Diabetology & Metabolic Syndrome

RESEARCH Open Access

Analysis of causal effects on metabolic syndrome and inflammatory bowel disease: a Mendelian randomization study

Danyang Zhang[1], Haitao Shi[1], Chongcao Wei[1], Fenrong Chen[1], Pan Zhang[1], Xin Gao[1] and Yan Wang[1*]

Abstract

Background Metabolic syndrome (MetS) is a conglomerate of metabolic abnormalities including hypertension, obesity, hyperglycemia, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). The relationship between MetS and Inflammatory Bowel Disease (IBD) has received a lot of attention lately. Epidemiological investigation has yet to determine if the two illnesses are causally related. To investigate the causal link between IBD and MetS levels, we screened publically available genome-wide association study (GWAS) data using Mendelian randomization (MR) analysis. The study aimed to comprehensively analyze the causal association of each component of MetS, including fasting blood glucose(FBG), HDL-C, triglyceride(TG), waist circumference(WC), and hypertension, on the risk of IBD and its subtypes via univariate, two-way, and multivariate MR (MVMR) methods.

Methods We selected independent genetic variants of MetS and IBD as instrumental variables (IVs) from published data from the IEU OpenGWAS project and IIBDGC (International Inflammatory Bowel Disease Genetic Consortium), used MR to infer potential causal effects between them, and used a variety of methods (random effect inverse variance weighting (IVW), weighted median, MR-Egger regression, etc.) to ensure the robustness of causal effects.

Results Univariate two-sample MR (TSMR) revealed that WC was significantly linked to the risk of Crohn's disease (CD) (OR = 1.659; 95% CI: 1.144–2.405; $p = 0.008$) and IBD (OR = 1.383; 95% CI: 1.050–1.822; $p = 0.021$). However, MVMR did not support this finding. In MVMR analysis, hypertension was predicted to be positively associated with the risk of IBD (OR = 2.322516, 95% CI: 1.097713–4.91392, $p = 0.0275365$), whereas FBG was confirmed to reduce the risk of CD in MVMR studies (OR = 0.4346427, 95% CI: 0.2685399–0.7034868, $p = 0.0006948939$). Other elements of the MetS did not significantly correlate with IBD.

Conclusion Although confounding factors cannot be completely ruled out, certain metabolic components, such as WC, may impact the risk of IBD. In addition to highlighting the need for more research to understand the underlying mechanisms and potential indirect effects between MetS components and IBD, this research offers insight into therapeutic treatment decisions for patients with IBD and MetS.

Keywords Metabolic syndrome, Inflammatory bowel disease, Mendelian randomization

*Correspondence:
Yan Wang
sarrye@163.com
[1]Department of Gastroenterology, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 of Xiwu Road, Xi'an, Shaanxi 710004, China

Background

MetS is a collection of metabolic risk factors such as obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL-C. Together, these variables contribute to an increase in the prevalence of different chronic illnesses and cancers [1]. MetS now affects roughly one-quarter of adults globally as a result of lifestyle and dietary habit changes [2]. Not only has it been confirmed to be a risk factor for cardiovascular diseases and cancer, but epidemiological studies have suggested that the incidence of IBD and MetS has shown a similar upward trend in recent decades, indicating that there may be a common pathophysiological mechanism between these two diseases. They were discovered to have similar clinically significant properties, such as an increased risk of cardiovascular disease, nonalcoholic cirrhosis, and obesity [3]. However, the connection between MetS and IBD is still poorly understood and warrants further exploration. Most previous investigations have been primarily observational [4], which renders the results susceptible to confounding factors interfering with the link between them. Because observational studies cannot determine the causative relationship of illness occurrence, more robust and accurate methodologies are needed to characterize the underlying mechanisms.

IBD is a collection of illnesses, primarily ulcerative colitis (UC) and CD, that are typified by persistent, nonspecific intestinal inflammation. Epidemiological statistics indicate that the incidence rate is approximately 0.3% worldwide [5]. Inflammation can develop in several intestinal regions, and its onset is concealed. It is a prevalent autoimmune condition. The illness was discovered in Western nations in the 18th century, and its prevalence is rising globally every year [6]. Although the specific cause of IBD is still unknown, it is generally accepted that genetics, environmental factors, aberrant immune responses, and other variables are involved [7]. As with other chronic conditions, patients experience a number of aftereffects or problems during long-term management, including cancer, rheumatic diseases, immunological disorders, malnutrition, etc [8]. which will impact the course and treatment of the illness. As a result, early detection of risk factors and illness associations can enhance patient quality of life and disease prognosis. With the advent of the notion of comorbidities, people have begun to pay more attention to the coexistence of various comorbidities, such as cardiovascular diseases, cognitive disorders, and MetS [9], and they have come to the realization that managing these conditions can help control IBD better.

MR is an epidemiological method for inferring causality that uses genetic diversity to identify the causal impact of risk factors on research outcomes [10]. Using genetic variation that is unchangeable and randomly assigned at the birth of individuals to avoid common confounding or reverse causality problems in observational studies [11], similar to clinical randomized controlled trials (RCTs), is the gold standard for causality inference, but it is not feasible to conduct RCTs with ethical issues. Therefore, we apply MR methods to reduce the possibility of reverse causality, exclude environmental factors and other interferences, and clarify the causal effects between them. MR uses Single Nucleotide Polymorphisms (SNPs) as IVs to assess the causal relationship between exposure factors and outcome events, univariate TSMR is used to assess the impact of a single exposure on the outcome, and MVMR allows simultaneous assessment of the impact of multiple exposures on the outcome, thus providing a comprehensive understanding of the independent impact of each factor on the disease outcome [12–14]. In this study, we used genetic data from large-scale genome-wide association studies to clarify the causal effects of each MetS component on IBD and its subtypes via the TSMR and MVMR methods, followed by reverse MR analysis to test the possibility of reverse causality.

Methods

Study design

We employed the TSMR and MVMR methods to determine the potential causality of MetS and IBD and performed reverse MR analysis to assess the possibility of reverse causality. Three hypotheses support the current investigation following the justification and fundamental presumptions of MR: (1) genetic IVs must be closely tied to exposure; (2) SNPs are not associated with any confounders of risk-outcome associations; and (3) the SNPs don't affect the outcome through any pathway other than the exposure of interest. The research framework is shown in Fig. 1.

Source of data

We used GWAS summary data mainly from the IEU OpenGWAS database(IEU OpenGWAS project (mrcieu.ac.uk)), the European Bioinformatics Institute database (EMBL-EBI homepage| EMBL-EBI), the FinnGen Consortium (FinnGen: an expedition into genomics and medicine| FinnGen) and International Inflammatory Bowel Disease Genetics Consortium (IIBDGC) (IBD Genetics Consortium (ibdgc.org), and univariate, multivariate, and bidirectional MR was performed. All original studies involved in this study received ethical approval, and SNPs related to exposure and outcome are displayed in Table 1.

SNPs associated with IBD, UC, or CD were identified from several previously published GWASs by the IIBDGC. The IBD dataset included 12,882 cases and 21,770 controls for a total of 12,716,084 SNPs. The genetic association data included 27,432 UC participants ($N = 6968$

