Type 1 diabetes mellitus, hyperlipidemia, and inflammatory bowel disease: a Mendelian randomization study

Graphical abstract

Highlights

• In this study, the Mendelian randomization approach is employed to mitigate the impact of confounding variables, thereby enhancing the robustness and accuracy of causal inferences, a significant improvement over traditional observational studies.

• There is no direct causal link between Type 1 diabetes mellitus, hyperlipidemia, and inflammatory bowel disease (IBD), indicating that these conditions arise independently rather than as a direct consequence of one another.

• This study holds significant implications for the safety assessment of the small molecule drug tofacitinib, offering valuable insights that could inform its clinical use and risk evaluation.

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In brief

Type 1 diabetes mellitus, hyperlipidemia, and inflammatory bowel disease have no direct causal relationship.
Type 1 diabetes mellitus, hyperlipidemia, and inflammatory bowel disease: a Mendelian randomization study

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ABSTRACT

Previous epidemiologic studies have shown a close association between type 1 diabetes mellitus (T1DM), hyperlipidemia, and inflammatory bowel disease (IBD), but the causal relationship has not been established. In the current study the causal relationships between T1DM and hyperlipidemia with IBD were assessed using Mendelian randomization (MR) analysis. A two-sample MR study was conducted utilizing accessible genome-wide association study data from public sources with the selection of suitable instrumental variables adhering to the principles of MR analysis. The primary technique utilized was the inverse variance weighted method, complemented by additional methods, such as MR-Egger regression, weighted median, simple mode, weighted mode, and the MR pleiotropy residual sum and outlier approach. Genetically determined T1DM had no causal relationship with IBD or IBD subtypes based on MR analysis. These findings were consistent across all supplementary methods used. In addition, genetically determined hyperlipidemia had no causal relationship with IBD or IBD subtypes, even after increasing the number of instrumental variables used. Our study supports the notion that there is no causal relationship between T1DM and IBD, as well as hyperlipidemia and IBD, which contradicts most observational studies.

Keywords: Type 1 diabetes mellitus, hyperlipidemia, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, Mendelian randomization studies

1. INTRODUCTION

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn’s disease (CD), results from a complex interplay between genetic and environmental factors that leads to persistent inflammation in the gastrointestinal tract. The epidemiology of IBD is characterized by an increasing prevalence in urban areas and younger populations, which underscores the growing importance of IBD as a global health issue. The etiology of IBD is complex in which genetic predispositions and environmental factors, such as diet, lifestyle, and the microbiome, have crucial roles. Currently, the primary treatment for IBD is pharmacotherapy [1]. Treatment usually begins with medications that have fewer side effects; and if these are ineffective, other medications may be prescribed, including aminosalicylates, corticosteroids, antibiotics, immunosuppressants, and biologics. Surgical intervention may be necessary if medication fails to provide relief. Surgery is typically reserved for patients with poor disease control, such as intestinal obstruction, perforation, or severe complications. Managing IBD also involves lifestyle and dietary modifications. Patients are advised to avoid foods and habits that exacerbate symptoms, like high-fat foods, tobacco, and alcohol [2]. Enhancing stress management and psychological support are also crucial aspects of care. Regular medical evaluations and monitoring are
essential for the long-term management of IBD patients and include routine blood tests, imaging studies, and endoscopic examinations to monitor disease activity and treatment effectiveness.

Type 1 diabetes mellitus (T1DM), an immune-mediated metabolic disorder [3], has been implicated in prior Mendelian randomization (MR) studies that suggest a causal association with IBD [4]. Nevertheless, corollary studies involving the influence of T1DM on the development of IBD are warranted. Burisch et al. [5] reported a higher prevalence of immune-mediated inflammatory diseases (IMIDs) before compared to after the onset of IBD. Given that T1DM is an IMID, there is a significant interest in determining whether T1DM contributes to the initiation of IBD episodes. Clarifying the inter-relationship between T1DM and IBD is essential for developing therapeutic strategies and prognosticating outcomes of individuals diagnosed with T1DM.

