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To explore the causal association between the serum lipid profile and inflammatory bowel disease using bidirectional Mendelian randomisation analysis

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ABSTRACT

Background Despite studies confirming that patients with inflammatory bowel disease (IBD) present with dyslipidaemia, the associations between IBD and the serum lipid profile have not been determined. The present study aimed to investigate the causal relationship between the serum lipid profile and IBD risk and elucidate the nature of the interactions between them.

Methods Two-sample Mendelian randomisation (MR) analysis was performed to investigate the causal links between total cholesterol (TC), total triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (Apo A), apolipoprotein B (Apo B) and lipoprotein (a) (Lp(a)) and IBD. The study was carried out using the R TwoSampleMR and Mendelian randomisation packages.

Results All MR methods, including the weighted median, weighted mode, inverse-variance weighted model, MR-PRESSO, contamination mixture and MR Egger, supported a null causal relationship between TG, TC, HDL-C, LDL-C, Apo A, Apo B and Lp(a) and between IBD, Crohn's disease and ulcerative colitis. Null causal effects of lipid indices on IBD were validated through independent genome-wide association studies (GWAS), indicating that the findings are robust.

Conclusion Our findings suggest that none of the seven lipid indices may be a potential risk factor for the onset of IBD. However, additional research is needed since our MR analyses cannot assess the potential non-linear causal relationship between serum lipids and IBD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mendelian randomisation (MR) analysis between patients with inflammatory bowel disease (IBD) and serum lipid profiles is scarce, and the analysis results are inconsistent.

WHAT THIS STUDY ADDS

⇒ MR analyses suggested that no lipid indices were a potential risk factor for the onset of IBD, Crohn's disease or ulcerative colitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although no evidence supports a causal relationship between serum lipids and IBD, relevant monitoring of those lipid indices is still recommended. However, further research is needed on whether a non-linear causal relationship exists between lipids and IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, non-specific intestinal inflammatory disease that involves the ileum, rectum, colon and even the entire digestive tract and includes mainly ulcerative colitis (UC) and Crohn's disease (CD). The main clinical manifestations are abdominal pain, diarrhoea, haematochezia and weight loss. This disease is characterised by a lengthy course and can persist for a lifetime. IBD is a growing global health concern, and its prevalence is highest in developed Western countries.[1] However, the incidence rate of IBD in Asia and Eastern Europe has steadily increased over the last decade.[2]

Previous studies have confirmed that patients with IBD present with dyslipidaemia,[3 4] which is a well-established risk factor for cardiovascular disease. Several studies have shown that lower total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and apolipoprotein A-I (Apo A-I) levels are associated with higher triglyceride (TG) and lipoprotein (a) (Lp(a)) levels in patients with IBD,[5–10] which are independently associated with more severe disease.[7 9 10] Additionally, compared with the general population, male patients with IBD have higher TG levels, while female patients with IBD have significantly lower TG levels.[7] However, one study indicated that patients with IBD have lower TG levels than healthy controls and that the Crohn's Disease Activity Index (CDAI) and Mayo score are not correlated with TG. In contrast, TC, HDL-C and

LDL-C levels are negatively associated with the CDAI.[11] Another study involving 497 patients with UC yielded similar results, indicating no significant correlation between TG levels and disease activity.[12] One study revealed that the Lp(a) level in patients with IBD was not significantly different from that in controls.[13] The results of studies on the relationship between IBD and serum lipid profiles are inconsistent, and they are cross-sectional studies, making it impossible to draw causal inferences about the relationship between IBD and serum lipid profiles. Currently, longitudinal prospective studies that thoroughly evaluate the correlation between IBD incidence and serum lipid profiles are rare, and the results are inconsistent or even contradictory.[14–16]

Mendelian randomisation (MR) analysis used genetic variants as non-confounded surrogates of the exposure and evaluates whether the exposure may have a causal effect on an outcome of interest. In an MR study, confounding and reverse causality are minimised, enabling plausible causal inferences. To investigate the causal relationship, we conducted an MR analysis to determine if the two attributes are causally correlated and, if so, the direction of correlation (ie, positive or negative). In an MR analysis, single nucleotide polymorphisms (SNPs) strongly associated with the exposure (eg, TG levels) are considered instrumental variables (IVs) for estimating the causal effects of the exposure on the outcome (eg, IBD). Such studies may aid in understanding the complex interplay between these variables and facilitate disease prevention and early intervention. This study aimed to explore the causal relationship between serum lipid profiles and IBD through MR analysis, shedding light on their interactions and offering guidance for clinical practice.