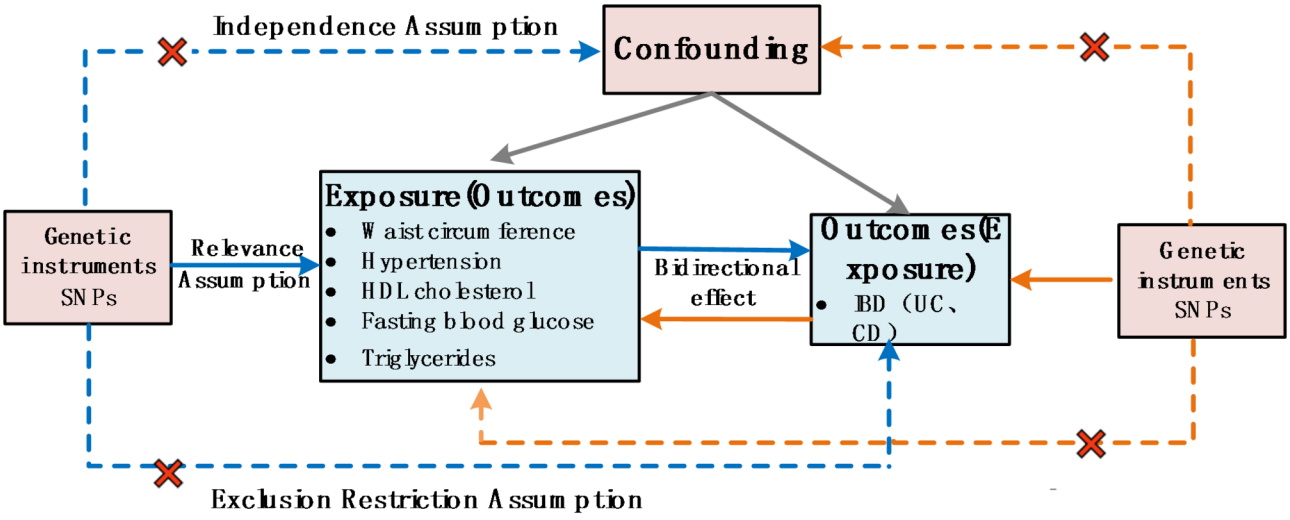

Fig. 1 The basic principles of Mendelian analysis

Table 1 Description of GWAS data sources and details

	GWAS ID	Year	Sample Size	Number of SNPs	Population	Consortium/PMID
Exposure(Outcomes)						
Waist circumference	ieu-a-66	2015	245746	2547573	European	GIANT /25673412
Hypertension	ebi-a-GCST90038604	2021	484598	9587836	European	NA/33959723
HDL cholesterol	ebi-a-GCST90018956	2021	315133	19051633	European	NA/34594039
Fasting blood glucose	ebi-a-GCST005186	2012	58074	2599409	European	NA/22581228
Triglycerides	ieu-b-111	2020	441016	123218752	European	UK Biobank/32203549
Metabolic disorders	finn-b-E4_METABOLIA	2021	218792	16380466	European	NA/NA
Outcomes(Exposure)						
IBD	ieu-a-31	2015	34,652	12,716,084	European	IIBDGC/26192919
CD	ieu-a-30	2015	20,883	12,276,506	European	IIBDGC/26192919
UC	ieu-a-32	2015	27,432	12,255,197	European	IIBDGC/26192919

cases, 20,464 controls), respectively, and 20,883 CD participants ($N=5956$ cases, 14,927 controls) covering 12,255,197 SNPs in UC patients and 12,276,506 SNPs in CD patients. Screening of IBD was diagnosed by recognized radiological, endoscopic, and histopathological assessments, and all included patients met the clinical diagnostic criteria for the disease. The datasets for MetS include WC (sample size 245,746), hypertension (129,909 cases and 354,689 controls), HDL-C (sample size 315,133), FBG (sample size 58,074), TG (sample size 441,016), and metabolic disorders (21,533 cases and 197,259 controls). For the purpose of this study, the MetS criteria were defined on the basis of the criteria of the International Diabetes Federation (IDF) [15]. All GWAS are based in Europe to guarantee the homogeneity of the population.

SNPs associated with IBD, UC, or CD were identified from several previously published GWASs by the IIBDGC. The IBD dataset included 12,882 cases and 21,770 controls for a total of 12,716,084 SNPs. The genetic association data included 27,432 UC participants ($N=6968$ cases, 20,464 controls), respectively, and 20,883 CD participants ($N=5956$ cases, 14,927 controls) covering 12,255,197 SNPs in UC patients and 12,276,506 SNPs in CD patients. Screening of IBD was diagnosed by recognized radiological, endoscopic, and histopathological

assessments, and all included patients met the clinical diagnostic criteria for the disease. The datasets for MetS include WC (sample size 245,746), hypertension (129,909 cases and 354,689 controls), HDL-C (sample size 315,133), FBG (sample size 58,074), TG (sample size 441,016), and metabolic disorders (21,533 cases and 197,259 controls). For the purpose of this study, the MetS criteria were defined on the basis of the criteria of the International Diabetes Federation (IDF) [15]. All GWAS are based in Europe to guarantee the homogeneity of the population.

IVs selection

SNPs that attained genome-wide significance ($P < 5 \times 10 - 8$) and independence (linkage disequilibrium r2 < 0.001, clustering window = 10,000 kb) were selected as IVs in all datasets. Approximate F statistics were used to evaluate the instrumental intensity of the SNPs in MR. IVs with F-statistics significantly greater than 10 were deemed free of instrumental variable bias [16].

Statistical analysis

We initially chose IVW as the main analysis approach for univariate TSMR to evaluate the genetic correlation betwee overall metabolic disorders and each component of MetS with IBD. Additionally, to guarantee robustness and confirm the consistency of the results, MR-Egger, the maximum likelihood approach, and the weighted median method were added. Lastly, we created a forest plot based on the results. Sensitivity analysis was performed using Cochran's Q heterogeneity test ($P < 0.05$), and potential pleiotropy was evaluated using the MR-Egger intercept test ($P < 0.05$). Additionally, we further construct other scatter plots, funnel plots, and leave-one-out plots to show the impact of each SNP on the results. Finally, reverse MR analysis was also performed to determine the direction of causality.

In the second step, the causal effects of MetS and its five components (WC, FBG, HDL-C, TG, and hypertension) on IBD, including its subtypes, were assessed using MVMR analysis. We used the same IVs as the univariate MR analysis; similarly, clustering genetic variables to establish independence (linkage 7 disequilibrium $r^2 <$ 0.001 within a 10,000 kb window). The software packages R (version 4.4. 1), TwoSampleMR (version 0.6. 8), MendelianRandomization (version 0.10. 0), and forestploter (version 1.1. 2) were used for all analyses in this study. The specific process design is shown in Fig. 2.

Results

Two-sample Mendelian randomization (TSMR)

In the TSMR analysis, we identified 14 metabolic disorder SNPs, 65 WC SNPs, 22 FBG SNPs, 277 hypertension SNPs, 313 TG SNPs, and 278 HDL-C SNPs. In total, 18 separate TSMR analyses were performed covering five MetS components (WC, FBG, HDL-C, TG, hypertension) [15, 17], overall metabolic disorders and three outcomes (IBD and the UC and CD subtypes).

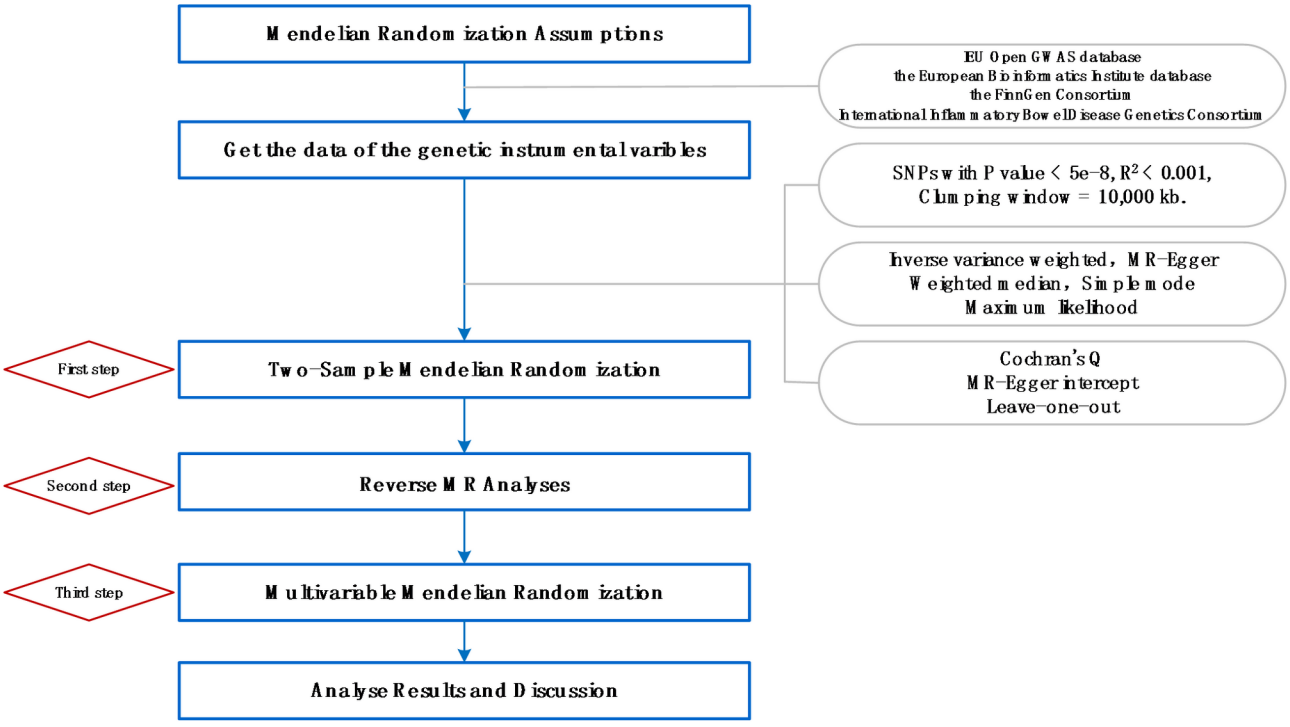

Fig. 2 Workflow of the MR study design

In terms of IBD, the IVW results of TSMR analysis revealed that only WC had a significant causal relationship with IBD (OR = 1.383; 95% CI: 1.050–1.822; $p = 0.021$), and the other MetS components consistently produced nonsignificant results: metabolic disorders (OR = 1.034; 95% CI: 0.912–1.173; $p = 0.605$), FBG (OR = 0.919; 95% CI: 0.661–1.277; $p = 0.614$), hypertension (OR = 1.526; 95% CI: 0.985–2.367; $p = 0.059$), TG (OR = 1.013; 95% CI: 0.902–1.134; $p = 0.824$) and HDL-C (OR = 0.945; 95% CI: 0.837–1.068; $p = 0.366$).

