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Unraveling the link between inflammatory bowel disease and perianal abscess: insights from bidirectional and multivariable Mendelian randomization study

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Abstract

Background Emerging epidemiological studies have identified associations between perianal abscess (PA) and inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), though the pathophysiological mechanisms underlying their comorbidity remain incompletely understood. To elucidate potential causal relationships between these clinical entities, we conducted a comprehensive investigation employing bidirectional two-sample Mendelian randomization (MR) analysis complemented by multivariable Mendelian randomization (MVMR) methodology. This analytical approach enables systematic evaluation of causal directionality while accounting for potential confounding factors inherent in observational studies.

Methods To establish valid instrumental variables, independent single nucleotide polymorphisms (SNPs) were selected from genome-wide association study (GWAS) summary statistics of European ancestry populations. Data for IBD were sourced from the IEU OpenGWAS repository, while PA datasets were obtained from FinnGen consortium and UK Biobank resources. Our bidirectional MR framework incorporated five complementary analytical methods: inverse variance weighted (IVW), weighted median, MR-Egger regression, weighted mode, and simple mode estimators. Methodological robustness was ensured through comprehensive sensitivity analyses: horizontal pleiotropy was evaluated via MR-Egger intercept testing, heterogeneity quantified using Cochran's Q statistic, and outlier detection implemented through MR-PRESSO (Mendelian Randomization Pleiotropy Residual Sum and Outlier) with supplementary leave-one-out validation to assess individual SNP influence on causal estimates.

Results Genetic liability analyses using IVW estimation revealed IBD) and its principal subtypes as risk factors for PA. In the discovery cohort, IBD conferred a 20% increased PA risk (OR = 1.20, 95%CI = 1.12–1.31, $p = 5.68 \times 10^{-5}$), with subtype-specific effects for CD (OR = 1.15, 95%CI = 1.06–1.24, $p = 0.0004$) and UC (OR = 1.11, 95%CI = 1.01–1.21, $p = 0.027$). These associations replicated consistently in the independent cohort (IBD: OR = 1.17, 95%CI = 1.09–1.27, $p = 3.92 \times 10^{-5}$; CD: OR = 1.12, 95%CI = 1.04–1.21, $p = 0.002$; UC: OR = 1.13, 95%CI = 1.03–1.24, $p = 0.009$). Conversely, IVW-based bidirectional analysis demonstrated non-significant associations between PA liability and IBD progression across both cohorts (all $p > 0.05$). Confounder-adjusted MVMR analyses confirmed direct causal effects of IBD

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(encompassing CD and UC) on PA risk after accounting for pleiotropy. In exploration cohorts, ulcerative ileocolitis in CD exhibited nominal association with elevated perianal disease risk (OR = 1.18, 95%CI = 1.01–1.38, $p = 0.04$) in hypothesis-generating analyses.

Conclusions Our analyses demonstrated significant associations between PA and both principal IBD subtypes (UC and CD), underscoring the necessity for mechanistic investigations into shared pathophysiology within the IBD spectrum.

Keywords Inflammatory bowel disease, Mendelian randomization, Perianal abscess, Single nucleotide polymorphism

Introduction

Inflammatory bowel disease (IBD), a chronic immune-mediated disorder of the gastrointestinal tract, is principally categorized into two distinct clinical entities: Crohn's disease (CD) and ulcerative colitis (UC). These subtypes exhibit heterogeneous phenotypic manifestations ranging from mild localized inflammation to severe transmural or extensive colonic involvement [1]. A pronounced epidemiological shift in IBD emerged in the mid-to-late 20th century, with incidence rates rising substantially throughout industrialized North America and Europe [2]. UC and CD demonstrate systemic inflammatory effects extending beyond their primary gastrointestinal pathology, manifesting with diverse extraintestinal involvement. Characteristic immune-mediated manifestations include dermatologic (such as erythema nodosum), ophthalmologic (such as uveitis), hepatobiliary (such as primary sclerosing cholangitis), and musculoskeletal complications (such as peripheral arthritis, axial spondyloarthritis), reflecting the multisystem nature of inflammatory bowel disease pathogenesis [3]. Accumulating epidemiological evidence indicates a rising global incidence of IBD, with pronounced acceleration in rapidly industrializing regions. This trend imposes a substantial lifelong disease burden, compounded by the lack of disease-modifying therapies and the incomplete elucidation of its multifactorial pathophysiology [4].

Perianal abscess (PA) pathogenesis begins with obstruction of anal crypt glands. This leads to bacterial proliferation within the occluded ducts, causing suppurative infection, localized pus formation, and tissue necrosis [5]. A Swedish nationwide cohort study reported an annual PA incidence of 16.1 per 100,000 person-years, establishing a robust epidemiological benchmark for this surgically important condition [6]. Perianal abscess (PA) is commonly complicated by fistula formation and systemic infection. Observational studies indicate PA may precede IBD diagnosis, with evidence suggesting it serves as an early indicator of CD [7]. One-third of patients in the United Kingdom (UK) had PA surgery prior to receiving a CD diagnosis [8]. PA can also be associated with UC [9]. Consequently, it has been suggested that cases of PA be continuously watched to follow the development of IBD. Perianal involvement has been shown as an independent predictor of stricturing and penetrating behavior in IBD (particularly, CD) as well as a rapid development to ileocolonic illness [10]. Early patient identification can facilitate the consideration of more efficacious medical therapy alternatives, such as biologics and thiopurines, at an earlier stage of the disease, potentially mitigating the necessity for intestinal resection in this high-risk patient population [11]. While observational studies have identified epidemiological associations between PA and IBD, the inherent limitations of such designs—including residual confounding, reverse causality, and selection bias—preclude definitive causal conclusions. Notably, while PA frequently co-occurs with IBD, particularly in CD, the bidirectional pathophysiological mechanisms governing this clinical intersection remain insufficiently elucidated, warranting mechanistic studies to disentangle shared etiological pathways from secondary complications.

