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# Crohn disease but not ulcerative colitis increases the risk of acute pancreatitis

## A 2-sample Mendelian randomization study

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**Abstract**

Accumulating evidence has indicated an increased risk of acute pancreatitis in individuals with inflammatory bowel disease (IBD); however, the establishment of a clear and direct causal connection between IBD and acute pancreatitis remains uncertain. Utilizing genetic data from publicly accessible genome-wide association studies (GWAS), we conducted a 2-sample MR analysis to identify the associations between IBD, ulcerative colitis (UC), Crohn disease (CD), and acute pancreatitis risk. Rigorous quality control steps ensured the selection of eligible single nucleotide polymorphisms (SNPs) with strong associations to IBD. The primary estimation used the inverse-variance weighted method. We also assessed heterogeneity, potential pleiotropy, and conducted sensitivity analyses. The direction of causality was confirmed using the Steiger test. The MR analysis showed that IBD increased the risk of acute pancreatitis (IVW: OR = 1.032, 95% CI: 1.006–1.06, $P$ = .015). Among the subgroup of IBD, CD (IVW: OR = 1.034, 95% CI: 1.008–1.06, $P$ = .007) indicates a significant increase in the risk of acute pancreatitis compared to UC (IVW: OR = 1.02, 95% CI: 0.99–1.051, $P$ = .189). The MR analysis assessing the association between CD and acute pancreatitis showed no evidence of heterogeneity or horizontal pleiotropy. Likewise, the leave-one-out (LOO) method indicated no significant influence of any individual SNP on the overall findings. In addition, the Steiger direction test revealed that CD was the cause for increased risk of acute pancreatitis, but not vice versa. In summary, this research pioneers in proposing a causal relationship between CD and acute pancreatitis among the European population.

**Abbreviations:** CD = Crohn disease, GWAS = genome-wide association study, IBD = inflammatory bowel disease, IIBDGC = International Inflammatory Bowel Disease Genetics Consortium, IV = instrumental variable, IVW = inverse-variance weighted, LOO = leave-one-out, MR = Mendelian randomization, OR = odds ratio, SNP = single nucleotide polymorphism, UC = ulcerative colitis, UKIBDGC = UK Inflammatory Bowel Disease Genetics Consortium, WM = weighted median.

**Keywords:** acute pancreatitis, Crohn disease, mendelian randomization, ulcerative colitis

## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that mainly comprises Crohn disease (CD) and Ulcerative Colitis (UC). In the United States and Western Europe, the annual incidence of CD ranges from 8 to 14 cases per 100,000 persons, while for UC, it ranges from 6 to 15 cases per 100,000 persons.[1,2] IBD is influenced by multiple factors, including genetic predisposition, environmental triggers, immunological responses, and the composition of gut microbiota. Moreover, IBD is a systemic disease associated with notable extraintestinal manifestations, affecting up to 40% of individuals with IBD.[3] Common extraintestinal manifestations in individuals with IBD encompass skin disorders such as erythema nodosum and pyoderma gangrenosum,[4] ocular involvement like uveitis and episcleritis,[5] as well as musculoskeletal issues including ankylosing spondylitis and arthritis.[6] Indeed, the incidence of pancreatic disorder also appears to be higher in patients with IBD compared to non-IBD individuals, and acute pancreatitis is the most frequent pancreatic manifestation in IBD.[7]

Recent studies indicate an elevated risk of acute pancreatitis among IBD patients compared to the matched controls.[8,9] The relationship between IBD and acute pancreatitis was

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*All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.*

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influenced by several factors. For instance, IBD, especially CD, has been found to correlate with an increased risk of gallstones.[10] Medications commonly used in treating IBD, such as azathioprine or mesalamine, have been implicated in the onset of acute pancreatitis.[11] Indeed, IBD can lead to nutritional deficiencies that may have adverse effects on the pancreas.[12] However, a case series revealed no significant rise in the occurrence of pancreatitis among individuals with IBD when compared to the general population.[13] Hence, the existence of a causal relationship between IBD and acute pancreatitis remains uncertain.