For UC, the IVW results of TSMR analysis indicated that there was no significant association between MetS components and UC, only MR analysis of hypertension and UC showed the strongest nonsignificant relationship (OR = 1.592; 95% CI: 0.970–2.613; $p = 0.066$). Other abnormal metabolic components suggest that there may be no direct causal effect on the risk of UC. The specific results are as follows: metabolic disorders (OR = 1.064; 95% CI: 0.907–1.248; $p = 0.448$), FBG (OR = 0.998; 95% CI: 0.685–1.455; $p = 0.993$), WC (OR = 1.291; 95% CI: 0.909–1.832; $p = 0.153$), TG (OR = 1.000; 95% CI: 0.877–1.140; $p = 0.998$) and HDL-C (OR = 0.958; 95% CI: 0.845–1.087; $p = 0.508$).

As for CD, the TSMR analysis IVW for CD revealed the same findings as for IBD, with WC being directly proportional to the risk of CD (OR = 1.659; 95% CI: 1.144–2.405; $p = 0.008$). The remaining MetS components didn't reveal consistent significant results: metabolic disorders (OR = 0.983; 95% CI: 0.829–1.165; $p = 0.841$), FBG (OR = 0.715; 95% CI: 0.483–1.060; $p = 0.095$), hypertension (OR = 1.326; 95% CI: 0.741–2.373; $p = 0.342$), TG (OR = 1.083; 95% CI: 0.923–1.271; $p = 0.327$) and HDL-C (OR = 0.940; 95% CI: 0.806–1.096; $p = 0.430$). All the above two-sample MR analysis results are shown in Fig. 3.

Sensitivity analysis and visualization

To corroborate the conservatism of the main findings, we verified the accuracy of the results using MR-Egger and weighted median estimation methods in addition to the

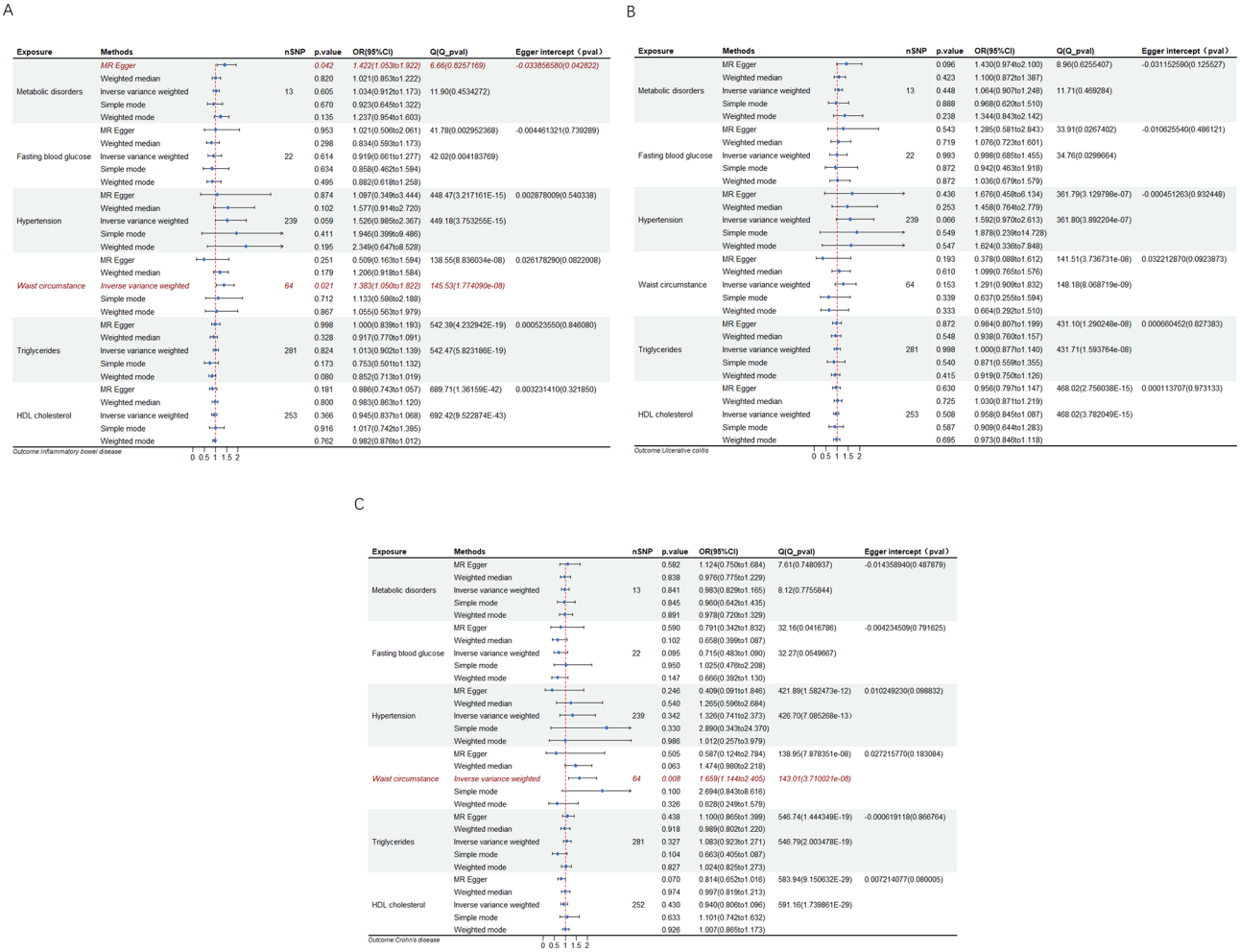

Fig. 3 The TSMR forest plots of causal links of IBD, UC, or CD with MetS. (**A**)The TSMR forest plots of causal links of IBD with MetS; (**B**)The TSMR forest plots of causal links of UC with MetS; (**C**)The TSMR forest plots of causal links of CD with MetS

main IVW analysis method, with MR-Egger regression indicating no potential pleiotropy and all $P > 0.05$. The Cochran-Q statistic was used to assess the heterogeneity test. The test results indicate that some MR analyses are heterogeneous. The particular results are shown in Fig. 3. However, we used the IVW random effects model as the main outcome when performing MR analysis. Therefore, even if there is some degree of heterogeneity among the original studies, this method can obtain accurate and stable results by giving each study the right weight. Moreover, a leave-one-out plot was used to assess the impact of a single SNP on the final MR results for MetS components that were found to have a causal relationship with IBD and its subtypes. The analysis results expressed that no single SNP was crucial to the final results, demonstrating the robustness, stability, and reliability of the MR study. The visualization results are shown in Supplementary Fig. 1.

Reverse MR analyses

Following the abovementioned MR investigation of MetS components and IBD, certain findings with noteworthy correlations were discovered. To further verify the causal relationship between exposure factors and outcomes, we used reverse MR analysis. Finally, there was no evidence of reverse causality. This could suggest that MetS disease is not directly caused by IBD disease, or that there is more to the association between MetS and IBD diseases than can be explained by a single causal chain. The symptoms of MetS are a collection of disorders that together impact the body's metabolic functions. Genetic and lifestyle variables are typically strongly associated with its occurrence. IBD may not be the main cause of this complex health state, but rather merely an indirect one. We acknowledge that there are limitations in the research process, including insufficient sample size, incomplete data, and lack of more sophisticated measurement tools, which may also make it difficult to identify possible weak associations or causality, but hope that this experiment will serve as a reference for further research in the future. Figure 4 displays specific data.

Multivariable Mendelian randomization (MVMR)

MVMR can more comprehensively control the influence of potential confounding factors and improve the reliability of causal inference. Thus, we used MVMR analysis to explore the relationships between the composition of multiple MetS components and the outcomes of IBD, CD and UC simultaneously after performing the univariate two-sample MR analysis. We obtained 285 SNPs as genetic tools for all and components of MetS (WC, FBG, hypertension, TG, HDL-C) when linkage disequilibrium was removed. In the MVMR analysis of IBD, we found that hypertension was significantly associated with IBD (OR = 2.322516, 95% CI: 1.097713–4.91392, $p = 0.0275365$), whereas other components were not statistically significant for the time being; Similarly, only hypertension was found to have a meaningful causal relationship with UC (OR = 2.567268, 95% CI: 0.744939–1.10019, $p = 0.0141063$), but despite this statistical significance, because the confidence interval of the OR value contains 1, the effect of its true outcome in practice may be small OR unstable; Also, FBG was found to be associated with a reduced risk of CD (OR = 0.4346427, 95% CI: 0.2685399–0.7034868, $p = 0.0006948939$). The analysis results are shown in Fig. 5.

