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ORIGINAL RESEARCH

Celiac Disease as a Genetic Predisposing Factor for Dermatitis Herpetiformis: A Two-Sample Mendelian Randomization Analysis

Yani Su[1,*], Peng Xu[2,*], Ming Zhang[3,*], Pengfei Wen[2], Ke Xu[2], Jiale Xie[2], Xianjie Wan[2], Lin Liu[2], Zhi Yang[2], Mingyi Yang[2]

[1]Department of Radiotherapy, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shaanxi, People's Republic of China; [2]Department of Joint Surgery, HongHui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China; [3]Department of General Practice, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mingyi Yang; Zhi Yang, Email ymy25808@163.com; hhyy_yangzhi@163.com

Objective: Observational studies have consistently highlighted a robust clinical association between celiac disease (CD) and dermatitis herpetiformis (DH). Building on this foundation, the present study aims to investigate whether this observed relationship is underpinned by a causal genetic mechanism, providing insights into the potential hereditary basis of their connection.

Methods: This study employed bidirectional two-sample Mendelian randomization (MR) analysis to investigate the potential genetic causality between CD and DH, utilizing genome-wide association study (GWAS) summary data. To comprehensively examine the genetic relationship between CD and DH, we applied multiple MR methodologies. Furthermore, to enhance the robustness and credibility of our results, we conducted extensive sensitivity analyses.

Results: The fixed-effects inverse variance weighted (IVW) analysis revealed a significant positive genetic causal relationship between CD and DH (P = 0.001, odds ratio [OR] 95% confidence interval [CI]: 1.546 [1.195–1.999]). In contrast, no significant genetic causality was found in the reverse direction, from DH to CD (P = 0.113, OR 95% CI: 1.039 [0.991–1.090]). Notably, the MR analysis revealed no evidence of heterogeneity, further reinforcing the reliability of the fixed-effects IVW model. Additionally, sensitivity analyses confirmed the stability and robustness of the results, further validating the integrity of the conclusions drawn from the MR analysis.

Conclusion: The results of our study indicate that CD acts as a genetic susceptibility factor for the development of DH. Furthermore, the occurrence of DH in individuals with a history of CD appears to be attributed to a causal genetic relationship, suggesting that the genetic predisposition linked to CD may drive the manifestation of DH.

Keywords: celiac disease, dermatitis herpetiformis, mendelian randomization, causal, genetic

Introduction

Celiac disease (CD) is a chronic autoimmune condition triggered by the ingestion of gluten, a protein complex found in wheat, rye, and barley, and represents one of the most prevalent inflammatory disorders affecting the small intestine.[1,2] This disease is marked by characteristic mucosal damage and impaired nutrient absorption in genetically predisposed individuals. The pathological mechanism is linked to an immune response activated by dietary proteins rich in proline and glutamine, commonly referred to as "gluten".[3] Typically, CD manifests during early childhood, around the age of 2, although a secondary peak in diagnosis is observed in individuals around the age of 40.[4] The clinical presentation of CD predominantly stems from nutrient and vitamin malabsorption, which results in a spectrum of symptoms including abdominal pain, bloating, diarrhea, unintentional weight loss, anemia, edema, and musculoskeletal complaints such as bone or joint pain.[5] The severity of gastrointestinal symptoms can vary widely; some individuals may experience subtle

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or nonspecific complaints, while others remain asymptomatic for extended periods despite the presence of significant mucosal lesions. Furthermore, CD is not confined to gastrointestinal manifestations. Extraintestinal complications, including osteoporosis, dental enamel defects, or neurological involvement affecting either the peripheral or central nervous system, can also emerge.[6] These systemic manifestations often contribute to delayed or missed diagnoses, highlighting the importance of heightened clinical awareness.