Mendelian randomization (MR) is an epidemiological methodology that employs genetic variants, primarily single-nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS), as instrumental variables (IVs) to infer causal relationships between exposures and outcomes. This approach capitalizes on the principle of genetic immutability – an individual's germline genetic composition is fixed at conception and thus unaffected by disease processes or environmental confounding postnatally – enabling robust evaluation of unidirectional causal effects. By leveraging the random assortment of genetic alleles during meiosis, MR approximates a natural randomized controlled trial design, effectively minimizing confounding bias through the exclusion of variables influenced by disease progression or behavioral factors [12]. We used bidirectional and multivariable Mendelian randomization to assess potential causal links between IBD and PA. Our approach employed robust methods to minimize genetic confounding, such as pleiotropy analysis.

Materials and methods

Data sources

The analytical schema of this investigation is comprehensively outlined in Fig. 1. In adherence to STROBE-MR guidelines, we executed bidirectional

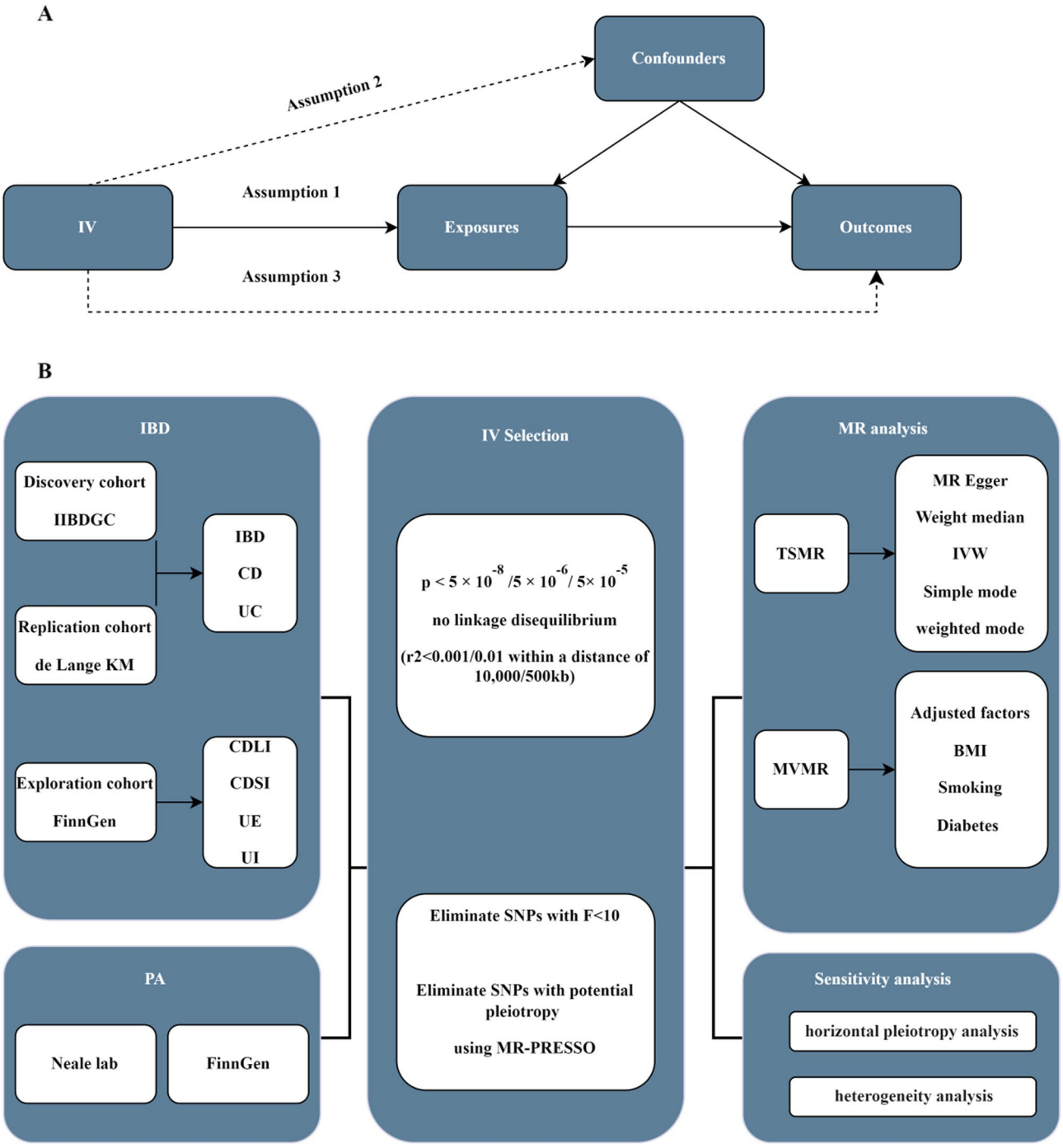


Fig. 1 Schematic representation of the comprehensive design of the Mendelian randomization analysis in the present study. SNP, single-nucleotide polymorphism; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; MR: Mendelian randomization; IV: instrumental variables; CDLI: CD of large intestine; CDSI: CD of small intestine; UE: ulcerative enterocolitis; UI: ulcerative ileocolitis; TSMR: two-sample Mendelian randomization; MVMR: multivariate Mendelian randomization; BMI: body mass index; MR-PRESSO: Mendelian Randomization Pleiotropy RESidual Sum and Outlier; IIBDGC: International IBD Genetics Consortium

two-sample Mendelian randomization analyses to systematically interrogate potential reverse causality between IBD and PA, thereby mitigating biases inherent to observational epidemiological designs [13].