Discussion

The study analyzed the causal relationships between MetS, including FBG, HDL-C, TG, WC and hypertension, and IBD by univariate TSMR and MVMR methods. Notably, our study demonstrated that increasing WC is a risk factor for increased CD risk, but there was no significant association between MetS and UC, and directional tests verified the accuracy of the causal direction. The total analysis of these results reveals that the association between MetS and IBD is complicated and diverse, demonstrating causative differences in metabolic levels between UC patients and CD patients. These findings can serve as a guide for preventing metabolic abnormalities in IBD patients.

In the TSMR analysis, we discovered that every standard deviation increase in WC increased the risk of IBD by 38.3%, and for CD, it raised the risk by 65.9%. However, this association was not confirmed in MVMR analysis. It is possible that other metabolic factors could have confused the effects observed in the TSMR analysis. The TSMR provides valuable preliminary judgment, while MVMR provides more reliable evaluation results when multiple metabolic factors are considered simultaneously. The inconsistencies between the TSMR and MVMR results emphasize the importance of explaining the interactions between different metabolic components.

Increased WC is linked to IBD, underscoring the possible role of central obesity in the development of this disease. Insulin resistance and systemic low-grade inflammation are caused by the release of proinflammatory factors and the suppression of the production of the anti-inflammatory factor adiponectin [18]. Adipose tissue represents metabolically and hormonally active organs that can produce proinflammatory adipokines with deleterious effects on disease activity, affecting metabolic disorders and gut microbial dysbiosis, and ultimately contributing to the development of IBD through mechanisms such as chronic inflammation and oxidative stress [19]. The incidence of IBD has consistently demonstrated a rising tendency due to genetics, dietary changes, environmental changes, and variations in lifestyle, especially

Exposures	Outcomes	Methods	nSNP	p.value	Q(Q_pval)	Egger intercept（pval）	OR (95% CI)
IBD	Metabolic disorders	MR Egger	55	0.570064300	54.43(0.4197024)	-0.004328079(0.378860)	1.0180487 (0.9574732 to 1.0824560)
		Weighted median		0.756941300			1.0048481 (0.9745383 to 1.0361010)
		Inverse variance weighted		0.467024100	55.24(0.4275114)		0.9919582 (0.9706079 to 1.0137780)
		Simple mode		0.576359600			1.0198134 (0.9523810 to 1.0920200)
		Weighted mode		0.480695300			1.0198134 (0.9660557 to 1.0765630)
	Fasting blood glucose	MR Egger	28	0.626573500	42.62(0.0211694)	0.001048097(0.606313)	0.9938757 (0.9698669 to 1.0184790)
		Weighted median		0.292855200			1.0067543 (0.9937372 to 1.0199420)
		Inverse variance weighted		0.961649200	43.07(0.0257588)		0.9997486 (0.9895542 to 1.0100480)
		Simple mode		0.959783500			1.0006897 (0.9751921 to 1.0268540)
		Weighted mode		0.404970700			1.0073286 (0.9909541 to 1.0239740)
	Hypertension	MR Egger	64	0.917456900	222.14(6.96E-20)	0.000124205(0.831221)	0.9996240 (0.9925630 to 1.0067300)
		Weighted median		0.204937100			0.9982080 (0.9954440 to 1.0009800)
		Inverse variance weighted		0.814590600	222.30(1.25E-19)		1.0003340 (0.9975440 to 1.0031300)
		Simple mode		0.097130600			1.0073420 (0.9988020 to 1.0159600)
		Weighted mode		0.502157500			0.9982950 (0.9933590 to 1.0032500)
	Waist circumstance	MR Egger	28	0.223740400	57.81(0.0003277)	-0.00245140(0.366071)	1.0204250 (0.9884950 to 1.0533700)
		Weighted median		0.203815700			1.0101230 (0.9945860 to 1.0259000)
		Inverse variance weighted		0.348632100	59.69(0.0002892)		1.0069840 (0.9924340 to 1.0217500)
		Simple mode		0.390151200			1.0099940 (0.9864000 to 1.0341500)
		Weighted mode		0.181244100			1.0106340 (0.9947440 to 1.0267800)
	Triglycerides	MR Egger	60	0.446583000	411.41(1.03E-54)	-0.002010038(0.304029)	1.0092490 (0.9857610 to 1.0333000)
		Weighted median		0.269000000			1.0039990 (0.9969190 to 1.0111300)
		Inverse variance weighted		0.655994000	419.04(1.03E-55)		0.9978260 (0.9883150 to 1.0074300)
		Simple mode		0.335609000			0.9891040 (0.9674650 to 1.0112300)
		Weighted mode		0.476889000			1.0043250 (0.9925270 to 1.0162600)
	HDL cholesterol	MR Egger	64	0.566600761	623.70(1.01E-93)	0.000307692(0.903807)	0.9908399 (0.9603020 to 1.0223490)
		Weighted median		0.008158685			0.9905202 (0.9835546 to 0.9975351)
		Inverse variance weighted		0.225751362	623.84(3.01E-93)		0.9926129 (0.9807761 to 1.0045926)
		Simple mode		0.270874399			0.9910876 (0.9755551 to 1.0068674)
		Weighted mode		0.081696816			0.9902102 (0.9794767 to 1.0010614)
UC	Metabolic disorders	MR Egger	34	0.096137000	46.12(0.0507799)	-0.015031690(0.084256)	1.0848100 (0.9884030 to 1.1906200)
		Weighted median		0.294847000			1.0181500 (0.9844580 to 1.0529900)
		Inverse variance weighted		0.963285000	50.69(0.0251706)		1.0006800 (0.9722880 to 1.0298900)
		Simple mode		0.400699000			1.0300100 (0.9622240 to 1.1025800)
		Weighted mode		0.292288000			1.0350000 (0.9718060 to 1.1023000)
	Fasting blood glucose	MR Egger	17	0.895140100	32.23(0.0059962)	-0.000754092(0.839912)	0.9973690 (0.9596890 to 1.0365300)
		Weighted median		0.076591700			0.9865420 (0.9718580 to 1.0014500)
		Inverse variance weighted		0.352235400	32.33(0.0090904)		0.9936200 (0.9803110 to 1.0071100)
		Simple mode		0.431476900			0.9891690 (0.9633520 to 1.0156800)
		Weighted mode		0.309805700			0.9879790 (0.9659030 to 1.0105600)
	Hypertension	MR Egger	37	0.450830900	92.95(3.76E-07)	0.000412966(0.507108)	0.9976047 (0.9914744 to 1.0037730)
		Weighted median		0.078249130			0.9974836 (0.9947470 to 1.0002280)
		Inverse variance weighted		0.710572200	94.15(4.26E-07)		0.9995203 (0.9969907 to 1.0020560)
		Simple mode		0.361016590			0.9972334 (0.9908204 to 1.0036880)
		Weighted mode		0.147019170			0.9965955 (0.9922198 to 1.0009900)
	Waist circumstance	MR Egger	16	0.792843000	48.54(0.0000107)	0.005220171(0.357778)	0.9923520 (0.9381060 to 1.0497300)
		Weighted median		0.201280000			1.0104490 (0.9944670 to 1.0266900)
		Inverse variance weighted		0.122062000	51.68(0.0000064)		1.0175470 (0.9953550 to 1.0402300)
		Simple mode		0.603641000			1.0064610 (0.9827880 to 1.0307000)
		Weighted mode		0.463796000			1.0071820 (0.9885660 to 1.0261500)
	Triglycerides	MR Egger	34	0.484875000	160.76(4.37E-19)	0.001769876(0.390793)	0.9927580 (0.9729450 to 1.0129700)
		Weighted median		0.115113000			1.0060260 (0.9985360 to 1.0135700)
		Inverse variance weighted		0.848430000	164.56(2.12E-19)		1.0008320 (0.9923290 to 1.0094100)
		Simple mode		0.432127000			1.0070530 (0.9897600 to 1.0246500)
		Weighted mode		0.106122000			1.0102750 (0.9981640 to 1.0225300)
	HDL cholesterol	MR Egger	36	0.100660500	201.51(1.12E-25)	0.002255839(0.344378)	0.9799190 (0.9571000 to 1.0032810)
		Weighted median		0.047941700			0.9924360 (0.9849970 to 0.9999310)
		Inverse variance weighted		0.048291900	206.96(2.79E-26)		0.9902620 (0.9806900 to 0.9999270)
		Simple mode		0.163118700			0.9889560 (0.9739620 to 1.0041820)
		Weighted mode		0.172822300			0.9898150 (0.9756460 to 1.0041900)
CD	Metabolic disorders	MR Egger	48	0.997280000	59.69(0.084770)	-0.001107672(0.8352235)	0.9999130 (0.9511640 to 1.0511600)
		Weighted median		0.701414000			1.0054300 (0.9779790 to 1.0336500)
		Inverse variance weighted		0.630251000	59.74(0.100502)		0.9950550 (0.9751700 to 1.0153400)
		Simple mode		0.769292000			1.0084160 (0.9538000 to 1.0661600)
		Weighted mode		0.589894000			1.0107620 (0.9724330 to 1.0506000)
	Fasting blood glucose	MR Egger	18	0.488657000	34.90(0.0041001)	-0.002340048(0.332365)	1.0071000 (0.9875950 to 1.0269800)
		Weighted median		0.603619000			1.0028900 (0.9920110 to 1.0139000)
		Inverse variance weighted		0.800398000	37.08(0.0032819)		0.9986500 (0.9882460 to 1.0091600)
		Simple mode		0.950251000			1.0006300 (0.9811940 to 1.0204600)
		Weighted mode		0.536796000			1.0037700 (0.9921010 to 1.0155700)
	Hypertension	MR Egger	50	0.949619000	321.85(3.28722E-42)	-9.128284e-05(0.911997)	0.9997560 (0.9922590 to 1.0073100)
		Weighted median		0.295452000			0.9987250 (0.9963410 to 1.0011100)
		Inverse variance weighted		0.709807000	321.94(8.28882E-42)		0.9993740 (0.9960820 to 1.0026800)
		Simple mode		0.527666000			1.0018220 (0.9962190 to 1.0074600)
		Weighted mode		0.533902000			0.9990690 (0.9961630 to 1.0019800)
	Waist circumstance	MR Egger	19	0.245224000	54.84(7.268693E-06)	-0.002280349(0.486547)	1.0162200 (0.9899380 to 1.0432100)
		Weighted median		0.220391300			1.0073200 (0.9954550 to 1.0193300)
		Inverse variance weighted		0.262361000	56.47(7.504191E-06)		1.0082000 (0.9939040 to 1.0227000)
		Simple mode		0.705685000			1.0041600 (0.9830950 to 1.0256700)
		Weighted mode		0.215116000			1.0075400 (0.9960610 to 1.0191500)
	Triglycerides	MR Egger	47	0.297544000	443.21(7.15752E-67)	-0.002679308(0.267397)	1.0116940 (0.9900550 to 1.0338100)
		Weighted median		0.986541000			0.9999510 (0.9942910 to 1.0056400)
		Inverse variance weighted		0.908891000	455.63(8.32889E-69)		1.0005710 (0.9908290 to 1.0104100)
		Simple mode		0.387450000			0.9934730 (0.9789660 to 1.0082000)
		Weighted mode		0.787222000			1.0009830 (0.9939070 to 1.0081100)
	HDL cholesterol	MR Egger	50	0.417522800	630.54(1.48063E-102)	0.001950424(0.519077)	0.9884090 (0.9611730 to 1.0164170)
		Weighted median		0.026100400			0.9933630 (0.9875510 to 0.9992080)
		Inverse variance weighted		0.587831200	636.08(4.15124E-103)		0.9967140 (0.9849190 to 1.0086500)
		Simple mode		0.436425100			0.9950820 (0.9829020 to 1.0074130)
		Weighted mode		0.061496800			0.9929360 (0.9857540 to 1.0001710)