The prevalence of clinically recognized CD varies geographically, ranging from 1 in 270 in Finland to 1 in 500 in North America.[7] Globally, CD affects 0.5% to 1.0% of the population, highlighting its significance as a widespread health concern.[1] The onset and progression of CD are influenced by genetic, environmental, and immune factors.[3] Genetic susceptibility, as evidenced by familial clustering and a 70%-75% concordance rate among monozygotic twins, plays a central role in CD pathogenesis.[3] Environmental triggers, such as gluten exposure, and immune dysregulation further complicate disease development. Untreated CD is associated with life-threatening long-term complications, including increased risk of secondary autoimmune conditions, small bowel adenocarcinoma, enteropathy-associated T-cell lymphoma, and other lymphoproliferative malignancies, such as non-Hodgkin lymphoma.[8–10] Epidemiological studies suggest individuals with CD have approximately double the cancer risk of the general population, underscoring the importance of early diagnosis.[8,10] Beyond health implications, CD imposes significant societal burden, with systemic manifestations involving multiple organ systems. Both genetic and environmental factors are crucial to its etiology, emphasizing the need for ongoing research and public health initiatives focused on prevention and early detection.[5]

Dermatitis herpetiformis (DH), a cutaneous manifestation of CD, is an autoimmune disorder marked by intensely pruritic, blistering eruptions, typically on extensor surfaces like elbows, knees, and buttocks.[11] The rash is polymorphic, including blisters, erythematous papules, and plaques, but severe itching and scratching often lead to excoriations, crusting, and post-inflammatory hyperpigmentation, obscuring primary lesions.[12] DH and CD share genetic predisposition, small intestinal mucosal changes, and autoimmune responses involving antibodies against tissue transglutaminase, highlighting their shared pathophysiology.[13] CD is often diagnosed in childhood, whereas DH typically presents around age 50, affecting adults more than children, with men showing slightly higher susceptibility.[12,13] DH prevalence varies, reaching 75 cases per 100,000 in some populations, with 13% of CD patients manifesting DH.[14,15] Incidence rates are 2.7 per 100,000 annually in Finland and 0.8 per 100,000 in the UK.[13–15] A key diagnostic feature is immunoglobulin A (IgA) deposits in the papillary dermis, identifiable by direct immunofluorescence microscopy, aiding in differentiation from other dermatological conditions.[12] Despite a nearly fourfold increase in CD prevalence, DH incidence has declined, likely due to improved detection of asymptomatic cases through serological screening.[14,15] The factors determining why only some individuals with undiagnosed or untreated CD develop DH remain unclear. The deposition of IgA and the cutaneous manifestations likely involve complex interactions between genetic, immune, and environmental factors. Investigating the genetic basis of the CD-DH relationship could provide insights into their shared and divergent pathways.

With the advancement of genome-wide association studies (GWAS), Mendelian randomization (MR) has become a powerful analytical tool in epidemiology and public health for causal inference. MR uses genetic variants, particularly single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to infer causal relationships between exposures and outcomes.[16] Based on Mendel's laws of inheritance, MR reduces confounding and reverse causation biases, offering an advantage over traditional observational studies. By analyzing associations between genetic instruments linked to exposures and outcomes, MR minimizes the impact of environmental and lifestyle factors and establishes causal directionality.[17] This ability to infer causation aids in understanding disease etiology, identifying modifiable risk factors, and guiding public health and clinical decisions. Recent applications of MR have expanded, demonstrating its utility in identifying genetic causal relationships across various diseases.[18,19] In this study, we employed a bidirectional two-sample MR approach to examine the genetic causal relationship between CD and DH, aiming to clarify their association and inform clinical and preventive strategies.

Materials and Methods

Data Source

The IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) is an open-source platform maintained by the research team of the University of Edinburgh in the UK, which is mainly used to provide public data related to GWAS. The GWAS