In the clinical setting hyperlipidemia is characterized by elevated levels of low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), as well as a reduction in high-density lipoprotein-cholesterol (HDL-C). Among individuals with IBD, there is a tendency for elevated LDL-C and TG levels and decreased HDL-C levels [6]. Koutroumpakis et al. [7] showed that sustained dyslipidemic profiles in IBD patients correlate with the active phase of the disease. Moreover, a reduction in HDL-C levels may elevate the risk of negative treatment outcomes of individuals diagnosed with T1DM.

MR studies utilize genetic variants identified through genome-wide association studies (GWASs) as instrumental variables (IVs) of exposure to investigate the causal relationship between exposure and outcomes [9]. These genetic variants are randomly allocated at conception. The selection of IVs for exposure factors must satisfy three assumptions: 1) The IV is strongly associated with the exposure. 2) The IV is not associated with any confounders. 3) The IV influences the outcome exclusively through the exposure [10]. Thus, MR studies could, to some extent, overcome the limitations of traditional observational research [11]. In the current study we utilized a two-sample MR approach to determine the causal relationships between T1DM, hyperlipidemia, and IBD, including UC and CD.

2. METHODS

Our investigation utilized a two-sample MR approach to assess the causal relationships between T1DM, hyperlipidemia, and IBD. A schematic overview of the study design and data sources is delineated in Supplementary Figure 1. All data utilized are publicly accessible GWAS summary statistics, which obviates the need for additional ethical approval or informed consent. We systematically queried the GWAS summary statistics to extract principal single nucleotide polymorphisms (SNPs) associated with T1DM, hyperlipidemia, or IBD as genetic IVs.

2.1 GWAS summary data of IBD, T1DM, and hyperlipidemia

To derive more robust causal inferences, we sourced eligible summary data for each trait from the largest publicly available GWAS repositories, as shown in Supplementary Figure 1. Because all data utilized were previously published in public databases, no additional ethical clearance was necessitated. Specifically, summary statistics for T1DM (cases: 9266; controls: 15,574) [12], hyperlipidemia (cases: 3310; controls: 6401) [13], IBD (cases: 4101; controls: 480,497) [14], UC (cases: 12,366; controls: 33,609) [15], and CD (cases: 12,194; controls: 28,072) [15] were extracted from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/datasets/). Diagnostic criteria and inclusion methodologies were as specified in the original publications. The detailed data sources are provided in Supplementary Table 12. Furthermore, the study exclusively included participants of European descent, ensuring no sample overlap between exposure and outcome traits, which helped reduce bias from confounding variables.

2.2 Selection of genetic IVs

Utilizing the GWAS summary data mentioned earlier, we followed a strict protocol to select suitable SNPs as IVs. Initially, we identified SNPs that were strongly linked to the exposure, achieving genome-wide significance at a p-value threshold < 5 × 10−8. To avoid bias due to linkage disequilibrium (LD), a pruning process was implemented using an LD threshold of R2 = 0.001 across a 10,000 kb window. Third, genetic variants linked with confounding factors were filtered out using the Phenoscanner database (http://www.phenoscanner.medschl.cam.ac.uk/). Moreover, to adhere more closely to the first fundamental assumption, the F-statistics for each SNP were calculated, excluding those SNPs with an F-statistic < 10 as weak instruments [16]. Finally, harmonization of exposure and outcome datasets was performed to eliminate palindromic and ambiguous SNPs with inconsistent allele definitions, thereby maintaining consistency in the allele effects on the exposure and outcome. Using these meticulous steps, the selected SNPs were rigorously vetted and utilized as the final IVs for the ensuing two-sample MR analysis.

2.3 Statistical analysis

Within our study, we utilized three methodologies (inverse variance weighted [IVW], MR-Egger, and weighted median approaches) to evaluate the causal relationship and effect estimates between exposure and outcome. The IVW method, often the most extensively applied in MR analyses, was implemented using a random-effects
model [17]. Fundamentally, the IVW approach synthesizes effect estimates from multiple studies in a meta-analysis to obtain an aggregated effect estimate, standardizing the effect of each study by the study variance, then computing a weighted average [18]. The weights were derived from the reciprocal of each study variance, assigning greater weight to studies with smaller variance, thus providing a more precise overall effect estimate.