While randomized trials are in principle the best way of determining the causal status of a particular exposure, they have some limitations such as expensive and time consuming. Two-sample Mendelian Randomization (MR) is an advanced epidemiological method that aims to establish a causal relationship between an exposure and an outcome by leveraging genetic variants, which is analogous to a randomized controlled trial. One of the key advantages of MR is its ability to mitigate common pitfalls associated with observational studies, including confounding factors and the potential for reverse causation. This enhances the robustness and reliability of causal inference between the exposure and outcome variables. To our knowledge, a definitive causal association between IBD and acute pancreatitis has yet to be established by MR study. In the present study, a 2-sample MR was conducted to assess the causal effects of IBD on acute pancreatitis using available large-scale genome-wide association study (GWAS) data.

## 2. Methods

The current study was carried out in compliance with the guidelines set forth by the "STROBE-MR" statement.[14]

### 2.1. Data sources pertinent to acute pancreatitis, CD, and UC

Data relevant to acute pancreatitis were sourced from an updated study, which includes a GWAS meta-analysis of the Estonian Biobank, FinnGen, and UK Biobank cohorts. Scalable and accurate implementation of generalized mixed models (SAIGE) method was developed to control case-control imbalance, sample relatedness, and population structure. SAIGE was used to obtain GWAS summary statistics of the UK Biobank, the Estonian Biobank, and the FinnGen cohorts as described.[15] The criteria for acute pancreatitis were based on the International Classification of Diseases (ICD)-10 entries (K85). The GWAS data was downloaded from the European Bioinformatics Institute (EBI) database (https://www.ebi.ac.uk/gwas/studies/GCST90255375), which includes 10,630 European ancestry cases and 844,679 European ancestry controls.

The data for IBD, which includes both UC and CD, were obtained from the combined meta-analysis of the UK Inflammatory Bowel Disease Genetics Consortium (UKIBDGC) and the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). The UKIBDGC consisted of a UK low-coverage whole genome sequencing IBD study and a UK HumanCoreExome genotyped IBD study, comprising 16,272 cases of IBD and 14,394 controls. The IIBDGC consisted of the Belgium, France, USA, Canada, Italy, Scotland, Germany, Sweden, Norway, and UK cohorts, comprising 12,882 cases of IBD and 21,770 controls. After removing non-European samples identified through principal component analysis with HapMap3 populations and eliminating overlapping samples, the combined meta-analysis comprised 25,042 cases of IBD and 34,915 controls, 12,366 cases of UC and 33,609 controls, as well as 12,194 cases of CD and 28,072 controls. The diagnosis of IBD was determined through accepted radiologic, endoscopic, and histopathologic evaluation.[16] The GWAS data was downloaded from the Wellcome Sanger Institute database (https://ftp.sanger.ac.uk/pub/project/humgen/summary_statistics/human/2016-11-07/).

### 2.2. Selection of genetic instruments

Criteria for genetic instrument selection: Single nucleotide polymorphisms (SNPs) exhibiting genome-wide significance ($P < 5 \times 10^{-8}$) in association with IBD, UC or CD; SNPs for IBD, UC or CD that were not in linkage disequilibrium (LD), as determined through a clumping process with an $r^2$ value <0.001 within a 10,000 kilobase window size. To evaluate the potential for weak instrumental variable bias of each SNP, we calculated F statistics using the formula $F = R^2(n - 2)/ (1 - R^2)$, where $R^2$ represents the proportion of the exposure variance explained by the instrumental variables, n signifies the sample size. An F statistic considerably >10 suggests a low likelihood of weak instrumental variable bias.[17] Phenoscanner V2 (http://www.phenoscanner.medschl.cam.ac.uk/) was applied to identify instrumental variables associated with pancreatitis or cholelithiasis.[18] Finally, we identified 117 index SNPs as instrumental variables for IBD, 62 index SNPs for UC, and 89 index SNPs for CD (Table S1, Supplemental Digital Content, http://links.lww.com/MD/M774).