MATERIALS AND METHODS

Experimental data

Two-sample MR analysis was performed to investigate the causal relationship between serum lipid profiles and IBD. The analysis was carried out using the MR-Base platform and R TwoSampleMR package,[17] with serum lipid profiles (TC, TG, HDL-C, LDL-C, Apo A, Apo B and Lp(a)) considered the exposure and IBD considered the outcome. The summary data for TC, TG, HDL-C and LDL-C were obtained from the latest release of the Global Lipids Genetics Consortium.[18] Multiple independent SNPs with low linkage disequilibrium (R^2<0.01) associated with the four lipid indices at genome-wide significance (p-value <5×10^{-8}) were selected. The genome-wide association studies (GWAS) used for Apo A, Apo B and Lp(a) were derived from the studies of Mbatchou *et al.*, Richardson *et al*, and Barton *et al.*[19–21] involving 355 859,

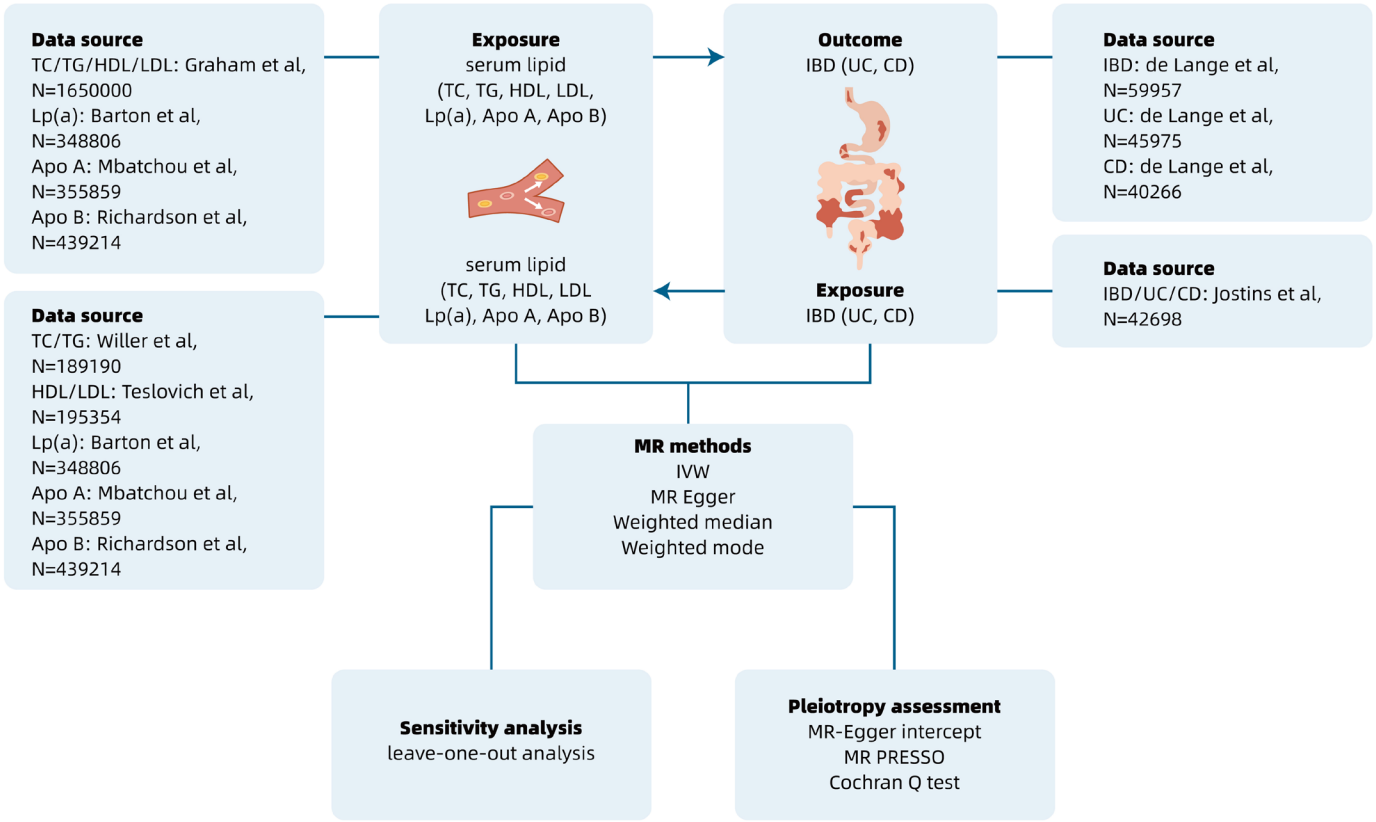

Figure 1 Study schema. Apo A, apolipoprotein A; Apo B, apolipoprotein B; CD, Crohn's disease; HDL-C, high-density lipoprotein cholesterol; IBD, inflammatory bowel disease; IVW, inverse-variance weighted; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TC, total cholesterol; TG, triglycerides; UC, ulcerative colitis.

439 214 and 348 806 individuals, respectively. Data from a GWAS conducted by de Lange *et al*,[22] which included 25 042 cases and 34 915 controls of European ancestry, were used for IBD, 12 366 cases and 33 609 controls of European ancestry were used for UC and 12 194 cases and 28 072 controls of European ancestry were used for CD. The adjusted covariates in the referenced GWAS are summarised in online supplemental table 1.

In the reverse MR analysis, the GWAS used for TG and TC was from Willer *et al*'s study,[23] which included 94 595 individuals. The GWAS data used for HDL-C and LDL-C were from Teslovich *et al*'s study,[24] which involved 99 900 individuals for HDL-C and 95 454 individuals for LDL-C. The GWAS studies for Apo A, Apo B and Lp(a) were the ones used in the forward MR analyses. The summary data for patients with IBD, CD and UC were obtained from the study by Jostins *et al*.[25]

In the final phase, recent summary data from the UK Biobank[21] (for the lipid profiles) and summary data from the FinnGen consortium (https://www.finngen.fi/en), release 9 (for IBD), were employed to validate the robustness of the findings obtained at the discovery stage.

Mendelian randomisation