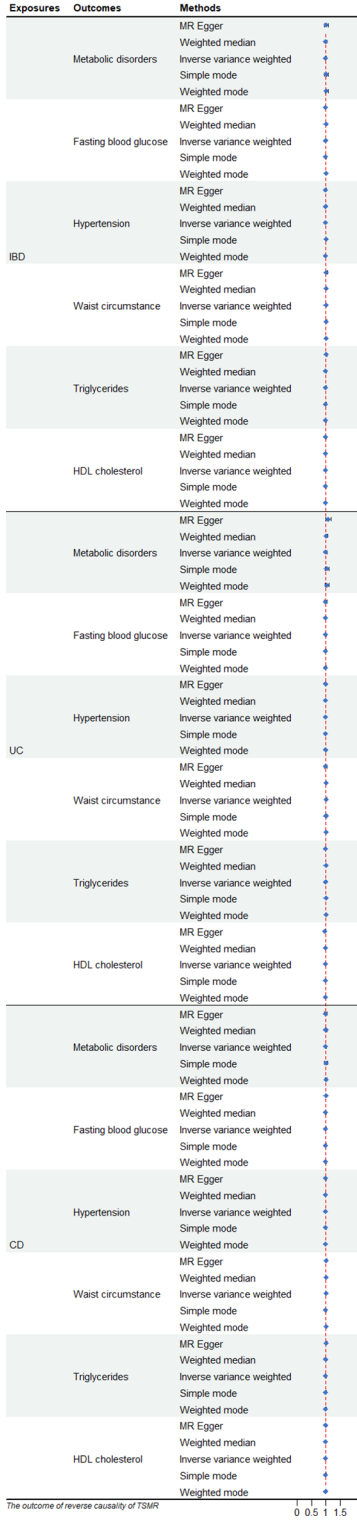

Fig. 4 Outcome of reverse causality of the TSMR

in developing countries [5, 20]. Our results are in line with some clinical investigations that demonstrated that WC is independently connected to an elevated risk of CD but not UC [21, 22]. The pathogenesis of CD may therefore be significantly influenced by visceral obesity. Visceral adipose tissue prediction may be a risk factor for the onset of this disease since adipose tissue is an active, multifunctional metabolic organ that functions in lipid

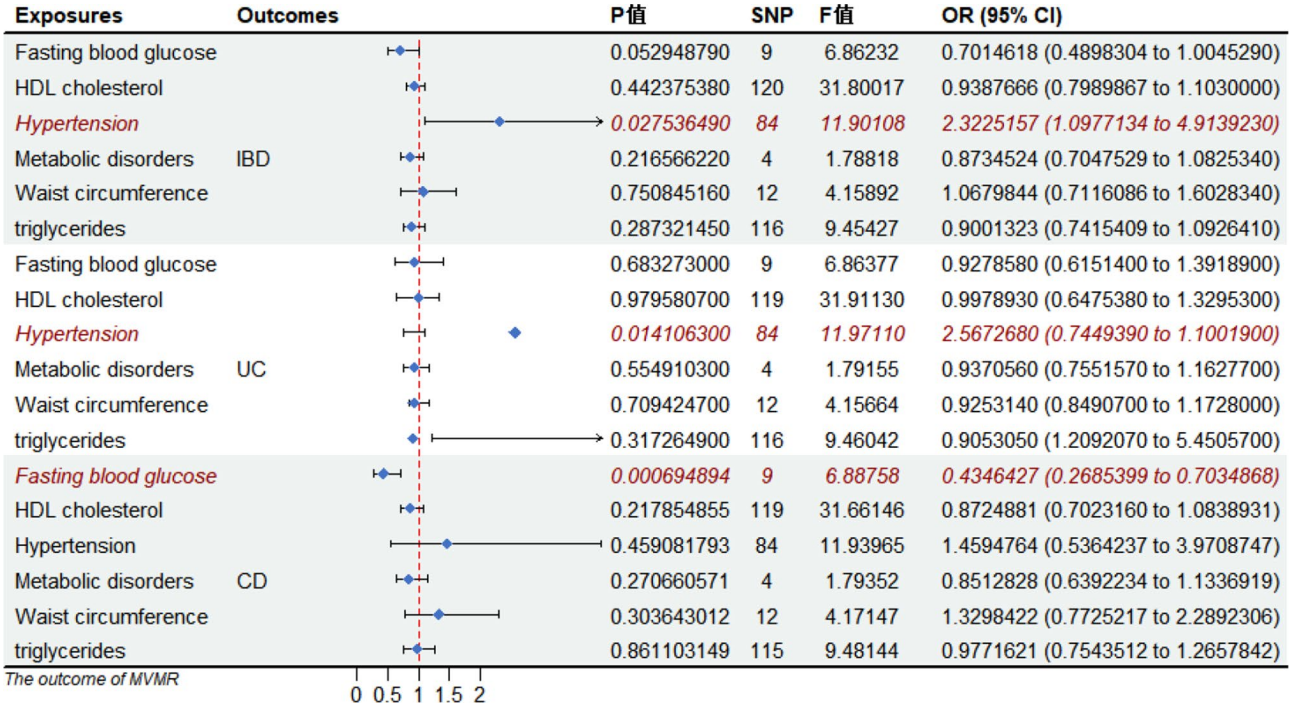

Fig. 5 The MVMR forest plots of causal links of IBD, UC, or CD with MetS

storage, immunological, and endocrine functions [23]. Cytokines related to CD (IL-4, IL-6, IL-8, IL-10, TNF-α, etc.) are derived mainly from mesenteric adipose tissue, and the degree of expression of inflammatory cytokines is related to the number of adipocytes in the test results [24]. On the other hand, the reaction of visceral adipose tissue with gut microbes contributes to the development of CD illness. Adipocytes are the main reservoir of bacteria in the mesentery, and altered bacterial composition in turn leads to altered intestinal barrier function [25]. During inflammation, gut bacteria affect inflammatory mediator release by invading adipose tissue, and visceral adipose tissue in CD patients is more susceptible to inflammation and colonization by commensal bacteria in the gut than in UC patients, resulting in adipocyte proliferation [26, 27]. In contrast, there is a lack of evidence for an association between visceral obesity and UC in human studies. In summary, the increase in WC, especially the increase of visceral adipose tissue and mesenteric adipose tissue base, may be a major component of the disease and development of CD.