### 2.3. Statistical analysis

The primary analysis was conducted using the random-effects inverse-variance weighted (IVW) method, complemented by MR-Egger and weighted median (WM) methods to furnish more robust estimations across diverse scenarios, characterized by broader confidence intervals and lower efficiency. The IVW method serves as an efficient tool when all selected genetic variants act as valid instrumental variables.[19] MR-Egger provides insights into potential pleiotropic effects that deviate from zero and offers credible causal effect estimations under the weaker InSIDE (Instrument Strength Independent of Direct Effect) assumption.[20] The WM method allows the inclusion of potentially invalid instrumental variables, given that at least 50% of the total variants employed are valid.[21] When the estimates direction derived from IVW, MR-Egger, and WM methods are consistent, it enhances the credibility of the causal claim. Cochran Q test was employed to assess the heterogeneity among the selected variants. We also incorporated MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis, setting the distribution number at 10,000, to mitigate heterogeneity in causal effect estimates by excluding SNPs (outliers) that exerted a disproportionate influence on the heterogeneity. To evaluate horizontal pleiotropy, we utilized both the Egger intercept test and leave-one-out (LOO) analyses. When horizontal pleiotropy is not present, IVW stands as the most efficient method with the greatest statistical power.[22] In addition, the Steiger test was used to validate the direction of observed causalities.[23] All statistical analyses were performed using the R software platform (version 4.3.1), utilizing the TwoSampleMR (version 0.5.7) and MR-PRESSO (version 1.0) packages. In this study, we conducted analyses involving 3 exposures (IBD, UC, and CD) and 1 outcome (acute pancreatitis). To address multiple testing, we employed a conservative approach by applying a Bonferroni-corrected significance level calculated as 0.05 divided by 3 ($\alpha = 0.05/3/1 = 0.0167$).[24] A $P$ value of <.0167 was considered strong evidence of a causal association, while a $P$ value <.05, but exceeding the Bonferroni-corrected significance threshold (.0167), was viewed as suggestive evidence for a potential association.

### 2.4. Ethics statement

This MR study was conducted using publicly accessible GWAS summary statistics. Original study participants provided written

consent, sanctioned by Institutional Review Board ethics committees. Thus, no further ethical approval or informed consent was required.

## 3. Results

The current MR study design is delineated through a flowchart (Fig. 1). We identified 117 index SNPs (F statistics range from 29.9 to 500.6) as instrumental variables for IBD, 62 index SNPs (F statistics range from 30.4 to 408.1) for UC, and 89 index SNPs (F statistics range from 29.7 to 489.5) for CD.

The MR-PRESSO analysis of IBD on acute pancreatitis demonstrated no potentially influential outliers. The evaluation of the causal impact of IBD on acute pancreatitis was articulated using specific MR analytical methods (Fig. 2A). The results of the MR analysis showed a statistically significant increase in the risk of acute pancreatitis among individuals with genetically predicted IBD (IVW: OR = 1.032, 95% CI: 1.006–1.06, $P$ = .015; MR-Egger: OR = 1.004, 95% CI: 0.956–1.055, $P$ = .855; WM: OR = 1.015, 95% CI: 0.974–1.052, $P$ = .465). Scatter plots portraying the significant associations derived from the MR analysis are illustrated in Figure 2B.

To rigorously assess the robustness and reliability of the preceding findings, we undertook sensitivity analyses utilizing a diversified toolkit inclusive of MR-Egger intercept test, Cochran Q test, and LOO analysis. Particularly, the intercept from the MR-Egger regression acted as a pivotal test to ascertain if any directional horizontal pleiotropy might be influencing the MR results. The MR-Egger intercept tests affirmed the nonexistence of horizontal pleiotropy in this study, evidenced by an intercept $P$ value of .192 for IBD. Indeed, the Cochran Q statistic indicated a lack of notable heterogeneity in the SNP-specific causal estimations, reflected by substantial values (IVW: Q = 102, Qdf = 91, Qp value = 0.196; MR-Egger: Q = 100, Qdf = 90, Qp value = 0.212). To further substantiate the resiliency of our findings, we employed the LOO method, a rigorous strategy for sensitivity analysis, the results of which are delineated in Figure 2C, no significant effect of individual SNPs on the overall results was observed. In general, genetically predicted IBD causally increases the risk of acute pancreatitis. To bolster the reliability of our conclusions, we subdivided IBD into CD and UC and conducted subgroup analyses.