In this MR analysis, the inverse-variance weighted (IVW) method was used for the primary analysis. In the IVW method, the effect of each variant on the outcome was initially weighed by its effect on the exposure using the Wald ratio method to generate individual MR estimates. These individual estimates were then combined into an overall summary value using a

Table 1 Results of Mendelian randomisation (MR) analyses for inflammatory bowel disease

Lipids (exposure)	MR method	OR	p-value	MR Egger intercept p-value	Heterogeneity test p-value
Triglycerides	IVW	0.962	0.421	0.924	<0.001
	MR-Egger	0.967	0.672		<0.001
	Weighted median	0.874	0.054		
	Weighted mode	0.875	0.077		
	MR-PRESSO	0.962	0.422		
Total cholesterol	IVW	0.872	0.158	0.098	<0.001
	MR-Egger	1.023	0.716		<0.001
	Weighted median	0.951	0.322		
	Weighted mode	0.919	0.156		
	MR-PRESSO	0.945	0.160		
High-density lipoprotein cholesterol	IVW	1.019	0.665	0.853	<0.001
	MR-Egger	1.009	0.899		<0.001
	Weighted median	1.034	0.588		
	Weighted mode	1.025	0.703		
	MR-PRESSO	1.019	0.666		
Low-density lipoprotein cholesterol	IVW	0.995	0.912	0.298	<0.001
	MR-Egger	1.051	0.469		<0.001
	Weighted median	0.975	0.671		
	Weighted mode	0.940	0.370		
	MR-PRESSO	0.995	0.912		
Lipoprotein (a)	IVW	1.125	0.051	0.857	0.014
	MR-Egger	1.120	0.103		0.018
	Weighted median	1.095	0.143		
	Weighted mode	1.143	0.016		
	MR-PRESSO	1.125	0.058		
Apolipoprotein A	IVW	0.918	0.059	0.514	<0.001
	MR-Egger	0.884	0.094		<0.001
	Weighted median	0.915	0.141		
	Weighted mode	0.917	0.172		
	MR-PRESSO	0.918	0.061		
Apolipoprotein B	IVW	1.043	0.339	0.721	<0.001
	MR-Egger	1.058	0.343		<0.001
	Weighted median	1.062	0.359		
	Weighted mode	1.065	0.233		
	MR-PRESSO	1.043	0.341		

IVW, inverse-variance weighted method.

meta-analysis. A proxy search (R^2>0.8) for unavailable SNPs was also conducted, and the strength of each SNP was assessed using its F-statistic. To address horizontal pleiotropy, more robust approaches including MR–Egger regression, weighted median and weighted mode, were used alongside the IVW method. Specifically, MR–Egger regression involved a weighted linear regression of SNP–outcome associations on SNP–exposure associations, the weighted median method used a median weighted by the precisions of individual MR estimates, and the weighted mode used the estimate based on the largest valid SNP cluster. The p-values were adjusted for multiple comparisons using Bonferroni's method.