First, GWAS summary statistics for IBD were sourced from the IEU OpenGWAS project, comprising data curated by the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). This multinational research consortium aggregated genome-wide

association data from 75,000 IBD cases across UC and CD subtypes. The final analytic dataset included 12,882 IBD cases versus 21,770 population-matched controls, with subtype-specific cohorts of 6,968 UC and 5,956 CD cases. All participants were of European ancestry to minimize population stratification bias [14]. All case diagnoses underwent rigorous validation through adherence to standardized diagnostic criteria incorporating endoscopic visualization, cross-sectional imaging modalities, and histopathological examination [15]. Summary statistics for IBD GWAS were derived solely from European ancestry cohorts to address population stratification concerns. For replication analyses, we employed an expanded sample from the multinational meta-analysis by de Lange et al. [16], which integrates harmonized datasets from the United Kingdom IBD Genetics Consortium (UKIBDGC) and the IIBDGC, thereby enhancing statistical power through cross-cohort validation. The research's discovery cohort used the IIBDGC dataset. These include the UK low coverage whole genome sequencing IBD study, the UK HumanCoreExome genotyped IBD project, and the IIBDGC genotyped IBD (including CD and UC) study. The UC and CD data, as well as the IBD data, which comprised 25,042 patients and 34,915 controls in the replication cohort. To further investigate whether the lesion extent of CD affects the incidence of PA, this study established the exploration cohorts, which of data were selected from the FinnGen (https://www.finngen.fi/en) (Table 1). In exploration cohort, CD of large intestine data included 807 patients and 210,300 controls. The CD of small intestine data included 968 patients and 210,300 controls. The ulcerative enterocolitis data included 486 patients and 210,300 controls. The ulcerative ileocolitis included 644 patients and 210,300 controls.

GWAS for PA were derived from two population-scale biobank resources: the UK Biobank (https://www.ukbiobank.ac.uk/) and the FinnGen consortium (https://www.finngen.fi/en), selected for their harmonized phenotyping protocols and European ancestry-matched cohort designs to ensure comprehensive coverage of PA phenotypes across demographic strata [17]. The 10th Edition of the International Classification of Diseases (ICD-10) diagnosis at the time of discharge or the reason of death was the primary factor used to decide which population to include. Based on ICD-10 K61 diagnosis, PA (abscess of anal and rectal regions) includes 1287 patients and 1053 patients from FinnGen, with 1053 patients having access to UKBB (UK Biobank). The details of the data for the cohort population were displayed in Table 1. Since the current study is a secondary review of publicly available data, no further ethical approval was needed.

Selection of genetic instrumental variables

A variety of quality control techniques were employed to find appropriate SNPs for IVs using the GWAS statistics. It is necessary to verify the following three assumptions [18]. The following three assumptions are made: (1) there is a strong connection between the IV and exposure; (2) the IV is independent of confounding variables and cannot influence the outcome; and (3) the IV only has an indirect influence on the outcome and does not directly affect the result (Fig. 1A).

In order to meet the correlation assumption, instrumental SNPs were identified based on the following criteria: (1): Genome wide strongly significant ($F > 10$; In forward MR analysis, $p < 5 \times 10^{-8}$ in discovery cohort and in replication cohort; $p < 5 \times 10^{-5}$ at a looser criterion in exploration cohort; In reverse MR analysis, $p < 5 \times 10^{-6}$

Table 1 List of genome-wide summary association studies (GWAS) in Mendelian randomization (MR) study

Cohort categories id	trait	ncase	date resource	sex	population	Sample size	ncontrol	nsnp
Discovery cohort								
ieu-a-31	Inflammatory bowel disease	12,882	IIBDGC	F/M	European	34,652	21,770	12,716,084
ieu-a-30	Crohn's disease	5,956	IIBDGC	F/M	European	20,883	14,927	12,276,506
ieu-a-32	Ulcerative colitis	6,968	IIBDGC	F/M	European	27,432	20,464	12,255,197
finn-b-K11_ABSCANAL	Abscess of anal and rectal regions	1,287	FinnGen	F/M	European	183,710	182,423	16,380,365
Replication cohort								
ebi-a-GCST004131	Inflammatory bowel disease	25,042	de Lange KM	NA	European	59,957	34,915	9,619,016
ebi-a-GCST004133	Ulcerative colitis	12,366	de Lange KM	NA	European	45,975	33,609	9,474,559
ebi-a-GCST004132	Crohn's disease	12,194	de Lange KM	NA	European	40,266	28,072	9,457,998
finn-b-K11_ABSCANAL	Abscess of anal and rectal regions	1,287	FinnGen	F/M	European	183,710	182,423	16,380,365
Exploration cohort								
finn-b-CHRONLARGE	Crohn's disease of large intestine	807	NA	F/M	European	211,107	210,300	16,380,453
finn-b-CHRONSMALL	Crohn's disease of small interstine	968	NA	F/M	European	211,268	210,300	16,380,454
finn-b-ULCERENTER	Ulcerative enterocolitis	486	NA	F/M	European	210,786	210,300	16,380,453
finn-b-ULCERILEO	Ulcerative ileocolitis	644	NA	F/M	European	210,944	210,300	16,380,452
ukb-d-K61	Abscess of anal and rectal regions	1053	Neale lab	F/M	European	361,194	360,141	9,446,877