In our subsequent subgroup analysis of IBD, we delved into the causal associations between UC, CD, and acute pancreatitis. The MR-PRESSO analysis of UC, and CD on acute pancreatitis demonstrated no potentially influential outliers. Then we also applied multiple established and robust MR methodologies, including IVW, WM, and MR-Egger regression, to discern the potential causative effects of these exposures on the outcomes. Within the subgroup analysis, results from the MR analysis indicated a significant increase in the risk of acute pancreatitis associated with CD (IVW: OR = 1.034, 95% CI: 1.008–1.06, $P$ = .007; MR-Egger: OR = 1.02, 95% CI: 0.956–1.089, $P$ = .536; WM: OR = 1.041, 95% CI: 1.005–1.08, $P$ = .025). In contrast, no significant rise in acute pancreatitis risk was observed for UC (IVW: OR = 1.02, 95% CI: 0.99–1.051, $P$ = .189; MR-Egger: OR = 0.974, 95% CI: 0.892–1.064, $P$ = .569; WM: OR = 1.004, 95% CI: 0.962–1.046, $P$ = .848) (Fig. 3A). Scatter plots portraying the associations derived from the MR analysis are illustrated in Figure 3B and C.

Furthermore, we executed tests for horizontal pleiotropy and heterogeneity to ensure the reliability of our findings. Results from the MR-Egger regression affirmed the absence of horizontal pleiotropy in both UC (intercept $P$ value = .282) and CD (intercept $P$ value = .662) (Fig. 3A). We then employed the Cochran Q statistic to measure heterogeneities; a $P$ value <.05 was taken as evidence of significant heterogeneity. Notably, we did not identify significant heterogeneity for either UC or CD (Fig. 3A). Advancing our analysis further, we conducted a LOO sensitivity test, systematically excluding each SNP to ensure the robustness of our findings (Fig. 3D and E). In addition, the Steiger direction test revealed that IBD and CD were causes for increased risk of acute pancreatitis, but not vice versa (Table 1). Upon synthesizing the data, it is evident that genetically predicted CD causally increases the risk of acute pancreatitis, whereas UC does not exhibit the same association.

## 4. Discussion

IBD, which principally includes CD and UC, typically presents as a chronic inflammatory condition chiefly impacting the gastrointestinal tract. Contrastingly, acute pancreatitis primarily affects the pancreas, representing another significant inflammatory disorder.[25,26] Notably, in the broader population, acute pancreatitis exhibits an incidence rate fluctuating between 10 and 44 cases per 100,000 individuals annually, positioning it as a predominant reason for hospital admissions and substantial healthcare expenditures related to digestive ailments.[27,28] There exists a growing consensus that individuals afflicted with IBD potentially face a heightened risk of developing acute pancreatitis.

The study draws decisive inferences, underscoring that genetically predicted IBD is causally linked with acute pancreatitis. When categorizing IBD into its primary subtypes, namely UC and CD, we delved deeper and discerned a causal association between CD and acute pancreatitis. A crucial finding to highlight is that, in the context of this study, it has been observed

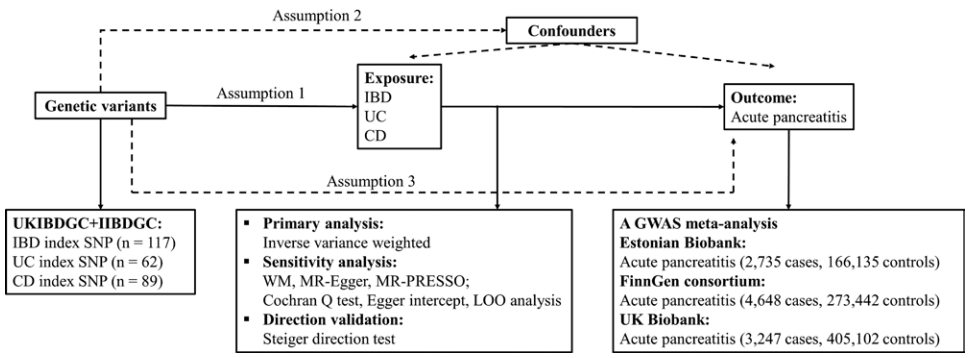
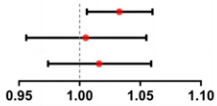