Furthermore, heterogeneity tests, assessments of horizontal pleiotropy and leave-one-out (LOO) analyses were performed. Cochran's Q tests were used to estimate SNP heterogeneity. A multiplicative random effects model was used when significant heterogeneity among SNPs was observed. Both the MR–Egger intercept term and the MR-PRESSO global test were employed to detect outliers and assess horizontal pleiotropic effects. A statistically insignificant intercept in MR–Egger indicates no directional horizontal pleiotropic effect. The MR-PRESSO outlier test was conducted to address potential horizontal pleiotropy, removing outliers when the p-value of the MR-PRESSO global test was less than 0.05. Additionally, the MR-PRESSO distortion test was used to evaluate significant distortions in the causal estimates, both before and after the exclusion of these outliers. These MR-PRESSO tests were performed using the R MR-PRESSO package. The estimated coefficients and corresponding p values of the corrected MR-PRESSO tests were included with the results of other MR methods. LOO analysis was performed to assess the presence of extreme SNPs or outliers. Figure 1 presents a flowchart illustrating the MR analyses performed in this study.

RESULTS

MR results for the serum lipid profiles and IBD status

Initially, univariate two-sample MR analyses were conducted to examine the relationships between specific serum lipid profiles and IBD. Using the random effects IVW model, weighted median, weighted mode, MR–Egger and MR-PRESSO, concordant null causal associations were identified between TG, TC, HDL-C, LDL-C, Apo A, Apo B, Lp(a) and IBD (table 1 and figure 2A). The Q statistics revealed significant heterogeneity among the individual MR estimates. Consequently, the results obtained using the random effects IVW method were presented for all analyses. Furthermore, the MR–Egger intercept terms indicated no substantial directional horizontal pleiotropy among the SNPs. Importantly, the F-statistics of these SNPs were calculated, and their values were all greater than 10, indicating minimal biases from weak instruments in this study. To further validate the validity of the selected SNPs as IVs for lipid types, a positive control experiment was performed in which the outcome of interest was coronary artery disease, a well-established trait associated with lipid indices. The results of the positive control MR analyses are presented in online supplemental table 2, which shows that the selected SNPs are eligible to represent lipid types.

Additionally, separate MR analyses stratified by the two subtypes of IBD (UC or CD) were conducted. In line with the overall IBD analysis, no significant associations were