Because WC lacks a valuable association in MVMR analysis, the direct causal effect of WC may be attenuated or confounded by these factors when other MetS components are considered. This finding emphasizes the importance of considering the interaction of different metabolic components when understanding the collective impact of abnormalities in different metabolic components on IBD.

Surprisingly, FBG had an inverse relationship with CD risk in the MVMR study. Because the incretin axis is crucial in the pathophysiology of IBD, glucagon-like peptides (GLP) such as GLP-1 and GLP-2 are released by endocrine cells in the intestinal mucosa during nutritional absorption [28]. They not only lower blood glucose and body weight, but also have immunomodulatory properties. They have been found to inhibit macrophage infiltration and inflammatory cytokine production in adipose tissue [29]. As an enteric insulinotropic hormone, GLP-1 could increase insulin sensitivity and hepatic metabolism, while GLP-2 significantly improves intestinal barrier function. GLP-1 Ras reduces intestinal inflammation by improving insulin sensitivity, decreasing oxidative stress, and modulating inflammatory pathways. The majority of people with CD have poor eating habits, which can upset the gut microbiota, causing ecological dysregulation and raising the risk of CD. In contrast, Dietary fiber is produced by a healthy diet and affects the makeup and function of the gut microbiota. This process supports the production of beneficial metabolites by the gut microbiota, such as short-chain fatty acids (SCFAs) and bile acids (BAs), which can enter the liver or influence intestinal permeability, stimulating the release of GLP-1 and GLP-2 and preventing the development of CD disease [30]. Furthermore, one possible explanation for this finding is the influence of hypoglycemic medications. A preclinical investigation found that glucose dysregulation worsens the severity of colitis and that treating with hyperglycemia reverses it [31]. Metformin, a hypoglycemic drug,

has been found to have anti-inflammatory and antioxidant effects in both in vitro and in vivo studies [32, 33], prevents various proinflammatory cytokine signaling pathways, enhances the integrity of the intestinal barrier in diabetic patients and restores the intestinal microbiota, thereby improving intestinal inflammation [34]. More mechanisms by which impaired fasting glucose may affect the incidence of CD remain unknown and warrant further investigation in the future. Because we did not reach the same conclusion in the TSMR analysis, and clinical trials have reported no changes in FBG levels in CD patients [35, 36], the relationship between them needs further analysis.

Conversely, hypertension and IBD are positively correlated. Hypertension and UC according to the MVMR analysis have a statistically significant relationship ($P < 0.05$). However, the confidence interval of its OR contains 1, which indicates that the results are contradictory and unstable, suggesting no statistical significance, even if the p-value is < 0.05. The causal relationship between them may be strongly affected by confounding factors, so we carefully consider their significant association. Compared with the general population, UC may be associated with a greater risk of hypertensive morbidity, according to a UK biobank cohort research [37]. Furthermore, no clinical research has found a connection between UC and hypertension; instead, the underlying mechanisms may involve systemic inflammation, vascular endothelial dysfunction, intestinal microbiota distribution, and immune dysfunction [38]. Hypertension is often accompanied by vascular endothelial dysfunction, which disrupts intestinal barrier function, causes damage to the intestinal mucosal structure, increases intestinal permeability, and allows bacteria and toxic products to enter the intestinal wall, triggering an inflammatory reaction [39]. Significant gut barrier dysfunction and intestinal microbiota abnormalities have been reported in hypertension patients in a number of investigations [40]. In 2017, Li et al. [41]. found that the richness, diversity, and gene number of the gut microbiota were lower in hypertensive patients than in healthy people. This resulted in a decline in gut barrier function, immunological function, resistance to gut colonization, and an increase in gut inflammation [42]. We are unable to conduct additional research due to the lack of effective genetic tools, which could cause discrepancies between the results and clinical investigations. Given the close relationship between hypertension and IBD, the genetic association will be explored in depth in the future. More potent genetic tools are needed.

We investigated the causal link between various MetS components and IBD via a number of Mendelian techniques. In that study, we found a positive correlation between WC and CD disease, which has been confirmed in clinical studies and is consistent with the reliability and accuracy of our findings. The result that fasting glucose may reduce the risk of CD disease needs to be interpreted with caution, but the importance of gut-liver-metabolic interactions in IBD-related metabolic dysfunction has been highlighted in the latest study and this hypothesis may be confirmed in future research. The influences of unmeasured or unknown confounding factors and reverse causality were avoided in MR analysis compared with those in clinical observational studies. The robustness of the results and the consistency of causal estimations are ensured by the outcomes of sensitivity and pleiotropy analysis. Lastly, MVMR research provides additional detail about causality, and the results provide potential implications for clinical work. We anticipate that these results will support clinical research on IBD and help in the development of patient-beneficial strategies.

Ecological dysbiosis, which is caused by a change in the gut microbiota's composition, has been associated with a number of illnesses, such as diabetes mellitus, IBD, and atherosclerosis. Tomas et al. reported that a high-fat diet caused changes in the intestinal microbiome, including a marked rise in the frequency of the phylum Aspergillus and Thickwellia [43]. Changes in the microbial composition, the emergence of distinct taxa, and their biochemical functions and outcomes may all be linked to obesity [44]. Additionally, the gut microbiota is a significant environmental factor that regulates the host's body's storage of fat, which ultimately influences the prevalence of obesity. Some physiologically helpful microbiota, such butyrate-producing bacteria, are fewer in T2DM patients, whereas pathogenic bacteria are more prevalent [45]. Ecological disruption of the gut microbiota can worsen lipid metabolism problems, and dyslipidemia has been shown to cause a disturbance in the gut microbiota in both in vitro and animal tests. Some studies have also revealed a lack of variety in the gut microbiota in a small percentage of hypertensive patients. Li et al. discovered that microbial abundance and diversity were significantly lower in prehypertensive and hypertensive populations compared to healthy controls [46]. MetS is a condition that results from the interaction of extrinsic (such as diet and lifestyle) and intrinsic (such as genetics and gut microbiome) host factors. It is frequently associated with a disorder in the gut microbiota, which triggers a low-grade inflammatory response by rupturing the intestinal barrier and causes insulin resistance through metabolites that impact host metabolism and hormone release. This vicious cycle exacerbates the MetS disease, especially when combined with IBD disease. According to gut microbiological research, IBD patients' gut microbiota composition differs significantly from that of healthy controls, with reduced abundance and diversity and high inter-individual heterogeneity in patient populations [46].

There is a decrease in the abundance of Roseburia and Phascolarctobacterium and a rise in Clostridium, which lowers the anti-inflammatory effects and exacerbates symptoms in IBD patients [47]. Thus, gut flora may be a suitable target for clinical treatment and a possible moderator of the causative link between MetS components and IBD in patients with MetS and IBD. Several studies have shown that the primary pathophysiological basis of both IBD and MetS is chronic low-grade inflammation, whereby bacteria or their components, like endotoxins, enter the bloodstream and cause low-level inflammation due to intestinal barrier disruption and intestinal microbiota discord [48]. IBD has traditionally been treated with immunomodulatory and anti-inflammatory measures. However, it has been discovered that gut microbial therapies, including probiotics, prebiotics, and synbiotics, can also alleviate or maintain IBD remission, lower the disease activity index, and boost the quantity of beneficial bacteria, particularly bifidobacteria, in IBD patients' guts [49]. By adjusting the immune response, colonic epithelial integrity, microbial composition, and related metabolites, this treatment mostly avoids or lessens the severity of IBD [50]. The findings provide more evidence in favor of using microecological agents to treat and control the disease, particularly UC. Additionally, gut microbiota-targeted therapy has been shown to significantly improve metabolic indicators like serum ALT, AST, and GGT enzyme levels [51], and there is a significant correlation with diastolic blood pressure, which may have an impact on blood pressure levels in T2DM patients [52]. Intake of microbial preparations promotes the development of beneficial bacteria in the gut, which generate compounds linked to decreased inflammation and enhanced insulin sensitivity [53]. In conclusion, metabolic illnesses may benefit from its use as a therapeutic target. Although there is presently debate regarding the findings of certain research on the therapeutic potential of microbes, it is undeniable that future probiotic personalized treatment strategies for patients with Mets and IBD patients.