F/M female and male, *SNP* single-nucleotide polymorphism, *NA* not available, *IIBDGC* International IBD Genetics Consortium

in all three cohorts) association with the exposure. For a single variant, the F statistic, which should be over 10 to avoid weak instrument bias, was calculated by the following equation [19]: $F = [\beta/se]^2$, where β means estimated effect size and se means standard error of β; and (2) independent SNPs are selected by linkage disequilibrium (LD) clumping (In forward MR analysis, r2 < 0.001, window size = 10000 kb in discovery cohort and replication cohort; r2 < 0.01, window size = 500 kb at a looser criterion in exploration cohort; In reverse MR analysis, r2 < 0.001, window size = 10000 kb). In order to meet the requirements of the independence and exclusion assumption, we examined every SNP linked to the exposure using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/), excluding SNPs that had significant association with the result and potential confounders. In order to guarantee SNPs with a minor allele frequency (> 0.01), unify the effect direction and effect allele, and eliminate the palindromic and incompatible SNPs, a further harmonization procedure was performed.

Directionality test with MR-Steiger

To establish causal directionality, we implemented *MR-Steiger* filtering during preliminary analyses to identify and exclude SNPs demonstrating reverse causality. This methodology operates on the premise that valid genetic instruments must explain greater variance in exposure traits than in outcome phenotypes. Genetic variants failing this criterion were classified as exhibiting bidirectional pleiotropy and systematically excluded from subsequent analyses. Following this quality control protocol, bidirectional two-sample MR was re-executed using directionally validated instruments to ensure robust causal inference. The relevant results are presented in the Supplementary Table S1.

MR analyses

The bidirectional two-sample MR framework integrated complementary analytical approaches — inverse variance weighted (IVW, primary estimator), weighted median (WM), MR-Egger regression, weighted mode, and simple mode — to systematically evaluate causal relationships between PA and IBD subtypes. Each method operates under distinct statistical assumptions: WM requires ≥ 50% valid instruments (SNPs satisfying core MR assumptions), while MR-Egger provides pleiotropy-robust estimates under the InSIDE assumption (Instrument Strength Independent of Direct Effect), albeit with reduced statistical power against weak instrument bias (F-statistic < 10). Sensitivity thresholds were established through Cochran's Q test for heterogeneity ($p < 0.05$) and MR-Egger intercept analysis for directional pleiotropy [20, 21]. The IVW method was selected as the primary estimator due to its balanced pleiotropy assumption, which accommodates random (non-directional) horizontal pleiotropy across IVs while maximizing statistical efficiency compared to alternative approaches. To ensure methodological robustness, we implemented a tiered sensitivity analysis framework: (1) Cochran's Q test ($p < 0.05$ threshold) quantified heterogeneity among IVs, with significant results triggering MR-PRESSO outlier correction (global test $p < 0.05$) and iterative reanalysis following outlier removal; (2) MR-Egger regression intercept analysis ($p > 0.05$ threshold) evaluated directional pleiotropy bias arising from IV-exposure-outcome pathway violations; (3) leave-one-out sensitivity analysis systematically assessed individual SNP influence on causal estimates. This multi-layered approach maintained causal inference validity while addressing potential violations of MR core assumptions. This investigation employed IVW as the primary analytical framework, integrating both fixed-effects (IVW-FE) and multiplicative random-effects (IVW-MRE) models [22]. This dual-model approach optimizes causal effect estimation by accounting for inter-SNP heterogeneity while preserving statistical efficiency through weighted aggregation of variant-specific ratio estimates. The IVW-MRE specification was prioritized when Cochran's Q test indicated significant heterogeneity ($p < 0.05$), thereby relaxing the homogeneity assumption inherent to IVW-FE through variance component estimation. Multivariable Mendelian randomization (MVMR) assesses direct causal effects of multiple exposures while minimizing bias. It achieves this by using genetic instruments that are statistically independent across correlated risk factors. This approach rigorously adjusts for pleiotropic pathways by conditioning on genetically proxied covariates, thereby isolating exposure-specific causal pathways as recommended by STROBE-MR guidelines for complex trait analyses [23]. To account for potential confounding effects, we implemented MVMR analyses to evaluate the direct causal relationship between IBD and PA, with comprehensive adjustment for genetically proxied covariates including body mass index (BMI), smoking, and diabetes mellitus (DM) liability.

Analysis of statistics

The study was a secondary analysis of the publicly accessible data; no changes were made to the original data. All statistical analyses and graphics were completed using R (version 4.2.1). To conduct the MR analysis, the "TwoSampleMR" and "MRPRESSO" packages were utilized. In order to account for multiple testing in our inquiry, a Bonferroni-corrected p-value of 0.025 or 0.0125 (0.05/2 or 0.05/4) was used to determine the statistical significance of the MR estimations in two-sample MR.