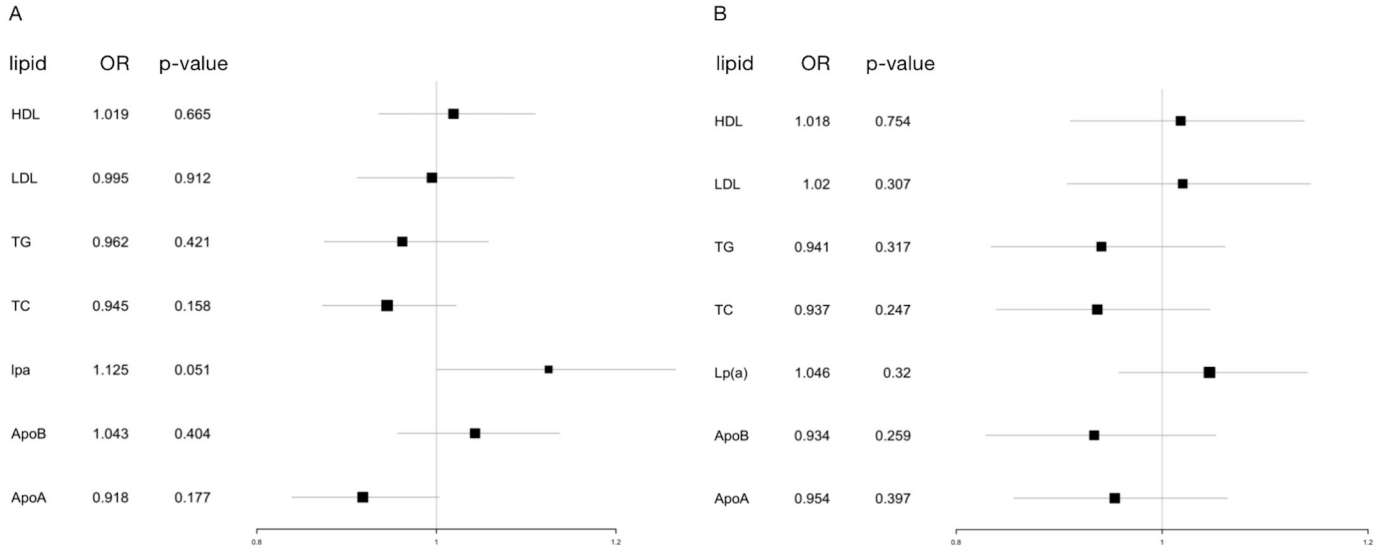

Figure 2 Forest plots of Mendelian randomisation analyses between lipid types and inflammatory bowel disease. (A) For the discovery set; and (B) for the validation set. Apo A, apolipoprotein A; Apo B, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); TC, total cholesterol; TG, triglyceride.

Table 2 Separate Mendelian randomisation (MR) analyses for Crohn's disease (CD) and ulcerative colitis (UC)

		CD		UC	
Lipids (exposure)	MR method	OR (p-value)	Heterogeneity and pleiotropy test	OR (p-value)	Heterogeneity and pleiotropy
Triglycerides	IVW	1.081 (0.217)	<0.001	1.026 (0.665)	<0.001
	MR-Egger	1.095 (0.379)	<0.001	1.070 (0.479)	<0.001
	Weighted median	0.902 (0.254)	MR-Egger	0.977 (0.783)	MR-Egger
	Weighted mode	0.960 (0.670)	Intercept:	0.972 (0.767)	Intercept:
	MR-PRESSO	1.081 (0.218)	0.877	1.026 (0.665)	0.576
Total cholesterol	IVW	0.929 (0.137)	<0.001	0.972 (0.561)	<0.001
	MR-Egger	1.072 (0.365)	<0.001	1.063 (0.431)	<0.001
	Weighted median	0.936 (0.336)	MR-Egger	0.978 (0.745)	MR-Egger
	Weighted mode	0.919 (0.314)	Intercept:	0.992 (0.924)	Intercept:
	MR-PRESSO	0.929 (0.138)	0.015	0.972 (0.562)	0.132
High-density lipoprotein cholesterol	IVW	0.948 (0.305)	<0.001	1.040 (0.471)	<0.001
	MR-Egger	0.894 (0.788)	<0.001	0.998 (0.981)	<0.001
	Weighted median	0.981 (0.788)	MR-Egger	1.051 (0.499)	MR-Egger
	Weighted mode	0.999 (0.990)	Intercept:	0.981 (0.803)	Intercept:
	MR-PRESSO	0.948 (0.306)	0.353	1.040 (0.471)	0.542
Low-density lipoprotein cholesterol	IVW	0.962 (0.485)	<0.001	1.036 (0.490)	<0.001
	MR-Egger	1.067 (0.439)	<0.001	1.059 (0.476)	<0.001
	Weighted median	0.861 (0.046)	MR-Egger	1.041 (0.576)	MR-Egger
	Weighted mode	0.891 (0.225)	Intercept:	0.964 (0.658)	Intercept:
	MR-PRESSO	0.963 (0.485)	0.109	1.036 (0.491)	0.723
Lipoprotein (a)	IVW	1.131(0.090)*	0.068	1.142(0.064)*	0.101
	MR-Egger	1.172(0.053)*	0.074	1.126(0.147)*	0.087
	Weighted median	1.156 (0.077)	MR-Egger	1.042 (0.642)	MR-Egger
	Weighted mode	1.170 (0.021)	Intercept:	1.150 (0.048)	Intercept:
	MR-PRESSO	1.131 (0.099)	0.281	1.142 (0.071)	0.668
Apolipoprotein A	IVW	0.931 (0.177)	<0.001	0.999 (0.980)	<0.001
	MR-Egger	0.887 (0.163)	<0.001	1.003 (0.974)	<0.001
	Weighted median	0.916 (0.220)	MR-Egger	0.914 (0.254)	MR-Egger
	Weighted mode	0.972 (0.698)	Intercept:	0.941 (0.418)	Intercept:
	MR-PRESSO	0.931 (0.261)	0.475	0.999 (0.980)	0.952
Apolipoprotein B	IVW	1.049 (0.384)	<0.001	1.026 (0.595)*	0.140
	MR-Egger	1.042 (0.586)	<0.001	1.048 (0.478)*	0.131
	Weighted median	1.082 (0.345)	MR-Egger	1.027 (0.757)	MR-Egger
	Weighted mode	1.029 (0.681)	Intercept:	1.016 (0.818)	Intercept:
	MR-PRESSO	1.049 (0.385)	0.871	1.026 (0.595)	0.636