The gut microbiota is influenced by many factors including diet, pharmacological interventions, socioeconomic conditions, smoking and alcohol consumption. Dietary influences have been confirmed in many studies as increased intake of high-fat and high-sugar diets has triggered many metabolic disorders such as obesity, diabetes, and MetS, as well as immune-related diseases such as IBD [54]. Gastrointestinal symptoms in approximately two-thirds of IBD patients are thought to be caused by irregular eating habits [55]. When metabolically healthy (e.g., in individuals eating a high-fibre diet), gut microbes can regulate the integrity of the gut through various mechanisms of action [56]. Ecological diseases brought on by diet have an impact on tissue function, systemic inflammation, and metabolism. A diet high in salt has a detrimental effect on the gut immune system, altering the gut microbiota in addition to the immunological components [57]. Exercise influences the composition of the gut microbiota, which improves metabolic function and lowers the risk of obesity and insulin resistance. Through exercise can independently change the composition and function of the gut microbiota, promoting the growth of beneficial flora and enhancing the function of the gut barrier [58]. IBD and MetS levels may potentially be impacted by drug use. Antibiotic abuse, for instance, can lead to dysbiosis of the intestinal flora, compromised intestinal barrier function, elevated intestinal permeability, and weakened immune systems. Additionally, the etiology of immunological or metabolic diseases is linked to the disrupted microbiota. Differences in disease risk can be explained by variations in antibiotic kind, dosage, and duration [59]. Antibiotic use has been linked in many studies to the development of CD and UC later on; in CD patients, the correlation is stronger [60]. According to cohort studies, the use of antibiotics may raise the incidence of type 2 diabetes and obesity, two conditions that are closely related to changes in the makeup and activity of human microbes [61]. Non-steroidal anti-inflammatory medications are frequently used in medical settings and have the potential to cause ecological dysbiosis and bacterial overgrowth in the small intestine. The development of MetS and IBD disorders may be influenced by such changes in intestinal flora in two ways: firstly, by leading to dysfunction of tight junctions, which play a key role in the increase of intestinal permeability; and secondly, by causing weight gain, insulin resistance, adipogenesis, fibrogenesis, and hepatic oxidative stress [62]. Both MetS components and gut microbiota can be impacted by lifestyle choices like diet, physical activity, and medication use (such as antibiotics and non-steroidal anti-inflammatory medicines). This has been identified in a growing number of observational clinical and epidemiological studies with potential effects on MetS and IBD diseases, which need to be further confirmed and investigated.

Naturally, we recognize that this study is not without limitations. Firstly, as the study population was exclusively European, the results may not be applicable to other groups. There is no clear causal relationship between IBD and MetS diseases, as it has been observed that in some individuals the OR between IBD and MetS approximates 1. In the GWAS larger sample study, even if the effect sizes are extremely small, statistical tests may give very small p-values (i.e. reach statistical significance $P<0.05$), but this statistical significance does not necessarily mean that the results are clinically or practically significant. Despite the implementation of adjustments for confounders, there is a possibility that unmeasured or inadequately adjusted variables remain, which could

potentially influence the outcomes. The presence of measurement bias, selection bias, and other such factors represents a significant challenge that must be completely eliminated in large-scale datasets. This represents a substantial limitation of the present study and underscores the necessity for meticulous interpretation of data and the undertaking of well-designed studies to substantiate our observations. Additionally, the absence of IVs and the inconclusive outcomes of analyses of various metabolic component abnormalities and IBD hindered a comprehensive investigation into the relationship between IBD and metabolic abnormalities. It is anticipated that this may be addressed in future studies through further advancements in genetic approaches.

Conclusion

In conclusion, this work used pooled GWAS data to demonstrate the causative association between MetS and IBD via MR, which revealed a potential causal link between WC, FBG, hypertension, and IBD. Additionally, the unexpected protective effect of FBG on IBD warrants more research, suggesting a potential influence of metabolic effects in the inflammatory process. The findings of this study offer several potential clinical implications. Each element of MetS has a different effect on IBD, and individualized evaluations are required to determine the risk of developing IBD. Our findings underline the value of long-term monitoring of IBD patients who also have concomitant MetS, including early identification of those who may be at risk to consider whether interventions can be made through lifestyle improvements. However, it is crucial to carefully evaluate the findings and take further clinical evidence into account. We hope that these findings will stimulate further clinical studies to develop more targeted strategies for the management of MetS. These results deepen our knowledge of the intricate connection between IBD and metabolic health, highlighting the need for more research to clarify the underlying mechanisms and possible indirect effects. It is believed that this could help medical professionals in considering the significance of metabolic trait interactions in metabolic dysfunction associated with IBD in more practical clinical interventions.

Abbreviations

IBD	Inflammatory Bowel Disease
MetS	Metabolic Syndrome
GWAS	Genome-Wide association study
MR	Mendelian Randomization
FBG	Fasting Blood Glucose
HDL-C	HDL Cholesterol
TG	Triglycerides
WC	Waist Circumference
MVMR	Multivariate Mendelian Randomization
IVs	Instrumental Variables
IVW	Inverse Variance Weighting
TSMR	Two-Sample Mendelian Randomization
IIBDGC	International Inflammatory Bowel Disease Genetic Consortium
CD	Crohn's Disease
UC	Ulcerative Colitis
RCTs	Randomized controlled trials
SNPs	Single Nucleotide Polymorphisms
GLP	glucagon-like peptides

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01704-w.

Supplementary Material 1

Acknowledgements

We thank all the participants in this study.

Author contributions

DZ: Data curation, Formal analysis, Investigation, Methodology, Writing– original draft; HS: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing– review & editing; CW: Data curation, Formal analysis, Investigation, Visualization, Writing original draft; FC: Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Writing– review & editing; PZ: Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Writing– review & editing; XG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing– original draft; YW: Writing– review & editing, Writing– original draft, Supervision, Visualization, Project administration. All authors read and approved the final manuscript.

Funding

Not applicable.

Data availability

The online version contains supplementary material available at https://figshare.com/s/e11ccfe10122487002d3https://figshare.com/s/e39c5efb9a71031d80f7.

Decalarations

Ethical approval

This study utilized publicly available data and summary statistics from previously published genome-wide association studies (GWAS). No new data were collected specifically for this study, and no additional ethics approval or consent to participate was required for this MR study.

Consent to participate

Not applicable.

Consent for publish

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 9 February 2025 / Accepted: 16 April 2025
Published online: 28 April 2025

References

1. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev. 2015;16:1–12.
2. Scott M. Grundy. Metabolic Syndrome Pandemic. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28:629–36.
3. Yorulmaz E, Adali G, Yorulmaz H, Ulasoglu C, Tasan G, Tuncer I. Metabolic syndrome frequency in inflammatory bowel diseases. Saudi J Gastroenterol. 2011;17:376–82.