To provide a stronger estimate of the causal effect, various supplementary methods were implemented, each based on different assumptions. These included MR-Egger regression, weighted median, simple mode, weighted mode, and the MR pleiotropy residual sum and outlier (MR-PRESSO) methods. MR-Egger regression allows for MR analysis using summarized genetic data, which relaxes the exclusive assumption when the instrument strength independent of direct effect (InSIDE) assumption is met, in which the SNP effect on the exposure is independent of the pleiotropic effects on the outcome, yielding consistent causal effect estimates irrespective of IV validity [19, 20]. The MR-Egger intercept indicates pleiotropy with a P-value < 0.05, suggesting the presence of horizontal pleiotropy. MR-Egger has relatively lower statistical power and we resorted to the IVW method unless there was evidence of systemic differences between the IVW and MR-Egger. The weighted median provides an accurate estimate even when up to 50% of the instruments are invalid [21]. The weighted mode approach calculates the causal effect of different genetic variants on the trait by weighting the genetic variants, then taking the mode of these weighted effects as the final causal estimate. MR-PRESSO is utilized to test for pleiotropy and outliers, thus ensuring the stability of our results with the number of distributions in the MR-PRESSO analysis set to 10,000 [22]. Heterogeneity was tested using Cochrane’s Q-statistic, with a P-value < 0.05 indicating heterogeneity. Therefore, a random-effects model was used. If heterogeneity was not present, a fixed-effects model was used [23]. Additionally, "leave-one-out" sensitivity analysis through IVW was performed post-sequential SNP exclusion to assess the potential impact of specific variants on the estimates.

All analyses were executed using the R statistical software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) and the TwoSampleMR package [24] (version 0.5.7).

3. RESULTS

3.1 Causal effects of T1DM on IBD

Through LD clumping and confounder exclusion via Phenoscanner, we eliminated five SNPs associated with confounding factors (rs6679677, rs211485, rs9273363, rs194749, and rs34536443). We discarded rs34954 due to incompatible alleles. We also excluded rs1131017 for being palindromic with intermediate allele frequencies. Ultimately, we ascertained 37 SNPs as IVs for T1DM, ensuring compliance with the three core assumptions of MR, with all F-statistics > 10 to eliminate weak instruments. The attributes of these 37 SNPs are detailed in Supplementary Table 1.

The MR estimates, which were derived from various analytical methods to assess the causal impact of T1D on IBD, are consolidated in Table 1. The findings indicate no causal link between T1D and IBD, with the IVW method yielding an odds ratio (OR) of 0.999 (95% confidence interval [CI]: 0.999-1.000; P = 0.357). Cochran’s Q test showed significant heterogeneity (P < 0.001), so we applied the IVW method with the random-effects model. Horizontal pleiotropy was detected using the MR-PRESSO method, and upon the exclusion of outlier SNPs (rs17125653, rs185774696, and rs609461), the pleiotropic distortion was rectified, with subsequent MR analysis showing no significant change in the IVW results (OR: 1.000, 95% CI: 0.999-1.000; P = 0.233), and heterogeneity was resolved. MR-Egger regression analysis did not reveal any pleiotropy (intercept = 9.132203e-05; P = 0.466). The outcomes of the sensitivity analysis are shown in Table 2, with the scatter and funnel plots illustrated in Figure 1. The results of the leave-one-out sensitivity and individual SNP risk analysis are presented in Supplementary Figure 2.

3.2 Causal effects of T1DM on CD

Palindromic SNPs with intermediate allele frequencies (rs10865468, rs17125653, rs2071647, rs34296259, rs506770, rs55996894, rs689, and rs9296062) were excluded from the analysis. Grounded in the triad of MR assumptions, we finalized 31 SNPs as instrumental variables for T1DM. Detailed information regarding these 31 SNPs is available in Supplementary Table 2. MR estimates, which were obtained from disparate methodologies to ascertain the causal relationship of T1D with CD, are shown in Table 1. The data demonstrates no causal association between T1D and CD, with the IVW method indicating an OR of 0.999 (95% CI: 0.993-1.072; P = 0.807). Due to significant heterogeneity, as indicated by Cochran’s Q test (P < 0.001), we utilized the IVW method combined with a random-effects model. After horizontal pleiotropy detection via MR-PRESSO, outlier SNPs (rs10774624, rs12722495, rs9719600, and rs6909461) were removed, negating the pleiotropic outliers and yielding a subsequent MR analysis IVW result that showed no significant deviation from the initial result (OR: 1.029, 95% CI: 0.981-1.080; P = 0.807) with heterogeneity eradicated. MR-Egger regression analysis revealed no pleiotropy (intercept = 0.022; P = 0.442). The findings of the sensitivity analysis are shown in Table 2. Scatter and funnel plots are displayed in Figure 1. The outcomes of the leave-one-out sensitivity and individual SNP risk assessments are shown in Supplementary Figure 2.