*the fixed-effect model was used.
IVW, inverse-variance weighted method.

observed between the seven lipid types and patients with CD or between the seven lipid types and patients with UC when employing the five MR methods. The results of these analyses are presented in table 2. In all the aforementioned analyses, no directional horizontal pleiotropy was detected, as evidenced by the MR–Egger intercept (p>0.05) following the removal of identified outliers through the MR-PRESSO tests. Again, all F-statistics of these SNPs were greater than 10.

Finally, further complement analyses using two additional MR methods, the contamination mixture and MR-mixture methods, were performed to evaluate the robustness of our findings. Again, the null causal relationships between lipid types and IBD, CD or UC were determined from these analyses. The results of these complement analyses are tabulated in online supplemental table 3.

Validations on FinnGen study

In the validation sets, concordant null causal effects between TG, TC, HDL-C, LDL-C, Apo A, Apo B, Lp(a) and IBD were obtained, suggesting that the findings concerning the impacts of these lipid indices on IBD are robust. The IVW results for the validation cohort were constructed as a forest plot (figure 2B).

Reverse MR analysis

Similarly, a reverse MR analysis was conducted where IBD was the exposure variable and TC, HDL-C, TG, LDL-C, Apo

Table 3 Results of reverse Mendelian randomisation (MR) for inflammatory bowel disease

Lipids (outcome)	MR method	OR	p-value	MR Egger intercept p-value	Heterogeneity test p-value
Triglycerides	IVW	0.992	0.561	0.146	<0.001
	MR-Egger	0.980	0.388		<0.001
	Weighted median	0.997	0.714		
	Weighted mode	0.996	0.510		
	MR-PRESSO	0.992	0.573		
Total cholesterol	IVW	1.007	0.409	0.196	<0.001
	MR-Egger	0.991	0.544		<0.001
	Weighted median	1.002	0.750		
	Weighted mode	0.999	0.910		
	MR-PRESSO	1.007	0.423		
High-density lipoprotein cholesterol	IVW	1.010	0.113	0.565	<0.001
	MR-Egger	1.016	0.184		<0.001
	Weighted median	1.006	0.487		
	Weighted mode	1.001	0.952		
	MR-PRESSO	1.010	0.117		
Low-density lipoprotein cholesterol	IVW	0.991	0.149	0.713	<0.001
	MR-Egger	0.995	0.645		<0.001
	Weighted median	0.987	0.141		
	Weighted mode	0.997	0.751		
	MR-PRESSO	0.991	0.161		
Lipoprotein (a)	IVW	0.998*	0.398	0.872	0.662
	MR-Egger	0.997	0.619		0.627
	Weighted median	0.994	0.147		
	Weighted mode	0.992	0.135		
	MR-PRESSO	0.998	0.401		
Apolipoprotein A	IVW	0.996	0.166	0.388	<0.001
	MR-Egger	1.001	0.871		<0.001
	Weighted median	0.992	0.029		
	Weighted mode	0.993	0.315		
	MR-PRESSO	0.996	0.170		
Apolipoprotein B	IVW	0.997	0.380	0.577	<0.001
	MR-Egger	0.993	0.390		<0.001
	Weighted median	0.994	0.090		
	Weighted mode	0.996	0.495		
	MR-PRESSO	0.997	0.382		

*the fixed-effect model was used.
IVW, inverse-variance weighted method.

A, Apo B and Lp(a) were the outcomes. Therefore, the impact of developing IBD on TC, HDL-C, LDL-C, Apo A, Apo B and Lp(a) levels was evaluated. Additionally, separate MR analyses stratified by the two subtypes of IBD (UC or CD) were conducted.

No significant reverse causal associations were detected between various lipid types and IBD, between lipid types and CD or between lipid types and UC when adjusted p-values were applied (tables 3 and 4).