summary data for CD analyzed in this study were obtained from the IEU OpenGWAS database. The dataset comprises 15,283 participants, including 4,533 cases and 10,750 controls, and encompasses a total of 523,399 SNP loci. The cohort included both male and female participants, all the participants are of European descent. Genotyping was conducted using the Illumina GoldenGate BeadXpress assays at multiple locations, including London, Hinxton, and Groningen. Imputation of genotypes for samples initially genotyped on the Hap300 platform was performed using BEAGLE software, employing CEU, TSI, MEX, and GIH reference panels from HapMap3.[20] The FinnGen database (https://www.finngen.fi/) is a large-scale genomic data resource jointly established by several universities, research institutions and hospitals in Finland. Its purpose is to explore the relationships between genetic factors and diseases, as well as health characteristics, through GWAS. For DH, GWAS summary data were sourced from the FinnGen consortium. This dataset includes 218,344 individuals, of whom 278 were identified as cases and 218,066 as controls, covering a comprehensive 16,380,466 SNP loci. Both male and female participants were included in the study, and all participants were of European descent. And DH cases were classified based on the M13 code from the International Classification of Diseases, 10th Edition (ICD-10). Genotyping utilized Illumina and Affymetrix chip arrays, supplied by Illumina Inc. (San Diego, California) and Thermo Fisher Scientific Inc. (Santa Clara, California, USA). Additional details concerning the dataset can be found on the FinnGen consortium's official website. The analyzed GWAS summary data are publicly available and derived from European populations, thus precluding the necessity for ethical approval or informed consent. A comprehensive description of the data utilized is provided in Supplementary Table 1.

IVs Selection

Throughout this analysis, we strictly adhered to the core assumptions of MR to ensure the validity of our findings: 1) IVs must demonstrate a strong and significant association with the exposure factors; 2) IVs should not be associated with the outcome or confounding variables; and 3) the effect of IVs on the outcome should occur exclusively through the exposure factors. To enhance the reliability of the genetic causal inferences, we employed a series of stringent quality control measures during the IV selection process. First, IVs were required to exhibit a robust association with the exposure factors ($P < 5 \times 10^{-8}$, F-statistic > 10), with the F-statistic calculated as $F = R^2(N-K-1)/K(1-R^2)$.[21] In instances where the number of IVs meeting this criterion was insufficient, adjustments to the p-value thresholds were guided by relevant literature. Second, to address potential biases arising from linkage disequilibrium (LD) between SNPs, we applied an LD threshold of $r^2 < 0.001$ within a 10,000-kb genomic window.[22] Third, in cases where target SNPs were unavailable in the summary GWAS data, proxy SNPs were identified using LDlink online platform.[23] Fourth, we ensured that the selected IVs were independent of the outcome, applying the same significance threshold ($P < 5 \times 10^{-8}$) as for exposure factors. Fifth, to control for potential confounding effects, SNPs associated with confounders were excluded. Confounders for forward MR analysis included factors such as gluten diets and iodide, which are linked to DH.[12,24] For reverse MR analysis, confounders included gluten diets, vitamin D deficiency, and gastrointestinal infections, known to be associated with CD.[25] Relevant confounding SNPs were identified and excluded using data from the GWAS Catalog database. Lastly, palindromic SNPs with intermediate allele frequencies were excluded to avoid strand ambiguity, ensuring alignment between the alleles associated with exposure and those linked to outcomes.[26]

MR Analysis

To investigate the genetic causal relationship between CD and DH, we employed a comprehensive array of MR methods. Specifically, eight distinct MR approaches were utilized: MR Egger, random-effects inverse variance weighted (IVW), weighted median, simple mode, weighted mode, maximum likelihood, penalized weighted median, and fixed-effects IVW. Among these, IVW was designated as the primary analytical framework. In cases where results from other methods diverged from those of the IVW analysis, with IVW serving as the reference standard in such cases. The IVW method can be further stratified into random-effects and fixed-effects models, depending on the heterogeneity detected in the data. When significant heterogeneity was present, the random-effects IVW model was prioritized to account for variability, while the fixed-effects IVW model was applied under conditions of lack heterogeneity. Data analysis was performed using R software (version 4.1.2), leveraging the "TwoSampleMR" package for conducting two-sample MR analyses. Statistical significance was determined using a P-value threshold of < 0.05, indicating a robust genetic causal

relationship between exposure and outcome. Additionally, an odds ratio (OR) greater than 1 was indicative of a positive causal relationship, whereas an OR less than 1 suggested a negative causal association.