4. Fitzmorris PS, Colantonio LD, Torrazza Perez E, Smith I, Kakati DD, Malik TA. Impact of metabolic syndrome on the hospitalization rate of Crohn's disease patients seen at a tertiary care center: a retrospective cohort study. Digestion. 2015;91:257–62.
5. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–78.
6. Aniwan S, Santiago P, Loftus EV, Park SH. The epidemiology of inflammatory bowel disease in Asia and Asian immigrants to Western countries. United Eur Gastroenterol J. 2022;10:1063–76.
7. Dixon LJ, Kabi A, Nickerson KP, McDonald C. Combinatorial effects of diet and genetics on inflammatory bowel disease pathogenesis. Inflamm Bowel Dis. 2015;21:912–22.
8. Goodman WA, Erkkila IP, Pizarro TT. Sex matters: impact on pathogenesis, presentation and treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020;17:740–54.
9. Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot J-F, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. Lancet Gastroenterol Hepatol. 2019;4:643–54.
10. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization JAMA. 2017;318:1925–6.
11. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
12. Hartley A, Sanderson E, Granell R, Paternoster L, Zheng J, Smith GD, et al. Using multivariable Mendelian randomization to estimate the causal effect of bone mineral density on osteoarthritis risk, independently of body mass index. Int J Epidemiol. 2022;51:1254–67.
13. Liu B, Ye D, Yang H, Song J, Sun X, Mao Y, et al. Two-Sample Mendelian randomization analysis investigates causal associations between gut microbial genera and inflammatory bowel disease, and specificity causal associations in ulcerative colitis or Crohn's disease. Front Immunol. 2022;13:921546.
14. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181:251–60.
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood Institute scientific statement. Circulation. 2005;112:2735–52.
16. Pierce BL, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. Int J Epidemiol. 2011;40:740–52.
17. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469–80.
18. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic syndrome: updates on pathophysiology and management in 2021. Int J Mol Sci. 2022;23:786.
19. Szilagyi A. Relationship(s) between obesity and inflammatory bowel diseases: possible intertwined pathogenic mechanisms. Clin J Gastroenterol. 2020;13:139–52.
20. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017;152:313–e3212.
21. Je Y, Han K, Chun J, Kim Y, Kim J-H, Hoon Youn Y, et al. Association of waist circumference with the risk of inflammatory bowel disease: a nation-wide cohort study of 10 million individuals in Korea. J Crohns Colitis. 2023;17:681–92.
22. Chan SSM, Chen Y, Casey K, Olen O, Ludvigsson JF, Carbonnel F, et al. Obesity is associated with increased risk of Crohn's disease, but not ulcerative colitis: A pooled analysis of five prospective cohort studies. Clin Gastroenterol Hepatol. 2022;20:1048–58.
23. Tsai Y-W, Fu S-H, Dong J-L, Chien M-W, Liu Y-W, Hsu C-Y, et al. Adipokine-Modulated immunological homeostasis shapes the pathophysiology of inflammatory bowel disease. Int J Mol Sci. 2020;21:9564.
24. Das UN. Is obesity an inflammatory condition? Nutrition. 2001;17:953–66.
25. Karaskova E, Velganova-Veghova M, Geryk M, Foltenova H, Kucerova V, Karasek D. Role of adipose tissue in inflammatory bowel disease. Int J Mol Sci. 2021;22:4226.
26. Gonçalves P, Magro F, Martel F. Metabolic inflammation in inflammatory bowel disease: crosstalk between adipose tissue and bowel. Inflamm Bowel Dis. 2015;21:453–67.
27. Zulian A, Cancello R, Ruocco C, Gentilini D, Di Blasio AM, Danelli P, et al. Differences in visceral fat and fat bacterial colonization between ulcerative colitis and Crohn's disease. An in vivo and in vitro study. PLoS ONE. 2013;8:e78495.
28. Brubaker PL, Drucker DJ. Structure-function of the glucagon receptor family of G protein-coupled receptors: the glucagon, GIP, GLP-1, and GLP-2 receptors. Recept Channels. 2002;8:179–88.
29. Lee Y-S, Park M-S, Choung J-S, Kim S-S, Oh H-H, Choi C-S, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. Diabetologia. 2012;55:2456–68.
30. Guney-Coskun M, Basaranoglu M. Interplay of gut microbiota, glucagon-like peptide receptor agonists, and nutrition: new frontiers in metabolic dysfunction-associated steatotic liver disease therapy. World J Gastroenterol. 2024;30:4682–8.
31. Francis KL, Alonge KM, Pacheco MC, Hu SJ, Krutzsch CA, Morton GJ, et al. Diabetes exacerbates inflammatory bowel disease in mice with diet-induced obesity. World J Gastroenterol. 2023;29:4991–5004.
32. Wu W, Wang S, Liu Q, Shan T, Wang Y. Metformin protects against LPS-Induced intestinal barrier dysfunction by activating AMPK pathway. Mol Pharm. 2018;15:3272–84.
33. Yang S, Park J-S, Hwang S-H, Cho K-H, Na HS, Choi J, et al. Metformin-Inducible small heterodimer partner interacting leucine zipper protein ameliorates intestinal inflammation. Front Immunol. 2021;12:652709.
34. Wanchaitanawong W, Thinrungroj N, Chattipakorn SC, Chattipakorn N, Shinlapawittayatorn K. Repurposing Metformin as a potential treatment for inflammatory bowel disease: evidence from cell to the clinic. Int Immunopharmacol. 2022;112:109230.
35. Zatorski H, Salaga M, Zielińska M, Mokrowiecka A, Jacenik D, Krajewska WM, et al. Colonic inflammation induces changes in glucose levels through modulation of incretin system. Pharmacol Rep. 2021;73:1670–9.
36. Bregenzer N, Hartmann A, Strauch U, Schölmerich J, Andus T, Bollheimer LC. Increased insulin resistance and beta cell activity in patients with Crohn's disease. Inflamm Bowel Dis. 2006;12:53–6.
37. He J, Zhang S, Qiu Y, Liu F, Liu Z, Tan J, et al. Ulcerative colitis increases risk of hypertension in a UK biobank cohort study. United Eur Gastroenterol J. 2023;11:19–30.
38. Cainzos-Achirica M, Glassner K, Zawahir HS, Dey AK, Agrawal T, Quigley EMM, et al. Inflammatory bowel disease and atherosclerotic cardiovascular disease: JACC review topic of the week. J Am Coll Cardiol. 2020;76:2895–905.
39. Druml W. [Intestinal cross-talk: the gut as motor of multiple organ failure]. Med Klin Intensivmed Notfmed. 2018;113:470–7.
40. Santisteban MM, Qi Y, Zubcevic J, Kim S, Yang T, Shenoy V, et al. Hypertension-Linked pathophysiological alterations in the gut. Circ Res. 2017;120:312–23.
41. Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017;5:14.
42. Yang Z, Liu Y, Wang L, Lin S, Dai X, Yan H, et al. Traditional Chinese medicine against COVID-19: role of the gut microbiota. Biomed Pharmacother. 2022;149:112787.
43. Tomas J, Mulet C, Saffarian A, Cavin J-B, Ducroc R, Regnault B, et al. High-fat diet modifies the PPAR-γ pathway leading to disruption of microbial and physiological ecosystem in murine small intestine. Proc Natl Acad Sci U S A. 2016;113:E5934–43.
44. Thingholm LB, Rühlemann MC, Koch M, Fuqua B, Laucke G, Boehm R, et al. Obese individuals with and without type 2 diabetes show different gut microbial functional capacity and composition. Cell Host Microbe. 2019;26:252–e26410.
45. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490:55–60.
46. Lal S, Kandiyal B, Ahuja V, Takeda K, Das B. Gut microbiome dysbiosis in inflammatory bowel disease. Progress in Molecular Biology and Translational Science [Internet]. Elsevier; 2022 [cited 2025 Mar 28]. pp. 179–204. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1877117322001326
47. Shan Y, Lee M, Chang EB. The gut Microbiome and inflammatory bowel diseases. Annu Rev Med. 2022;73:455–68.
48. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542:177–85.
49. Su H, Kang Q, Wang H, Yin H, Duan L, Liu Y, et al. Effects of glucocorticoids combined with probiotics in treating Crohn's disease on inflammatory factors and intestinal microflora. Exp Ther Med. 2018;16:2999–3003.
50. Shinde T, Perera AP, Vemuri R, Gondalia SV, Karpe AV, Beale DJ, et al. Synbiotic supplementation containing whole plant sugar cane fibre and probiotic spores potentiates protective synergistic effects in mouse model of IBD. Nutrients. 2019;11:818.

51. Mahapatro A, Bawna F, Kumar V, Daryagasht AA, Gupta S, Raghuma N, et al. Anti-inflammatory effects of probiotics and synbiotics on patients with non-alcoholic fatty liver disease: an umbrella study on meta-analyses. Clin Nutr ESPEN. 2023;57:475–86.
52. Amini-Salehi E, Mahapatro A, Korsapati RR, Korsapati AR, Jain SM, Babaeizad A, et al. Exploring the relationship between gut Microbiome modulation and blood pressure in type 2 diabetes: an umbrella review. Nutr Metabolism Cardiovasc Dis. 2024;34:2046–54.
53. Canfora EE, Meex RCR, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM. Nat Rev Endocrinol. 2019;15:261–73.
54. Christ A, Lauterbach M, Latz E. Western diet and the immune system: an inflammatory connection. Immunity. 2019;51:794–811.
55. Simrén M, Månsson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, et al. Food-related Gastrointestinal symptoms in the irritable bowel syndrome. Digestion. 2001;63:108–15.
56. Cani PD. Human gut microbiome: hopes, threats and promises. Gut. 2018;67:1716–25.
57. Miranda PM, De Palma G, Serkis V, Lu J, Louis-Auguste MP, McCarville JL, et al. High salt diet exacerbates colitis in mice by decreasing Lactobacillus levels and butyrate production. Microbiome. 2018;6:57.
58. Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the gut microbiome: A review of the evidence, potential mechanisms, and implications for human health. Exerc Sport Sci Rev. 2019;47:75–85.
59. Fenneman AC, Weidner M, Chen LA, Nieuwdorp M, Blaser MJ. Antibiotics in the pathogenesis of diabetes and inflammatory diseases of the Gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2023;20:81–100.
60. Nguyen LH, Örtqvist AK, Cao Y, Simon TG, Roelstraete B, Song M, et al. Antibiotic use and the development of inflammatory bowel disease: a National case-control study in Sweden. Lancet Gastroenterol Hepatol. 2020;5:986–95.
61. Vliex LMM, Penders J, Nauta A, Zoetendal EG, Blaak EE. The individual response to antibiotics and diet - insights into gut microbial resilience and host metabolism. Nat Rev Endocrinol. 2024;20:387–98.
62. Utzeri E, Usai P. Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease. World J Gastroenterol. 2017;23:3954–63.

Publisher's note