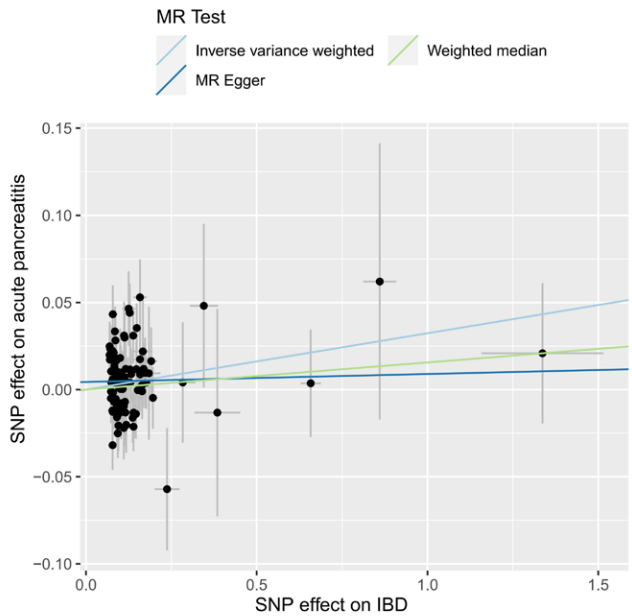

**Figure 1.** Flowchart of the present Mendelian randomization study. The comprehensive framework of the MR analysis utilized in this research is delineated in a detailed flowchart, illustrating the step-by-step procedure undertaken in the current study. Assumption 1, genetic variants are robustly associated with exposure; Assumption 2, genetic variants are not associated with confounders; Assumption 3, genetic variants affect the outcomes only through the exposure of interest. CD = Crohn disease, IBD = inflammatory bowel disease, IIBDGC = International Inflammatory Bowel Disease Genetics Consortium, LOO = leave-one-out, SNP = single nucleotide polymorphism, UC = ulcerative colitis, UKIBDGC = UK Inflammatory Bowel Disease Genetics Consortium, WM = weighted median.

A

| Method | nSNPs | P | OR(95%CI) | Q | Qdf | Intercept P |
|---|---|---|---|---|---|---|
| IVW | 92 | 0.015 | 1.032 (1.006, 1.06) | 102 | 91 | |
| MR Egger | 92 | 0.855 | 1.004 (0.956, 1.055) | 100 | 90 | 0.192 |
| Weighted Median | 92 | 0.465 | 1.015 (0.974, 1.059) | | | |




B

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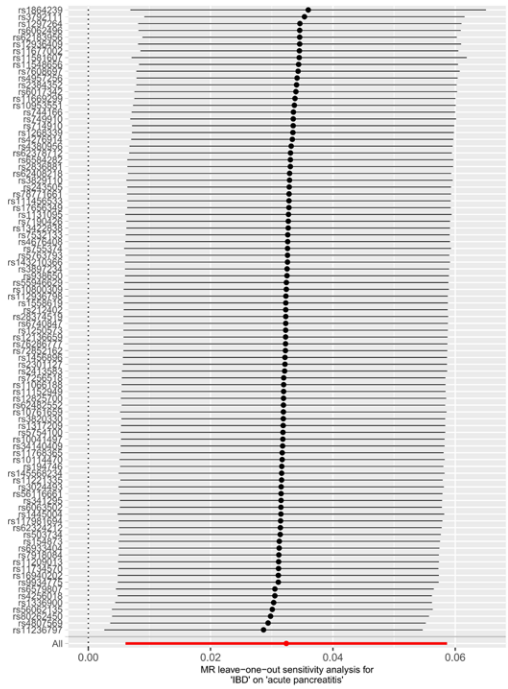