3.3 Causal effects of T1DM on UC

Additionally, no causal relationship was identified between T1D and UC. Palindromic SNPs with intermediate allele frequencies were ascertained from various Supplementary Table 3. MR estimates, which were obtained from disparate methodologies to ascertain the causal relationship of T1D with UC, are shown in Table 1. The data demonstrates no causal association between T1D and UC, with the IVW method indicating an OR of 0.999 (95% CI: 0.993-1.072; P = 0.807). Due to significant heterogeneity, as indicated by Cochran’s Q test (P < 0.001), we utilized the IVW method combined with a random-effects model. After horizontal pleiotropy detection via MR-PRESSO, outlier SNPs (rs10774624, rs12722495, rs9719600, and rs6909461) were removed, negating the pleiotropic outliers and yielding a subsequent MR analysis IVW result that showed no significant deviation from the initial result (OR: 1.029, 95% CI: 0.981-1.080; P = 0.807) with heterogeneity eradicated. MR-Egger regression analysis revealed no pleiotropy (intercept = 0.022; P = 0.442). The findings of the sensitivity analysis are shown in Table 2. Scatter and funnel plots are displayed in Figure 1. The outcomes of the leave-one-out sensitivity and individual SNP risk assessments are shown in Supplementary Figure 2.
allele frequencies (rs10865468, rs17125653, rs2071647, rs34296259, rs506770, rs55996894, rs689, and rs9296062) were excluded from consideration. A total of 31 SNPs were meticulously selected as IVs for T1D, with details shown in Supplementary Table 3.

The MR estimates for the causal impact of T1DM on UC are shown in Table 1, with the IVW method yielding an OR of 1.033 (95% CI: 0.975-1.094; P = 0.2585696). Given the significant heterogeneity indicated by Cochran's Q test (P < 0.001), we applied the IVW method under a random-effects model. After detection of horizontal pleiotropy using the MR-PRESSO method (P < 0.001) and subsequent exclusion of outlier SNPs (rs10774624 and rs2144013), the aberrations were nullified, leading to a consistent MR IVW analysis (OR: 1.024, 95% CI: 0.982-1.068; P = 0.256) with the previous heterogeneity resolved. MR-Egger regression analysis detected no evidence of pleiotropy (intercept = −0.016; P = 0.438). The results of the sensitivity analysis are shown in Table 2. Scatter and funnel plots are depicted in Figure 1. The outcomes of the leave-one-out sensitivity and individual SNP risk evaluations are detailed in Supplementary Figure 2.

3.4 Causal effects of hyperlipidemia on IBD
We identified five SNPs as IVs for hyperlipidemia, with the specifics shown in Supplementary Table 4. The MR estimates for the putative causal influence of hyperlipidemia on Inflammatory Bowel Disease (IBD) are catalogued in Table 3. No causal association was discerned between hyperlipidemia and IBD, with the IVW method indicating an OR for IBD of 0.999 (95% CI: 0.998-1.000; P = 0.263). The MR-PRESSO methodology did not detect any evidence of horizontal pleiotropy. MR-Egger regression analysis also detected no indication of pleiotropy (intercept = −0.0006; P = 0.162). Heterogeneity was not observed in the analysis of hyperlipidemia with IBD as per Cochran's Q statistics (P = 0.089). Pertinent sensitivity checks are included in Table 4. Scatter and funnel plots are depicted in Figure 2. The outcomes of the leave-one-out sensitivity and individual SNP risk assessments are shown in Supplementary Figure 3.

