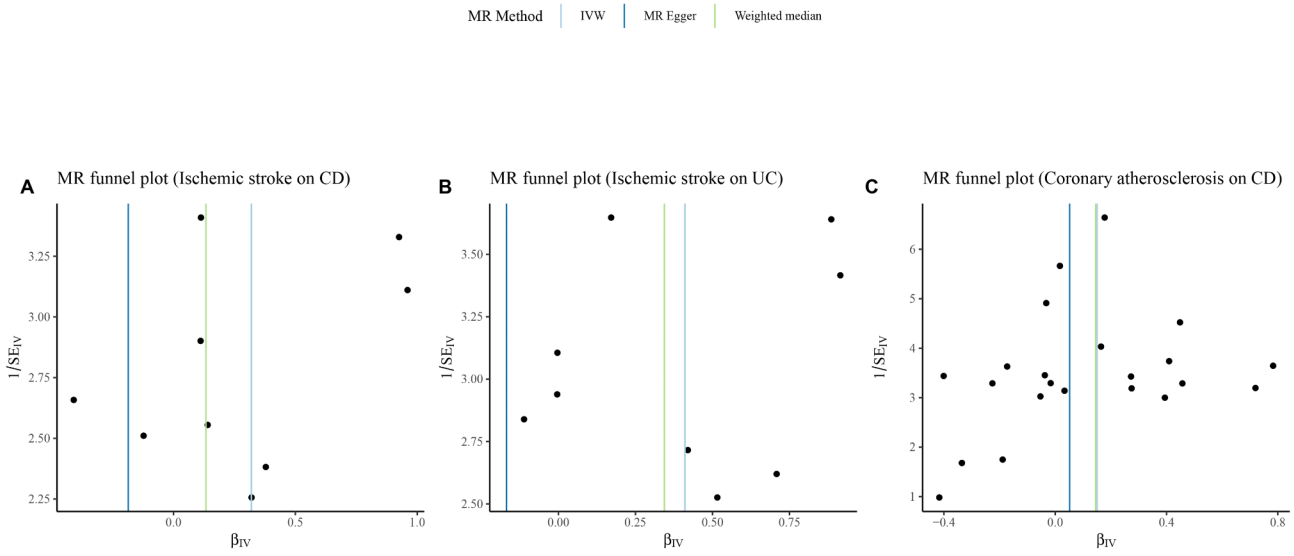

Fig. 3 The Funnel plot symmetry generally showing significant genetic heterogeneity or measurement bias. **A**: SNPs related to IS on CD, **B**: SNPs related to IS on UC, **C**: SNPs related to coronary atherosclerosis on CD

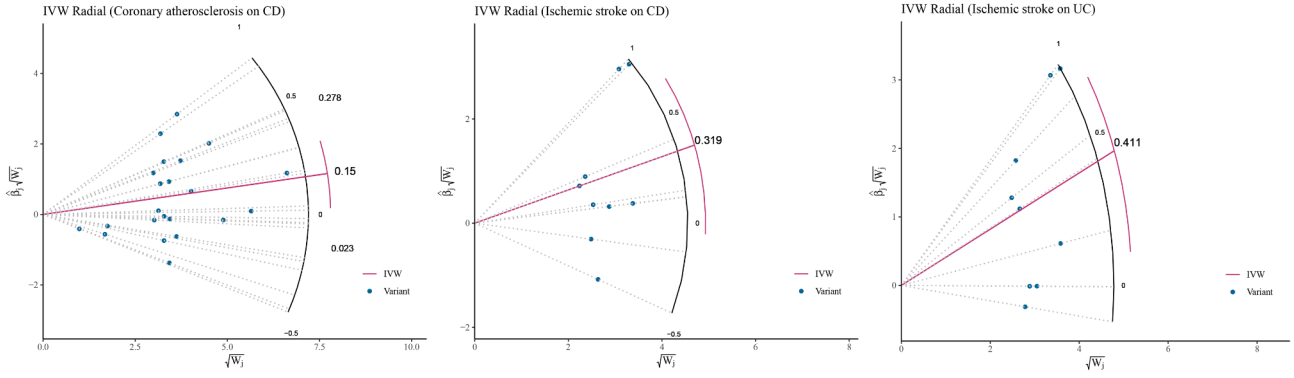

Fig. 4 The Radial plot showing the associations of coronary atherosclerosis with CD as well as IS with CD and UC. **A**: SNPs related to coronary atherosclerosis on CD, **B**: SNPs related to IS on CD, **C**: SNPs related to IS on UC