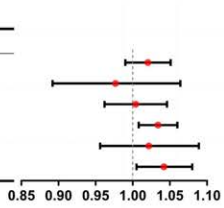

**Figure 2.** MR analyses of IBD on acute pancreatitis. (A) Forest plot of estimate is shown (IVW, MR-Egger, and weighted median), along with Cochran Q statistic (Q) and the associated df (Qdf), and the *P* value for the MR-Egger intercept (Intercept P); (B) Scatter plot for genetically predicted IBD on acute pancreatitis; (C) MR leave-one-out sensitivity analysis for IBD on acute pancreatitis. IBD = inflammatory bowel disease, IVW = inverse-variance weighted, MR = Mendelian randomization.

that UC does not directly increase the risk of acute pancreatitis. From a clinical perspective, this may be attributed to the different digestive tract locations affected by the 2 diseases. Typically, CD predominantly affects the terminal ileum and colon, yet it can span anywhere from the mouth to the anus, even affecting the perianal skin.[29] The disease manifestations are diverse, with approximately 35% of patients experiencing it in the small intestine alone, 20% solely in the colon, and about 45% reporting afflictions in both the terminal ileum and colon.[30–32] A study from the Mayo Clinic indicates that among all CD-affected patients, the prevalence of esophageal, stomach, and duodenal CD ranges from approximately 0.5% to 4.0%.[33] Yet, the actual incidence might be substantially greater, reaching up to 19%, as observed in a cohort of asymptomatic patients undergoing routine esophagogastroduodenoscopy (EGD).[34,35] It is paramount to underscore this aspect, considering that most adult patients with CD do not routinely undergo EGD unless exhibiting symptoms, leading to potential underreporting of upper gastrointestinal CD incidences. Notably, duodenal CD can lead to segmental inflammation, nodularity, diminished distensibility, and/or constriction. If the duodenal papilla is affected, it could result in a pronounced obstruction at the end of the bile duct. On the other hand, UC predominantly affects the colon and rectum. Although it does not characteristically impinge on the duodenum, sporadic cases of duodenal involvement have been chronicled, positioning them as atypical presentations of UC.[36] In addition, a detailed meta-analysis demonstrates a significantly elevated occurrence of gallstones in individuals with IBD compared to those in the control group. Subgroup analyses further delineate that this heightened risk is pronounced in CD patients while remaining non-significant among those with UC.[7]

It is noteworthy that medications utilized in the treatment of IBD can potentially cause acute pancreatitis. As early as 1973, an article published in The New England Journal of Medicine reported cases of azathioprine-induced acute pancreatitis.[37] Consistently, numerous studies have highlighted an increased incidence of acute pancreatitis associated with the use of azathioprine and mercaptopurine,[38,39] Another group of medications, aminosalicylates, encompassing drugs like mesalamine, has been correlated with an elevated risk of developing acute pancreatitis.[40,41] The precise mechanisms behind these drugs inducing acute pancreatitis remain unclear. The current body of literature indicates that these medications may induce acute pancreatitis by directly causing toxic effects, such as pancreatic congestion and edema, consequently resulting in drug-induced pancreatitis. Furthermore, corticosteroids, which include agents such as prednisone and budesonide, are frequently employed in IBD management. These drugs serve as potent anti-inflammatory

A

| Exposure | Method | nSNPs | P | OR(95%CI) | Q | Qdf | Intercept P |
|---|---|---|---|---|---|---|---|
| UC | IVW | 49 | 0.189 | 1.02 (0.99, 1.051) | 51 | 48 | |
| | MR Egger | 49 | 0.569 | 0.974 (0.892, 1.064) | 50 | 47 | 0.282 |
| | Weighted Median | 49 | 0.848 | 1.004 (0.962, 1.046) | | | |
| CD | IVW | 72 | 0.007 | 1.034 (1.008, 1.06) | 86 | 71 | |
| | MR Egger | 72 | 0.536 | 1.02 (0.956, 1.089) | 86 | 70 | 0.662 |
| | Weighted Median | 72 | 0.025 | 1.041 (1.005, 1.08) | | | |