3.5 Causal effects of hyperlipidemia on CD
Upon exclusion of SNP rs1501908 due to its palindromic nature with intermediate allele frequencies, four SNPs remained as IVs for hyperlipidemia. The details are specified in Supplementary Table 5. The MR estimates assessing the potential causal nexus between hyperlipidemia and CD are compiled in Table 3. No evidence was found to suggest a direct causal relationship between hyperlipidemia and CD, with the IVW method yielding an OR of 1.03 (95% CI: 0.924-1.161; P = 0.540). The MR-PRESSO analysis detected no horizontal pleiotropy. Directional pleiotropy was also not observed in the MR-Egger regression (intercept = 0.001; P = 0.984). Heterogeneity was detected in the analysis between hyperlipidemia and CD via Cochran's Q statistics (P = 0.026). Nevertheless, the
random-effects model sanctioned the reliability of the IVW method. Related sensitivity analyses are included in Table 4. Scatter and funnel plots are shown in Figure 2 and the results of leave-one-out sensitivity and individual SNP risk assessments are presented in Supplementary Figure 3.

3.6 Causal effects of hyperlipidemia on UC

Following the removal of SNP rs1501908 due to its palindromic sequence with intermediate allele frequencies, four SNPs remained as IVs for hyperlipidemia, with the details shown in Supplementary Table 6. The MR estimates derived from assorted methodologies evaluating the causal impact of hyperlipidemia on UC are shown in Table 3. All of the methods use agreed regarding the absence of a causal relationship between hyperlipidemia and IBD, with the IVW method indicating an OR of 0.992 (95% CI: 0.930-1.058). No horizontal pleiotropy was detected using the MR-PRESSO approach (P = 0.851). Likewise, the MR-Egger regression analysis did not unveil any horizontal pleiotropy (intercept = –0.016; P = 0.649). Cochran’s Q statistics did not reveal any heterogeneity in the analysis correlating hyperlipidemia with UC (P = 0.826). Correlated sensitivity analyses are available in Table 4. Scatter plots and funnel diagrams are depicted in Figure 2, and the outcomes of the leave-one-out sensitivity and individual SNP risk analyses are shown in Supplementary Figure 3.

4. DISCUSSION

In the current study our two-sample MR analysis did not directly demonstrate a causal association between T1DM, hyperlipidemia, and IBD (including UC and CD). Therefore, we cannot prove that T1DM and hyperlipidemia are risk factors for IBD.

Recent reports suggest that the likelihood of developing another IMID increases when a patient already has an IMID. Treating patients afflicted with IBD and another IMID remains a challenge for clinicians, necessitating a multidisciplinary management approach. Moreover, IBD patients with multiple co-existing IMIDs often experience more severe disease courses, resulting in a worse quality of life. Therefore, understanding the relationships between these diseases is crucial for prevention and treatment strategies. In the current study we collected data on 4377 IBD patients (CD: 3879 [27%], UC: 9212 [64%], and unclassified IBD: 1286 [9%]), showing that additional IMIDs were more frequently diagnosed before than after the onset of IBD (CD: 2600 cases [18.1%] and UC: 870 cases [6.1%]) [5]. However, an observational study cannot establish a causal relationship. Then, we transferred our focus to T1DM, one of the most prevalent IMIDs [25] using MR. After adjusting for confounding factors in our study we showed that T1DM did not directly contribute to IBD (P > 0.05). Additionally, another observational study reported an increased prevalence of IBD in patients with T1DM,
Figure 1 | (A) The scatter plot of the causal effect of T1DM on IBD and its subtypes risk. Analyses were conducted using the inverse-variance weighted, MR-Egger, Weighted Median, Simple Mode, and Weighted Mode methods. The slope of each line corresponding to the causal estimates for each method. (B) The funnel plot of the causal effect of T1DM on IBD and its subtypes risk. Individual SNP was delineated in the background. T1DM, Type 1 diabetes mellitus; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; SNP, single nucleotide polymorphism.
which may be attributed to adverse factors, such as inflammation, malabsorption, and severe hyperglycemia, rather than being directly caused by T1DM [26]. In the future we can further investigate the association of these adverse factors with IBD. Patients with T1DM, especially those patients with diabetic kidney disease (DKD), often experience gastrointestinal dysfunction, which may increase susceptibility to IBD [27]. IBD and DKD share several common genes, such as MMP2, HGF, FGF2, IL-18, IL-13, and CCL5, which are key risk genes for the co-occurrence of DKD and IBD. Investigating the relationships between these genes could provide a clearer understanding of the direct link between T1DM and IBD [28]. Additionally, this research could aid in the development of new drugs by identifying potential therapeutic targets. Although our analysis showed that T1DM is not associated with IBD, the treatment and care of T1DM, especially in patients with severe complications, should include close monitoring of gastrointestinal symptoms caused by T1DM and prompt screening for IBD when symptoms appear [29].