Results

Selection of instrumental variables of MR analysis

Data for 82,967 people of European heritage who took part in the discovery cohorts were gathered from the IBD, CD, and UC collections using integrated genome-wide SNP datasets. Following the completion of LD clumping and harmonization procedures, no outlier SNPs associated to IBD, CD, or UC were found using the MR-PRESSO test. In order to assess the causal effects on PA, 62 confounder-independent SNPs associated to IBD, 51 confounder-independent SNPs related to CD, and 35 UC-related SNPs were detected (Table 2 for details). IVs were chosen for the replication cohort based on the previously mentioned selection criteria. Consequently, the IVs estimation of IBD, CD, and UC of mixed population matched the criteria for 101 (removing rs145568234), 79 (removing rs145568234), and 52 SNPs, respectively (Table 2 for details). We employed the less restrictive selection criteria mentioned above in the exploration cohort to look into potential associations between PA and the site of inflammatory bowel disease. Ultimately, the MR-PRESSO test did not identify any outlier SNPs in the exploration cohort following the finish of the LD clumping and harmonization procedures. For CD of the large intestine, CD of the small intestine, ulcerative enterocolitis, and ulcerative ileocolitis, there are, in order, 105, 111, 94, and 87 SNPs (Table 2 for details).

We additionally examined at the effect of PA as an exposure factor on IBD and its subtypes. In the discovery cohort, 9, 9, and 10 PA-related SNPs were found to assess the causal effects on IBD (removing rs144717024, rs184357366, rs72796315), CD (removing rs144717024, rs72796315), and UC (removing rs144717024) following LD clumping, harmonization processes, and outlier SNPs removal. In the meantime, eight SNPs linked to PA were found in the replication cohort in order to assess the causative impact on IBD, CD, and UC. To assess the causative effects on IBD, CD, and UC, 12 PA-related SNPs were found in the exploraton cohort (Table 2 for details).

Table 2 Two-sample MR analysis results of inflammatory bowel disease and perianal abscess

exposure	outcome	method	NSNP	OR	OR_LCI	OR_UCI	*p*
Forward MR							
Discovery cohort							
IBD	PA	IVW-MRE	62	1.196	1.096	1.305	5.68×10^{-5}
CD		IVW-MRE	51	1.146	1.063	1.236	0.0004
UC		IVW-FE	35	1.106	1.011	1.210	0.027
Replication cohort							
IBD	PA	IVW-MRE	101	1.173	1.087	1.266	3.92×10^{-5}
CD		IVW-MRE	79	1.124	1.044	1.210	0.002
UC		IVW-FE	52	1.129	1.031	1.236	0.009
Exploration cohort							
CDLI	PA	IVW-FE	105	1.00002	0.9999	1.0001	0.756
CDSI		IVW-FE	111	1.00004	0.9999	1.0001	0.467
UE		IVW-FE	94	0.99999	0.9999	1.0001	0.888
UI		IVW-FE	87	1.00010	1.000004	1.0002	0.0417
Reverse MR							
Discovery cohort							
PA	IBD	IVW-FE	9	1.027	0.962	1.096	0.423
	CD	IVW-FE	9	1.043	0.972	1.119	0.242
	UC	IVW-FE	10	1.022	0.966	1.081	0.457
Replication cohort							
PA	IBD	IVW-FE	8	0.996	0.968	1.024	0.780
	CD	IVW-MRE	8	1.005	0.957	1.056	0.840
	UC	IVW-FE	8	0.993	0.958	1.030	0.719
Exploration cohort							
PA	CDLI	IVW-FE	12	3.26E-07	8.10E-27	1.31669E + 13	0.517
	CDSI	IVW-FE	12	6.49E-10	8.45E-30	49,854,918,864	0.365
	UE	IVW-FE	12	28511051.79	3.17E-18	2.56E + 32	0.558
	UI	IVW-FE	12	182590.0922	2.15E-17	1.55E + 27	0.638

Site-specific IBD subtype analyses are exploratory and limited by instrument scarcity. Nominal associations ($p<0.05$) require independent validation. *NSNP* number of single nucleotide polymorphisms number, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *PA* Perianal abscess, *MR* Mendelian randomization, *IVW-FE* inverse variance weighted-fixed effects, IVWMRE: weighted-multiplicative random effects, *OR* odds ratio, *CI* confidence interval, *CDLI* CD of large intestine, *CDSI* CD of small intestine, *UE* ulcerative enterocolitis, *UI* ulcerative ileocolitis, *UCI* upper limit of the 95% confidence interval, *LCI* lower limit of the 95% confidence interval

Forward mendelian randomization analysis

In the discovery cohort, generally, the results of IVW showed that the causal relationship between IBD and PA was significant (OR: 1.20, 95%CI: 1.12–1.31, $p = 5.68 \times 10^{-5}$). Further analysis of two subtypes showed that UC and CD increased the risk of PA (CD: OR: 1.15, 95% CI:1.06–1.24, $p = 0.0004$; UC: OR: 1.11, 95% CI: 1.01–1.21, $p = 0.027$), which showed that UC and CD had a positive causal relationship for PA (Table 2 for details). Although heterogeneity was observed in some of the results after the Cochran Q test, heterogeneity was acceptable with IVW analysis as the main result. There was no interference caused by pleiotropy (Table 3 for details), which also confirmed the robustness of our results.

In the replication cohort, the results of IVW showed that the causal relationship between IBD and PA was significant (OR: 1.17, 95%CI: 1.09–1.27, $p = 3.92 \times 10^{-5}$). Further analysis of two subtypes showed that UC and CD increased the risk of PA (CD: OR: 1.12, 95% CI:1.04–1.21, $p = 0.002$; UC: OR: 1.13, 95% CI: 1.03–1.24, $p = 0.009$) (Table 2 for details), demonstrated a positive causal association between UC and CD and PA. Heterogeneity was acceptable even if it was also seen in some of the results following the Cochran Q test (see Table 3 for specifics). Pleiotropy did not create any interference, demonstrating the resilience of our findings (Table 3 for details).