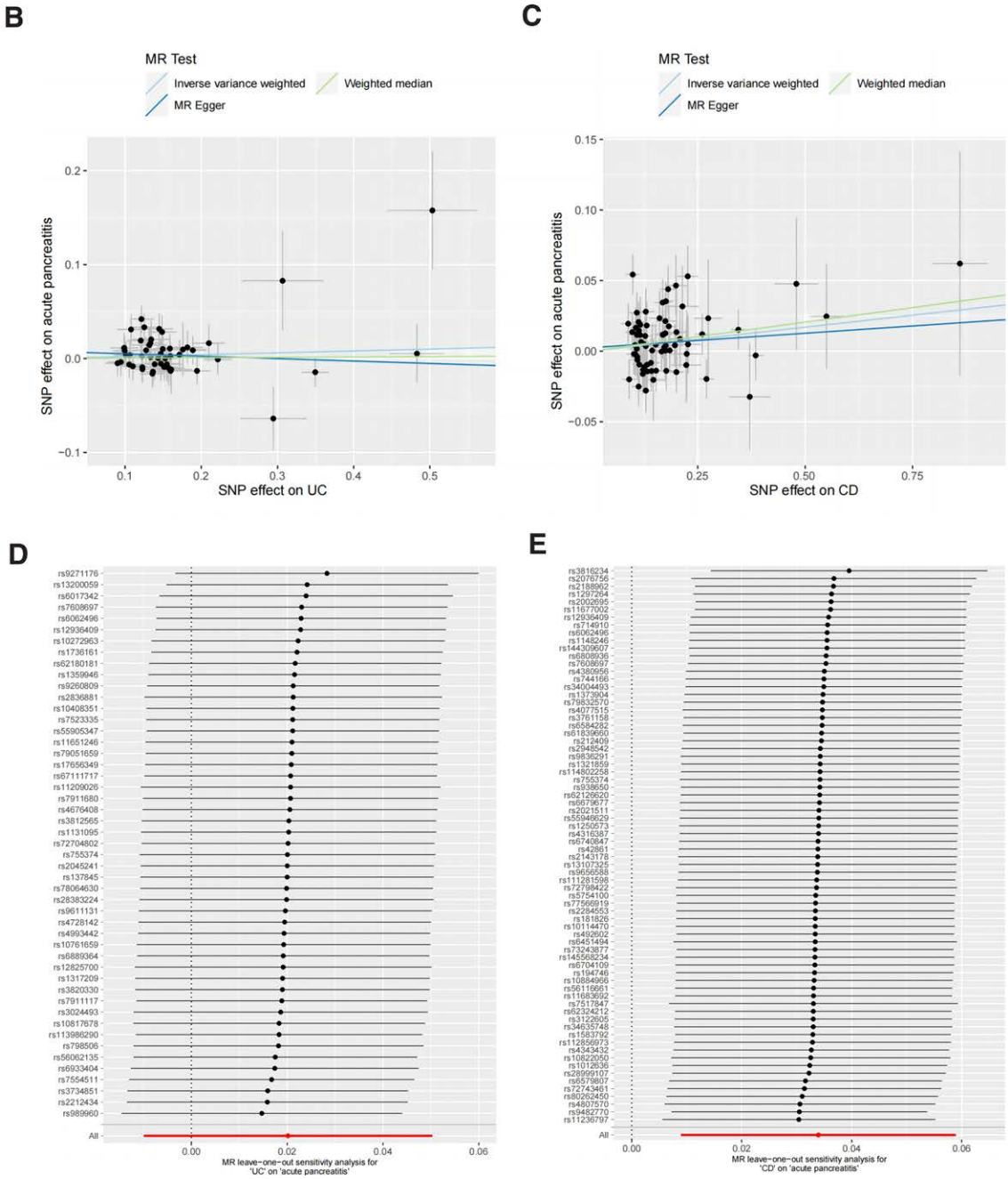




**Figure 3.** MR analyses of UC, and CD on acute pancreatitis. (A) forest plot of the 2 estimates is shown (IVW, MR-Egger, and weighted median), along with Cochran Q statistic (Q) and the associated df (Qdf), and the *P* value for the MR-Egger intercept (Intercept P); (B) Scatter plot for genetically predicted UC on acute pancreatitis; (C) Scatter plot for genetically predicted CD on acute pancreatitis; (D) MR leave-one-out sensitivity analysis for UC on acute pancreatitis; (E) MR leave-one-out sensitivity analysis for CD on acute pancreatitis. CD = Crohn disease, IVW = inverse-variance weighted, MR = Mendelian randomization, UC = ulcerative colitis.

agents, significantly attenuating inflammation through immune response modulation, thereby facilitating remission in active disease states. Although short-term use is preferred to limit the adverse effects linked with prolonged corticosteroid therapy, there have been instances where their usage has been associated with acute pancreatitis.[42] The underlying mechanism could

**Table 1**

**Steiger direction test from IBD and CD to acute pancreatitis.**

| Exposure | IBD | CD |
|---|---|---|
| Outcome | Acute pancreatitis | Acute pancreatitis |
| Direction | TRUE | TRUE |
| Steiger *P* | <.001 | <.001 |

CD = Crohn disease, IBD = inflammatory bowel disease.

be related to the ability of corticosteroids to encourage hypertriglyceridemia, a known precursor to acute pancreatitis. This condition manifests as increased triglyceride levels, promoting crystal deposition within the pancreatic ducts, potentially leading to ductal obstruction and consequently initiating pancreatitis.[43] Despite recognizing the potential risk of acute pancreatitis linked to certain IBD medications, it is crucial to maintain a balanced approach. Clinicians should carefully weigh the benefits and risks when prescribing these medications, and patients should undergo regular monitoring to promptly detect any signs of acute pancreatitis. Future research should aim to delineate the exact biological pathways underlying this association, steering toward the refinement of IBD management strategies to curtail this risk.