DISCUSSION

Numerous studies have reported abnormal lipid levels in patients with IBD; however, these findings are inconsistent. Several studies have shown lower levels of TC, HDL-C, LDL-C, ApoB, Apo A-I and apoA-IV along with higher TG and Lp(a) levels in patients with IBD than in healthy controls,[6–8 10 26 27] with correlations with disease activity.[9 10 26] Animal experiments demonstrated that Apo A-I mimetics reduced inflammatory levels in intestinal tissue and plasma.[28 29] However, research has indicated that the apoA-IV and Lp(a) levels in the UC group are not associated with disease activity.[11 26] Following treatment with infliximab, significant increases in TC, HDL-C and Apo A-I were observed compared with baseline, while no changes were noted in TG, LDL-C, Apo B100 or LP (a).[30] Discrepancies persist, with one study noting reduced LDL-C exclusively in patients with CD[7] and another reporting elevated LDL-C in patients with IBD.[31] Additionally, one investigation revealed no significant changes in TG or HDL-C levels in patients with IBD.[32] A cross-sectional study revealed significantly elevated TG levels in patients with CD undergoing intestinal resection.[33] Conversely, patients with

Table 4 Separate reverse Mendelian randomisation (MR) analyses for ulcerative colitis and Crohn's disease

		Crohn's disease		Ulcerative colitis	
Lipids	MR method	OR (p-value)	Heterogeneity and pleiotropy	OR (p-value)	Heterogeneity and pleiotropy
Triglycerides	IVW	1.008 (0.197)	<0.001	0.998 (0.630)	<0.001
	MR-Egger	0.993 (0.468)	<0.001	0.995 (0.305)	<0.001
	Weighted median	0.997 (0.415)	MR-Egger	0.996 (0.236)	MR-Egger
	Weighted mode	0.997 (0.390)	Intercept:	0.993 (0.011)	Intercept:
	MR-PRESSO	1.008 (0.216)	0.049	0.998 (0.642)	0.329
Total cholesterol	IVW	1.007 (0.169)	<0.001	0.997 (0.416)	<0.001
	MR-Egger	1.007 (0.398)	<0.001	0.996 (0.346)	<0.001
	Weighted median	1.003 (0.439)	MR-Egger	0.995 (0.234)	MR-Egger
	Weighted mode	1.001 (0.607)	Intercept:	0.995 (0.140)	Intercept:
	MR-PRESSO	1.007 (0.192)	0.987	0.997 (0.435)	0.600
High density lipoprotein cholesterol	IVW	1.002 (0.678)	<0.001	0.991 (0.149)	0.001
	MR-Egger	0.989 (0.059)	<0.001	0.995 (0.645)	0.001
	Weighted median	0.995 (0.228)	MR-Egger	0.987 (0.141)	MR-Egger
	Weighted mode	0.996 (0.266)	Intercept:	0.997 (0.751)	Intercept:
	MR-PRESSO	1.002 (0.697)	0.007	0.991 (0.162)	0.372
Low density lipoprotein cholesterol	IVW	1.001 (0.769)	<0.001	0.997 (0.363)*	0.111
	MR-Egger	1.005 (0.420)	<0.001	1.000 (0.938)*	0.107
	Weighted median	1.000 (0.983)	MR-Egger	0.996 (0.477)	MR-Egger
	Weighted mode	1.000 (0.977)	Intercept:	0.998 (0.621)	Intercept:
	MR-PRESSO	1.001 (0.777)	0.427	0.997 (0.381)	0.438
Lipoprotein (a)	IVW	0.997 (0.197)*	0.562	1.000 (0.928)*	0.209
	MR-Egger	0.992 (0.188)*	0.557	0.996 (0.696)*	0.180
	Weighted median	0.996 (0.204)	MR-Egger	0.993 (0.098)	MR-Egger
	Weighted mode	0.996 (0.269)	Intercept:	0.992 (0.228)	Intercept:
	MR-PRESSO	0.997 (0.193)	0.359	1.000 (0.928)	0.701
Apolipoprotein A	IVW	0.993 (0.007†)	<0.001	0.998 (0.530)	<0.001
	MR-Egger	1.010 (0.176)	<0.001	0.996 (0.658)	<0.001
	Weighted median	0.998 (0.485)	MR-Egger	0.992 (0.034)	MR-Egger
	Weighted mode	1.000 (0.991)	Intercept:	0.991 (0.043)	Intercept:
	MR-PRESSO	0.993 (0.009)	0.123	0.998 (0.533)	0.812
Apolipoprotein B	IVW	0.995 (0.052)	<0.001	0.993 (0.033)	<0.001
	MR-Egger	1.002 (0.756)	<0.001	0.995 (0.681)	<0.001
	Weighted median	0.998 (0.481)	MR-Egger	0.992 (0.048)	MR-Egger
	Weighted mode	0.998 (0.586)	Intercept:	0.996 (0.612)	Intercept:
	MR-PRESSO	0.995 (0.056)	0.264	0.993 (0.038)	0.808