The diagnosis of hyperlipidemia is commonly made in the clinical setting when the following laboratory values are observed: TC ≥ 6.2 mmol/L; LDL-C ≥ 4.1 mmol/L; TG ≥ 2.3 mmol/L; and HDL-C < 1.0 mmol/L. A study involving data from 497 UC patients with detailed lipid profiles

### Table 3 | MR analysis of the causality of hyperlipidemia on IBD.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Number of SNPs</th>
<th>F statistic</th>
<th>Methods</th>
<th>OR (95% CI)</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>IBD</td>
<td>5</td>
<td>502.655</td>
<td>MR-Egger</td>
<td>1.001 (0.999-1.003)</td>
<td>0.001</td>
<td>0.311</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weighted median</td>
<td>0.999 (0.998-1.000)</td>
<td>0.0004</td>
<td>0.515</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IVW</td>
<td>0.999 (0.998-1.000)</td>
<td>0.0005</td>
<td>0.263</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simple mode</td>
<td>0.999 (0.998-1.000)</td>
<td>0.0005</td>
<td>0.431</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weighted mode</td>
<td>0.999 (0.998-0.998)</td>
<td>0.0004</td>
<td>0.657</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>CD</td>
<td>4</td>
<td>502.655</td>
<td>MR-Egger</td>
<td>1.031 (0.691-1.540)</td>
<td>0.204</td>
<td>0.892</td>
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<td></td>
<td></td>
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<td></td>
<td>Weighted median</td>
<td>1.022 (0.943-1.109)</td>
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<td>0.584</td>
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<td></td>
<td>IVW</td>
<td>1.036 (0.924-1.1610)</td>
<td>0.058</td>
<td>0.540</td>
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<td></td>
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<td></td>
<td></td>
<td>Simple mode</td>
<td>1.010 (0.909-1.122)</td>
<td>0.053</td>
<td>0.863</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Weighted mode</td>
<td>1.014 (0.925-1.112)</td>
<td>0.046</td>
<td>0.781</td>
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<tr>
<td>Hyperlipidemia</td>
<td>UC</td>
<td>4</td>
<td>502.655</td>
<td>MR-Egger</td>
<td>1.040 (0.863-1.252)</td>
<td>0.094</td>
<td>0.718</td>
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<td>Weighted median</td>
<td>0.999 (0.924-1.081)</td>
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<td>IVW</td>
<td>0.992 (0.930-1.058)</td>
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<td>Simple mode</td>
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<td>0.961</td>
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<td></td>
<td>Weighted mode</td>
<td>1.004 (0.920-1.096)</td>
<td>0.044</td>
<td>0.925</td>
</tr>
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</table>

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; SE, standard error.

### Table 4 | Sensitivity analyses of MR.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>MR-PRESSO global outlier test</th>
<th>MR-Egger regression</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>Outlier</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>IBD</td>
<td>0.1511</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>0.0786</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>UC</td>
<td></td>
<td>0.8518</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*MR analysis using the IVW method after removing outliers identified by the MR-PRESSO method.

#Heterogeneity test after removing outliers.

IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; T1DM, type 1 diabetes mellitus; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval; SE, standard error.
Figure 2 | (A) The scatter plot of the causal effect of Hyperlipidemia on IBD and its subtypes risk. Analyses were conducted using the inverse-variance weighted, MR-Egger, Weighted Median, Simple Mode, and Weighted Mode methods. The slope of each line corresponding to the causal estimates for each method. (B) The funnel plot of the causal effect of Hyperlipidemia on IBD and its subtypes risk. Individual SNP was delineated in the background. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; SNP, single nucleotide polymorphism.
reported that 278 patients (55.9%) were diagnosed with dyslipidemia and 72 patients (14.5%) presented with severe complications [30]. In another MR study, there was no direct causal association found between LDL-C or TG levels and IBD; only the HDL-C level demonstrated a negative causal relationship with IBD [31]. The aforementioned studies focused solely on the relationship between lipid indices related to hyperlipidemia and IBD, without investigating a direct link between hyperlipidemia and IBD.