Despite being the first to establish a definitive causal relationship between IBD, CD, and acute pancreatitis, our current study has several limitations that warrant discussion. Firstly, the causal estimates derived from MR analyses are generally not directly interpretable as the anticipated effects of interventions on the exposure in real-world settings. The change in an outcome resulting from a genetic change in the exposure may well differ from the change resulting from a pharmacological or clinical intervention on the exposure. Estimates from MR should therefore not be interpreted naively as the expected impact of an intervention in the exposure of interest in practice. While MR serves as a powerful tool to garner evidence backing causal hypotheses, it necessitates subsequent in-depth research to elucidate the fundamental mechanisms grounding these hypotheses. Secondly, the study cohort was exclusively European, rendering the implications of IBD, UC, and CD on acute pancreatitis and diseases in diverse ethnic populations undetermined. Lastly, MR inherently lacks the capacity to furnish details on the temporal dynamics between exposure and outcome, a crucial aspect in comprehending the multifaceted outcomes rooted in varying IBD durations. It is vital to approach the findings with a nuanced understanding of these limitations.

In summary, this research pioneers in proposing a causal relationship between CD and acute pancreatitis, while it could not affirm such a relationship between UC and acute pancreatitis, thereby reinforcing the findings of previous observational studies that have suggested acute pancreatitis as an extraintestinal manifestation of CD. In clinical practice, it is imperative for clinicians to be vigilant of the onset of acute pancreatitis in patients with CD.

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## Author contributions

**Conceptualization:** Xuewei Fu, Hao Wu.
**Data curation:** Chao Deng.
**Formal analysis:** Chao Deng.
**Investigation:** Bocheng Yang.
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**Supervision:** Bocheng Yang, Chao Deng.
**Visualization:** Chao Deng.
**Writing – original draft:** Xuewei Fu, Hao Wu.
**Writing – review & editing:** Chao Deng.

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