*the fixed-effect model was used.
†Deemed as statistically significant.
IVW, represents inverse-variance weighted method.

UC who underwent ileal-anal anastomosis exhibited notably reduced serum TG levels.[34] Furthermore, a comprehensive analysis of 9 706 026 subjects revealed that lower TC and HDL-C levels were linked to an increased incidence of CD, while lower LDL-C and TG levels were similarly associated.[35] High HDL-C levels are positively correlated with complete mucosal healing.[36] Although these cross-sectional studies suggest a potential link between IBD and serum lipid profiles, they do not imply causation.

Current MR research on IBD and serum lipids is scarce,[14–16] with results suggesting a causal relationship between elevated LDL-C and HDL-C levels and a reduced risk of IBD (including UC and CD),[14 15] while findings on the causal relationship between TC and UC are contradictory.[15 16] The results of these three MR analyses are inconsistent and even contradictory, and they have focused on traditional lipid indices without considering new indices such as Lp(a). Therefore, this study was conducted to determine the causal relationship between serum lipids and IBD in a more comprehensive cohort.

This study found no causal relationships between TG, TC, HDL-C, LDL-C, Apo A, Apo B, or Lp(a) and IBD. This observation can be explained as follows. First, improving living standards has led to significant shifts in dietary habits, particularly the increased prevalence of high-fat diets. Such changes might

contribute to an elevated incidence of dyslipidaemia; however, one recent study suggested that the contribution of lipid overload to the incidence of IBD is still not fully defined.[37] One study suggested that dyslipidaemia may accelerate inflammatory responses.[3] In an animal experiment, C57BL/6 mice fed a high-fat diet for 12 weeks exhibited significantly increased plasma TG concentrations, demonstrating that trinitrobenzene sulfonic acid-induced colitis occurred in an experimental mouse model.[38] However, these studies showed that, on the basis of the original disease, dyslipidaemia may aggravate inflammation but could not indicate that dyslipidaemia is the cause of intestinal inflammation onset.

Second, one study suggested that a dysregulated immune response in IBD induces inappropriate activation of intestinal mucosal inflammation and the release of numerous inflammatory cytokines, such as tumour necrosis factor-α, interferon-γ and interleukin-6,[39] and chronic inflammatory damage can alter lipid metabolism, leading to dyslipidaemia in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[40–42]; however, no relevant studies have been conducted on IBD, so the evidence of chronic inflammation causing dyslipidaemia in SLE and RA cannot be extrapolated directly to IBD. In addition, resection can also lead to changes in the lipid profile in patients with IBD due to therapeutic drugs, malnutrition, intestinal dysfunction or malabsorption.[43 44] Therefore, the coexistence of dyslipidaemia and IBD may be the result of multiple factors, and whether there is a causal relationship between IBD and dyslipidaemia and the underlying mechanisms deserve further research.

This study, however, has three limitations. First, the study population predominantly consisted of individuals of European ancestry, potentially curtailing the applicability of the results to broader populations. Second, the sample sizes of the considered GWAS studies were limited. Consequently, these findings should be further validated through prospective studies encompassing larger and more diverse populations. Finally, potential horizontal pleiotropy is a major issue in MR studies, invalidating SNPs as instruments and thus resulting in false findings. Nevertheless, we performed a series of sensitivity analyses to eliminate or control for horizontal pleiotropy; thus, this study should suffer marginally from this issue.

CONCLUSION

Using the latest and largest GWAS summary data, this MR study revealed that none of the lipid types was a potential risk factor for the onset of IBD. Furthermore, this null causal relationship between individual lipid types and IBD was replicated in an independent validation, indicating that the results of our MR analyses are very robust. Since a non-linear causal association between these lipid indices and IBD cannot be eliminated by the current MR analyses, further investigation is necessary.

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