In the exploration cohort, based on the above results, both UC and CD seem to be related to the occurrence of PA. In order to explore the possible effect of the site of disease in inflammatory bowel disease on PA, we further conducted MR analysis of the causal effect of different sites of disease in inflammatory bowel disease on PA. Exploratory analyses suggested a nominal association between ulcerative ileocolitis in CD and perianal disease risk ($p = 0.04$) (Table 2 for details), though statistical significance was marginal and requires validation. There was no interference caused by pleiotropy and heterogeneity, which showed the robustness of our results (Table 3 for details). Supplementary Figure S1 presents scatter plots of important MR estimations. Supplementary Figure S3 and S2 exhibit the forest plots and leave-one-out sensitivity analyses of all suggestively relevant regulators. Supplementary Figure S4 presents a funnel plot.

Reverse mendelian randomization analysis

In the discovery cohort, results showed that PA would not increase the risk of IBD (UC and CD) occurrence: PA on IBD (OR: 1.02, 95%CI: 0.96–1.10, $p = 0.42$); PA on CD (OR: 1.04, 95%CI: 0.97–1.12, $p = 0.241$); PA on UC (OR: 1.02, 95%CI: 0.97–1.08, $p = 0.46$) (Table 2 for details). In the replication cohort, results showed that PA would not increase the risk of IBD (UC and CD) occurrence: PA on IBD (OR: 0.99, 95%CI: 0.97–1.02, $p = 0.78$); PA on CD (OR: 1.01, 95%CI: 0.96–1.06, $p = 0.84$); PA on UC (OR: 0.99, 95%CI: 0.95–1.029, $p = 0.72$) (Table 2 for details). In the exploration cohort, Both IVW and the supplementary methods showed no causal effects (all $p > 0.05$) of PA on the site of disease in inflammatory bowel disease (Table 2 for details). In the three study cohorts described above, horizontal pleiotropy (all $p > 0.05$) was observed in the sensitivity analyses in reverse MR analysis (Table 3 for details). And there is no heterogeneity by IVW (all $P > 0.05$) (Table 3 for details). Supplementary Figure S1 displays scatter plots of valuable MR predictions. Supplementary Figure S3 and S2 exhibit the leave-one-out sensitivity analyses and forest plots of all suggestively relevant regulators. Supplementary Figure S4 presents a funnel plot illustration.

Multivariable mendelian randomization analysis

To better assess the genetically predicted causal relationship between IBD and PA, we performed MVMR analysis by adjusting for BMI, smoking, and diabetes. The multivariate IVW MR method was used to estimate causality. In the discovery cohort, when we adjust for BMI, smoking, diabetes respectively, there was a direct causal effect between IBD (including CD and UC) and increased risk of PA (all $p < 0.05$) (Supplementary Table S1 for details). When we adjusted for all three factors, strong evidence which was genetically predicted showed that IBD could increasing the risk of PA (for IBD: OR = 1.21, 95% CI = 1.10–1.33, $p = 0.0001$; for CD: OR = 1.15, 95% CI = 1.06–1.25, $p = 0.0005$; for UC, OR = 1.14, 95% CI = 1.03–1.27, $p = 0.008$) (Table 4 for details).

In the replication cohort, when we adjusted for BMI, smoking, diabetes respectively, there was a direct causal effect between IBD (including CD and UC) and increased risk of PA (all $p < 0.05$) (Supplementary Table S1 for details).When we adjusted for all three same factors, strong evidence which was genetically predicted showed that IBD could increasing the risk of PA (for IBD: OR = 1.22, 95% CI = 1.10–1.35, $p = 0.0001$; for CD: OR = 1.11, 95% CI = 1.03–1.21, $p = 0.005$; for UC, OR = 1.14, 95% CI = 1.03–1.26, $p = 0.007$) (Table 4 for details).

Discussion

This bidirectional MR study, to our knowledge the first to systematically investigate the causal relationship between PA and IBD, demonstrates unidirectional causality wherein genetic predisposition to IBD and its subtypes elevates PA risk, corroborating observational evidence while addressing confounding through pleiotropy-robust multivariable MR adjustments. Crucially, the absence of reverse causation positions PA as an early clinical manifestation rather than an etiological driver in IBD pathogenesis. The identification of ileocolonic CD

Table 3 Tests for horizontal Pleiotropy and heterogeneity in the MR analysis

exposure	outcome	Horizontal pleiotropy test			Heterogeneity test			
		egger_intercept	se	pval	method	Q	Q_df	Q_pval
Forward MR								
Discovery cohort								
IBD	PA	0.0100	0.0201	0.6227	MR Egger	80.864	60	0.0376
					IVW	81.194	61	0.0430
CD		−0.0113	0.0197	0.5699	MR Egger	66.890	49	0.0455
					IVW	67.337	50	0.0514
UC		0.0157	0.0253	0.5384	MR Egger	41.548	33	0.1460
					IVW	42.035	34	0.1620
Replication cohort								
IBD	PA	0.0106	0.0093	0.2608	MR Egger	133.605	99	0.0117
					IVW	135.330	100	0.0107
CD		0.0166	0.0168	0.3265	MR Egger	104.344	77	0.0208
					IVW	105.665	78	0.0202
UC		−0.0020	0.0215	0.9282	MR Egger	62.025	50	0.1184
					IVW	62.036	51	0.1384
Exploration cohort								
CDLI	PA	-3.34×10^{-5}	3.96×10^{-5}	0.4013	MR Egger	112.180	103	0.2520
					IVW	112.954	104	0.2579
CDSI		7.14×10^{-6}	3.65×10^{-5}	0.8454	MR Egger	96.325	109	0.8019
					IVW	96.363	110	0.8199
UE		-7.15×10^{-6}	3.25×10^{-5}	0.8261	MR Egger	76.222	92	0.8824
					IVW	76.271	93	0.8960
UI		-6.03×10^{-6}	4.07×10^{-5}	0.8826	MR Egger	111.021	85	0.0306
					IVW	111.049	86	0.0359
Reverse MR								
Discovery cohort								
PA	IBD	−0.01359	0.03288	0.69179	MR Egger	10.327	7	0.171
					IVW	10.578	8	0.2267
	CD	−0.01459	0.02579	0.58709	MR Egger	9.837	8	0.2767
					IVW	10.230	9	0.3322
	UC	−0.00480	0.02001	0.81592	MR Egger	13.457	9	0.14299
					IVW	13.543	10	0.1949
Replication cohort								
PA	IBD	0.00467	0.00913	0.62768	MR Egger	5.666	6	0.4616
					IVW	5.927	7	0.5483
	CD	−0.00083	0.01729	0.96307	MR Egger	12.937	6	0.04405
					IVW	12.942	7	0.07354
	UC	0.00545	0.01161	0.65553	MR Egger	4.231	6	0.64546
					IVW	4.451	7	0.7266
Exploration cohort								
PA	CDLI	−0.14460	0.06989	0.06540	MR Egger	5.807	10	0.8312
					IVW	10.087	11	0.5226
	CDSI	0.08020	0.06992	0.27808	MR Egger	11.986	10	0.2860
					IVW	13.563	11	0.2581
	UE	−0.00435	0.08888	0.96196	MR Egger	5.964	10	0.8183
					IVW	5.966	11	0.8756
	UI	−0.04215	0.07828	0.60204	MR Egger	9.372	10	0.4972
					IVW	9.662	11	0.5610

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *PA* Perianal abscess, *MR* Mendelian randomization, *IVW* inverse variance weighted, *OR* odds ratio, *CI* confidence interval, *CDLI* CD of large intestine, *CDSI* CD of small intestine, *UE* ulcerative enterocolitis, *UI* ulcerative ileocolitis

Table 4 Multivariate MR analysis results of inflammatory bowel disease and perianal abscess

exposure	outcome	NSNP	OR	OR_LCI	OR_UCI	*p*
Discovery cohort						
IBD	PA	36	1.207	1.098	1.327	0.0001
CD		27	1.156	1.066	1.254	0.0005
UC		19	1.143	1.034	1.265	0.0090
Replication cohort						
IBD	PA	60	1.22	1.103	1.348	0.0001
CD		46	1.117	1.034	1.206	0.0048
UC		38	1.143	1.038	1.259	0.0067

NSNP number of single nucleotide polymorphisms number, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *PA*: Perianal abscess, *MR* Mendelian randomization, *OR* odds ratio, *UCI* upper limit of the 95% confidence interval, *LCI* lower limit of the 95% confidence interval

as a PA risk modifier underscores the prognostic value of disease localization, supporting three clinical translation pathways: First, integration of IBD polygenic risk scores (PRS) into clinical practice could enhance risk stratification, where high genetic burden (such as PRS > 90th percentile) may justify intensified surveillance protocols for ileocolonic CD patients, such as biannual anorectal exams combined with fecal calprotectin monitoring - an approach aligned with ECCO guidelines recommending proactive monitoring in high-risk phenotypes [24]. Second, new-onset PA with clinical red flags (IBD family history, prodromal symptoms) should prompt expedited investigation. A stepwise diagnostic cascade using fecal immunochemical testing (FIT) followed by cross-sectional imaging (such as rapid pelvic MRI) is feasible within current practice, as endorsed by recent consensus for early IBD detection in symptomatic cohorts [25–27]. Third, our causal evidence strengthens existing recommendations to prioritize anti-TNF agents over step-up therapy in PA-complicated IBD, reflecting clinical trial data demonstrating superior fistula healing rates with early biologic intervention [28]. These strategies collectively advance precision management of IBD-associated perianal complications. While genetic risk profiling requires further validation for routine use, PA-triggered diagnostic pathways leverage widely accessible tools. Implementation challenges (such as primary care education, resource allocation) should be addressed through pilot studies.

PA is an IBD complication that might exacerbate the disease and impair a patient's quality of life. Specifically, severe PA might result in complex anal fistula and ultimately necessitate surgical intervention, making the management of IBD more challenging [29, 30]. Some previous observational studies have shown that the incidence of perianal lesions in CD patients worldwide ranges from 20 to 40% [31, 32]. PA is the most common type of perianal lesion of CD. Similar results were found in patients with UC [9, 33]. However, there are few studies on the causal relationship between IBD and PA. Our results support previous observational studies showing that PA is mainly associated with IBD, including CD and UC by bidirectional MR analysis. The causal relationship between IBD and PA may be confused by some potential factors such as BMI, diabetes mellitus (DM) and smoking. Some studies observed that smoking, the ascending BMI and DM could increase the risk of PA [6, 34, 35]. After adjustment of the mixing factors by MVMR, we found that IBD, including CD and UC may increase the risk of PA genetically, which further confirmed the genetic association between IBD and PA. An observational study showed that following adjustment for the potential confounding factors above, the risk of CD and UC was higher in the PA cohort compared to the control population. Subjects with diagnoses of CD or UC were pooled and the risk of IBD was found to be higher in the PA cohort compared to the control population [36]. This also supported the results of this study.

A prospective cohort study showed that ileocolic lesions were significantly elevated in patients with perianal lesions compared to those without perianal lesions in CD patients [37]. Multiple regression analyses further confirmed that ileocolic site was significantly and independently associated with a high incidence of perianal lesions compared to CD patients with colitis and ileum lesions [37]. In exploratory subgroup analyses, ulcerative ileocolitis showed a nominally significant genetic association with perianal disease ($p = 0.04$). While biologically plausible given ileocolonic involvement in CD pathogenesis, these findings should be interpreted with caution due to: marginal statistical significance, limited instrument numbers for site-specific subtypes, absence of multiple testing correction.These hypothesis-generating observations warrant replication in larger cohorts before clinical implications can be considered. In addition, studies in Asian populations have found similar conclusions [38, 39]. However, another study showed that colonic involvement was significantly associated with perianal lesions in CD patients [40]. In general, earlier studies have shown that PA can be influenced by genetic factors in IBD, such as *NOD2*/*CARD15*, *IBD5* (5q31), *ATG16L1* [41, 42]. In recent studies, novel perianal CD

related genes have been identified. Genes encoding extracellular matrix and scaffold proteins (*USH1C*, *HAS3*, *NDFIP2*, *TMCO7*), TNF pathway (*NUCB2* and *DAPK1*), and autophagy (*DAPK1*) may be involved in development of perianal CD [40, 42]. In conclusion, the disease range of CD may affect the development of PA and is closely related to genetic factors. However, further studies are needed to clarify the mechanism.

Our MR framework advances causal inference in PA-IBD relationships by circumventing confounding through robust genetic instrument selection (F-statistic > 10), with multivariable MR further adjusting for related confounders (BMI, smoking, DM) to isolate IBD-specific effects. However, key limitations temper clinical interpretability: (1) absence of PA subclassification (such as anatomical complexity grades) in GWAS data precludes precision phenotyping; (2) reliance on lifetime IBD incidence obscures dynamic PA risk modulation across disease activity states (quiescent or flare); (3) summary-level data restrict individual-level adjustment for endoscopic severity or immunomodulator use; (4) heterogeneous covariate definitions between FinnGen/UK Biobank necessitate categorical approximations, potentially attenuating adjustment fidelity. We explicitly qualify all non-primary findings as hypothesis-generating, requiring validation in deeply phenotyped cohorts with longitudinal activity indices. Crucially, we explicitly acknowledge a key limitation regarding the reverse MR analyses. Despite the adequate strength of the individual instruments used (F-statistic > 20), the statistical power of these analyses was substantially constrained by the relatively small number of independent SNPs available as instruments. Therefore, the non-significant results obtained in the reverse direction must be interpreted with caution and cannot be taken as definitive evidence ruling out a causal effect of PA on IBD. This limitation in power is a direct consequence of the sparse instrument set. To address this in future research, larger GWAS for PA are needed to identify more instruments. Furthermore, approaches like Bayesian Mendelian randomization could offer enhanced reliability for inference when instrument numbers are limited. The discussion now cautions against clinical application of exploratory subgroup associations absent replication, while emphasizing MR's unique capacity to deconvolute lifelong causal effects from transient clinical observations.

Conclusion

This MR study demonstrates that genetic predisposition to IBD exerts a unidirectional causal relationship with PA risk, supporting the integration of PA into risk-stratified surveillance protocols for IBD patients. In exploratory analyses, ileocolonic CD showed a nominal association with PA susceptibility. While these preliminary findings may inform future research directions, they require rigorous validation due to marginal statistical significance and inherent limitations in subtype MR power. If replicated, such associations could potentially advocate for: (1) enhanced anorectal examination frequency in CD patients with proximal disease localization, and (2) consideration of early anti-TNF therapies in PA-positive IBD cases to achieve deep remission targets. However, current evidence does not support immediate clinical implementation. While PA may serve as a sentinel manifestation of subclinical IBD in genetically predisposed populations, its diagnostic utility for de novo IBD detection requires validation through prospective studies with endoscopic phenotyping. These findings reposition PA not merely as a complication, but as a clinically actionable biomarker guiding precision monitoring in IBD management.

Abbreviations

CD	Crohn's disease
CI	Confidence interval
FIT	Fecal immunochemical testing
GWAS	Genome-Wide Association Studies
IBD	Iinflammatory bowel disease
ICD	International Classification of Diseases
IIBDGC	International Inflammatory Bowel Disease Genetics Consortium
IV	Instrument variables
IVW	Inverse variance weighted
MR	Mendelian randomization
MVMR	Multivariate Mendelian randomization
OR	Odds ratio
PA	Perianal abscess
PRS	Polygenic risk scores
SE	Standard error
SNP	Single-nucleotide polymorphism
UC	Ulcerative colitis
UKIBDGC	United Kingdom IBD Genetics Consortium

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Design and concept study: H.Z. Data collection and analysis: H.Z., Interpretation of data: H.Z. Drafting of the manuscript: H.Z., Critical revision and approval: H.Z., J.P.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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