We conducted a MR study with hyperlipidemia as the exposure and IBD as the outcome, selecting 5 SNPs as IVs based on a genome-wide significance threshold p < 5x10^{-8}. There was no evidence suggesting a causal relationship between hyperlipidemia and IBD. This finding may be related to the limited number of SNPs. To acquire more IVs, we relaxed the genome-wide significance threshold to a p < 1x10^{-6}. We identified independent SNPs through LD clustering (R^2 > 0.001), retaining those SNPs with the smallest p values. Genetic variants associated with confounding factors were excluded using the Phenoscaner database.

After broadening the selection criteria in the MR analysis of hyperlipidemia and IBD, a total of 10 SNPs were extracted as IVs for hyperlipidemia (Supplementary Table 9). These instruments had F-statistics > 10, indicating strong instruments. The results of the IVW analysis were as follows: OR, 0.999; 95% CI, 0.999-1.000; and P = 0.25. For the analysis involving hyperlipidemia and CD, after removing SNPs that were palindromic with intermediate allele frequencies, such as rs1501908, we identified 8 SNPs as the exposure instruments (Supplementary Table 10). The IVW analysis indicated no causal relationship (OR: 1.030, 95% CI: 0.956-1.109; P = 0.435). In the hyperlipidemia and UC analysis after widening the selection criteria and removing SNPs, such as rs1501908, for being palindromic with intermediate allele frequencies, we ultimately selected 8 SNPs as IVs (Supplementary Table 11). The IVW results, which was similar to our previous analysis results, are as follows: OR, 0.989; 95% CI, 0.934-1.047; and P = 0.704. All of the above studies were tested using methods, including MR-PRESSO, MR-Egger, and Cochran’s Q statistics. The MR estimates from different methods assessing the causal relationship between hyperlipidemia with IBD and IBD subtypes are shown in Supplementary Table 7. Heterogeneity tests are presented in Supplementary Table 8. Scatter and funnel plots are shown in Supplementary Figure 3. The results of leave-one-out sensitivity and single SNP risk analysis are shown in Supplementary Figure 4.

Hyperlipidemia is primarily characterized by elevated levels of TC, LDL-C, and TG, as well as low levels of HDL-C. However, as a marker of dyslipidemia, past research indicates a negative correlation between HDL-C and IBD that may be due to the anti-inflammatory properties of HDL. HDL-C is only one of the hyperlipidemia markers and does not fully represent hyperlipidemia [32]. Additionally, our existing data volume was relatively small, affecting the robustness of this study. The causal relationship between hyperlipidemia and IBD requires further investigation. In the future, we plan to analyze larger datasets of hyperlipidemia GWAS data, as this may yield new insight into the association between T1DM, hyperlipidemia, and IBD.

In the small molecule drug (tofacitinib) UC trial, the concentrations of LDL-C and HDL-C increased after 8 weeks of treatment, and the TC-to-HDL-C ratio stabilized and normalized after discontinuation [33]. Corticosteroid medications are frequently used in the pharmacologic treatment of IBD, which leads to increased blood lipid and glucose levels. Our findings point out that T1DM and hyperlipidemia are not directly related to IBD, so in evaluating the efficacy and safety of such drugs, it is not necessary to consider the changes in efficacy caused by the increase in blood glucose and lipids, but only to evaluate the risk of hyperglycemia and hyperlipidemia.

The data we chose were derived from the most recent GWAS datasets, which ensured the relevance and timeliness. However, it is important to note that our data exclusively originated from European populations, which might restrict the universality of our findings across different ethnic and geographic groups. The inherent limitations of MR analysis, which are influenced by the size of the GWAS dataset and the homogeneity of the sample population, indicate that our conclusions might not be fully applicable to or account for situations beyond the European context.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES