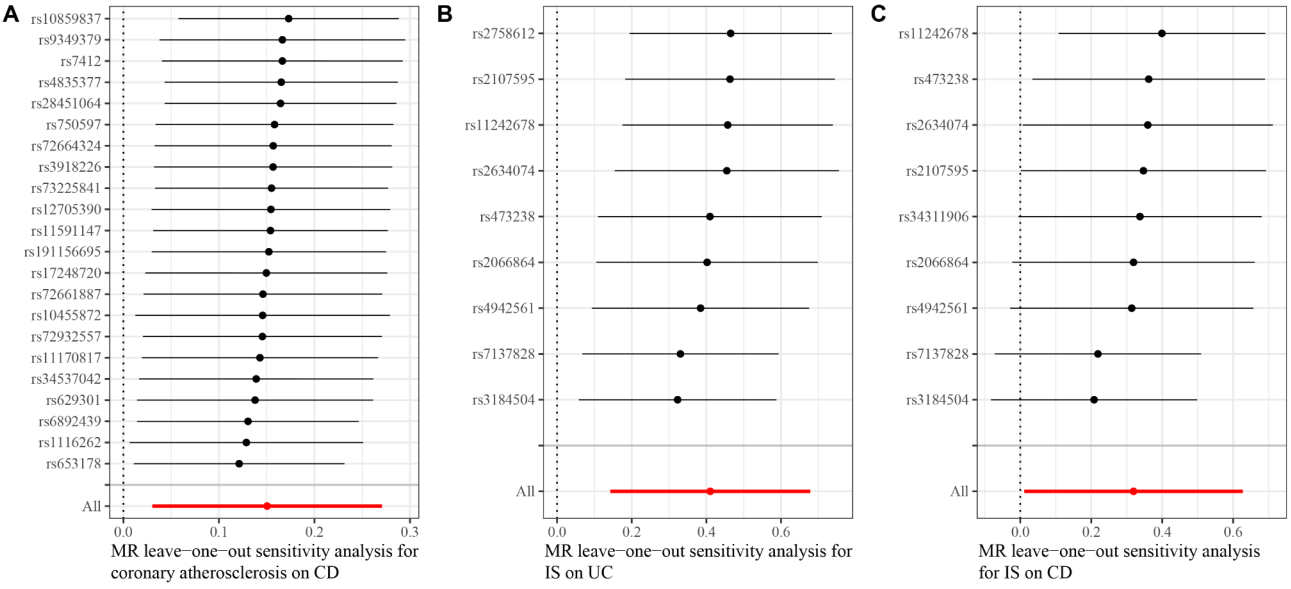

Fig. 5 Leave-one-out analysis showing omitting single SNP on the associations of coronary atherosclerosis with CD (**A**), IS with UC (**B**), and IS with CD (**C**)

and improvement of clinical management of IBD in the future.

Previously, a Danish study revealed that the ischemic heart disease risk is highest in the year following an IBD diagnosis, indicating that the presence of atherosclerosis may have preceded the development of IBD for a considerable period [26]. The Swedish and US studies conducted in 2016 and 2021, respectively, indicated that the utilization of statins, which effectively lowered the levels of low-density lipoprotein and consequently reduced the inflammatory burden associated with atherosclerosis, might potentially mitigate the risk of incident IBD [27, 28]. The study conducted by Sappati et al. suggested that individuals with IBD experienced myocardial infarction within a span of 3 months, especially in the absence of underlying cardiovascular comorbidities, which implied that the presence of pre-existing atherosclerotic-related disease might precede the development of IBD [29]. These evidence was allied with the findings in this study. We found that coronary atherosclerosis and IS were causally related to the risk of CD. While IS was causally related to the risk of UC.

The mechanisms underlying the causal associations of coronary atherosclerosis and IS with CD as well as IS with UC were still unclear. The possible mechanisms might be that as an inflammatory condition commonly observed in the aging population, atherosclerosis was reported to have a potential association between diet and the development of IBD [30]. Atherosclerosis was associated with a reduction in the concentration of Firmicutes and the production of butyrate [31, 32], which can result in the apoptosis of epithelial cells, leading to subsequent dysfunction of the intestinal barrier and initiating an inflammatory cascade [33]. The mechanisms explaining the causal associations of coronary atherosclerosis and IS with CD as well as IS with UC still require more exploration in the future.

Although the observed OR between coronary atherosclerosis and Crohn's disease was modest (OR = 1.16), this slight increase in risk may still carry important implications. In the context of Mendelian Randomization studies, even small effect sizes can reflect meaningful lifelong exposure risks due to the stability of genetic variants. Moreover, when considering the high and rising incidence of CD in the general population, such modest increases in risk could translate into a substantial public health burden at the population level. It is also important to note that small effect sizes may exert more pronounced impacts when acting in accordance with other risk factors, suggesting potential cumulative or synergistic effects. Additionally, our findings are consistent with previous studies, which have reported mild to moderate increases in cardiovascular or atherosclerotic disease risks among patients with IBD [34, 35]. These results, when interpreted alongside existing epidemiological evidence, support the plausibility and relevance of a causal link, even if the effect magnitude appears relatively small.

Another important consideration is the observed heterogeneity and potential horizontal pleiotropy among the SNPs associated with coronary artery disease. Despite employing robust MR methods such as MR-Egger, MR-PRESSO, and Radial MR to mitigate the influence of outliers and pleiotropic effects, certain CAD-related SNPs still exhibited signs of heterogeneity. This suggests that some variants may influence CD through pathways beyond CAD alone, including lipid metabolism and

inflammatory processes. In our MR analysis, the association between CAD and CD attenuated after adjusting for fat intake and alcohol consumption, indicating that these lifestyle factors may act as mediators in the causal pathway. Several biological mechanisms support this hypothesis: (1) High-fat diets can alter gut microbiota composition, reduce beneficial butyrate-producing bacteria, and compromise intestinal barrier integrity, thus heightening systemic inflammation and susceptibility to CD [36]. (2) Alcohol consumption may impair gut barrier function and modulate immune responses, potentially exacerbating systemic and intestinal inflammation [37]. (3) CAD and CD may converge on common pro-inflammatory signaling pathways, including IL-6 and TNF-α. Diet-induced upregulation of these cytokines could reinforce a feedback loop between vascular and intestinal inflammation [38]. Taken together, these findings suggest that fat intake and alcohol consumption may partially mediate the relationship between CAD and CD, potentially through inflammation-related mechanisms. Nevertheless, further experimental and longitudinal studies are required to validate these intermediary mechanisms and elucidate the complete causal chain.

The strength of this study was that the causal link between atherosclerosis and IBD, UC and CD were analyzed via two-sample MR, which avoided the influence of confounding in traditional epidemiology, and provide a reference for the etiology exploration, prevention and treatment of IBD and its subtypes. Based on the results in our study, the prevention of atherosclerosis may have significant implications not only in limiting the progression of cardiovascular disease but also in mitigating the overall inflammatory burden and development of IBD. One important limitation of this study is that all genetic data used in the MR analyses were derived from individuals of European ancestry. While this homogeneity minimizes confounding due to population stratification, it also restricts the generalizability of our findings to non-European populations. Indeed, the epidemiological patterns and risk factors for both atherosclerosis and IBD are known to vary significantly across different ethnic groups. Given that allele frequencies, linkage disequilibrium structures, and environmental exposures can differ by ancestry, the causal relationships observed in this study may not hold in other populations. Therefore, caution is warranted when extrapolating these results to individuals of non-European descent. To address this, future MR analyses should incorporate data from more diverse ethnic backgrounds or conduct ancestry-stratified meta-analyses to examine whether the observed associations are consistent across populations. Such efforts will enhance the external validity of causal inferences and contribute to more inclusive and globally applicable evidence.

In order to comprehensively discuss the causal relationship between atherosclerosis and IBD, a P threshold 5×10^{-6} was applied to identify SNPs related to cerebral atherosclerosis, CPAmax, CPSmax, and bfPWV as no eligible SNP could be identified based on a P threshold 5×10^{-8}. Except for the heterogeneity of CPAmax with IBD and UC, all the other instrumental variables selected by the $P = 5 \times 10^{-6}$ passed the horizontal pleiotropy test, heterogeneity test, and the F value > 10, which suggested that these SNPs can be used as instrumental variables to represent CPAmax, CPSmax, bfPWV, and cerebral atherosclerosis. However, there might be potential weak instrumental variables and insufficient statistical power. Further studies are needed to support the findings in our study.

Conclusions

The causal associations of atherosclerosis related biomarkers and diseases with the IBD risk were analyzed using MR analysis in this study. We found the causal associations of coronary atherosclerosis and IS with CD as well as IS with UC. The findings might offer more evidence for future prevention and management of IBD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12959-025-00722-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6: The MR-CAUSE plot on the causal association of CAD with CD.

Supplementary Material 7: The MR-CAUSE plot on the causal association of CAD with UC.

Supplementary Material 8: The MR-CAUSE plot on the causal association of CAD with IBD.

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Author contributions

(1) Wenjuan Guo, Shiyu Du, conceiving and designing the study; (2) Wenjuan Guo, Na Peng, collecting the data; (3) Wenjuan Guo, Na Peng, analyzing and interpreting the data; (4) Wenjuan Guo, writing the manuscript; (5) Shiyu Du, providing critical revisions that are important for the intellectual content; (6) Wenjuan Guo, Na Peng, Shiyu Du, approving the final version of the manuscript.Acknowledgements: Thanks for the support from the National Natural Science Foundation of China (NO.12301645); Elite Medical Professionals Project of China-Japan Friendship Hospital (NO.ZRJY2024-GG04); National High Level Hospital Clinical Research Funding.

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Data availability
The datasets used and/or analysed during the current study were publicly available from the open-source public database.

Declarations

Ethics approval and consent to participate
Not applicable, our study is based on open-source public database, and the China Japan Friendship Hospital do not require research using publicly available data to be submitted for review to their ethics committee, so there are no ethical issues and other conflicts of interest.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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