Sensitivity Analysis

To ensure the robustness and reliability of the findings derived from MR analysis, we conducted a series of rigorous sensitivity analyses. Heterogeneity in the MR estimates was evaluated using two distinct approaches: Cochran's Q statistic applied to the MR-IVW method and Rucker's Q statistic used within the MR-Egger framework.[27] To further assess horizontal pleiotropy, we employed the MR-Egger intercept test alongside the global test provided by the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) framework.[19] Radial IVW methods were utilized to visually detect potential outliers,[28] while the distortion test embedded within MR-PRESSO was applied to systematically identify outlying variants influencing MR estimates.[19] If there are outliers, a second round of MR analysis is performed after removing them. Additionally, a leave-one-out analysis was conducted to evaluate the influence of individual SNPs on the overall MR results, ensuring that no single SNP disproportionately impacted the findings.[29] Lastly, the Shapiro–Wilk normality test, incorporated in the MR Robust Adjusted Profile Score (MR-RAPS) method, was employed to confirm that the MR estimates followed a normal distribution, further validating the statistical properties of the results.[28] Criteria for heterogeneity, pleiotropy, and distribution assessments were standardized, with P-values > 0.05 indicating the absence of significant heterogeneity and horizontal pleiotropy, as well as compliance with the assumption of normality. These comprehensive analyses reinforced the reliability of the genetic causal inferences in the study.

Results

Genetic Causality Between CD to DH (Forward MR Analysis)

Through the application of a rigorous significance threshold ($P < 5 \times 10^{-8}$) and ensuring the F-statistic exceeded the critical value of 10, we identified a total of 12 SNPs that demonstrated a significant association with CD. Importantly, all 12 SNPs were cross-referenced and confirmed in the GWAS summary data for DH, with no proxy SNPs detected. These genetic variants were also assessed for associations with DH and other potential confounding factors, none of which were identified as significant. Further scrutiny revealed that none of the selected SNPs exhibited palindromic properties, ensuring the integrity of the subsequent instrumental variable analysis. As a result, the final set comprised 12 SNPs deemed suitable as IVs for robust evaluations of genetic causality between CD and DH (Supplementary Table 2).

The random-effects IVW analysis revealed a significant positive genetic causal relationship between CD and DH (P = 0.001, OR 95% confidence interval [CI]: 1.546 [1.195–1.999]). Consistent results were obtained using fixed-effects IVW analysis, which also identified a significant positive genetic causal association (P = 0.001, OR 95% CI: 1.546 [1.195-–1.999]). Among the six additional MR methods, only MR Egger and the weighted mode indicated no evidence of a causal relationship, while the remaining four methods provided support for a positive genetic causal relationship between CD and DH (Figures 1 and 2A). Cochran's Q statistic from the MR-IVW method and Rucker's Q statistic from MR Egger suggested no significant heterogeneity (P > 0.05). Additionally, assessments for horizontal pleiotropy, including the intercept test from MR Egger and the global test from MR-PRESSO, found no evidence of pleiotropy (P > 0.05) (Table 1). Radial MR evaluations, conducted through IVW and MR Egger delineations, confirmed the absence of outliers in the genetic instrumental variables used for MR analyses (Figures 2B). Moreover, MR-PRESSO's distortion test detected no outlier variants (Table 1). The robustness of these findings was further supported by leave-one-out analysis, which demonstrated that no individual SNP unduly influenced the observed positive genetic causal relationship between CD and DH (Figure 2C). Furthermore, MR-RAPS analysis confirmed the normality of the causal estimate distribution based on the Shapiro–Wilk test (P > 0.05) (Figure 2D and Table 1). In summary, both random-effects and fixed-effects IVW analyses robustly demonstrate a significant positive genetic causal relationship between CD and DH. The comprehensive sensitivity analyses, showing no evidence of heterogeneity, horizontal pleiotropy, or undue SNP influence, confirm the reliability of these findings. Based on these results, we validate the fixed-effects IVW analysis as a strong indicator of a positive genetic causal relationship between CD and DH.

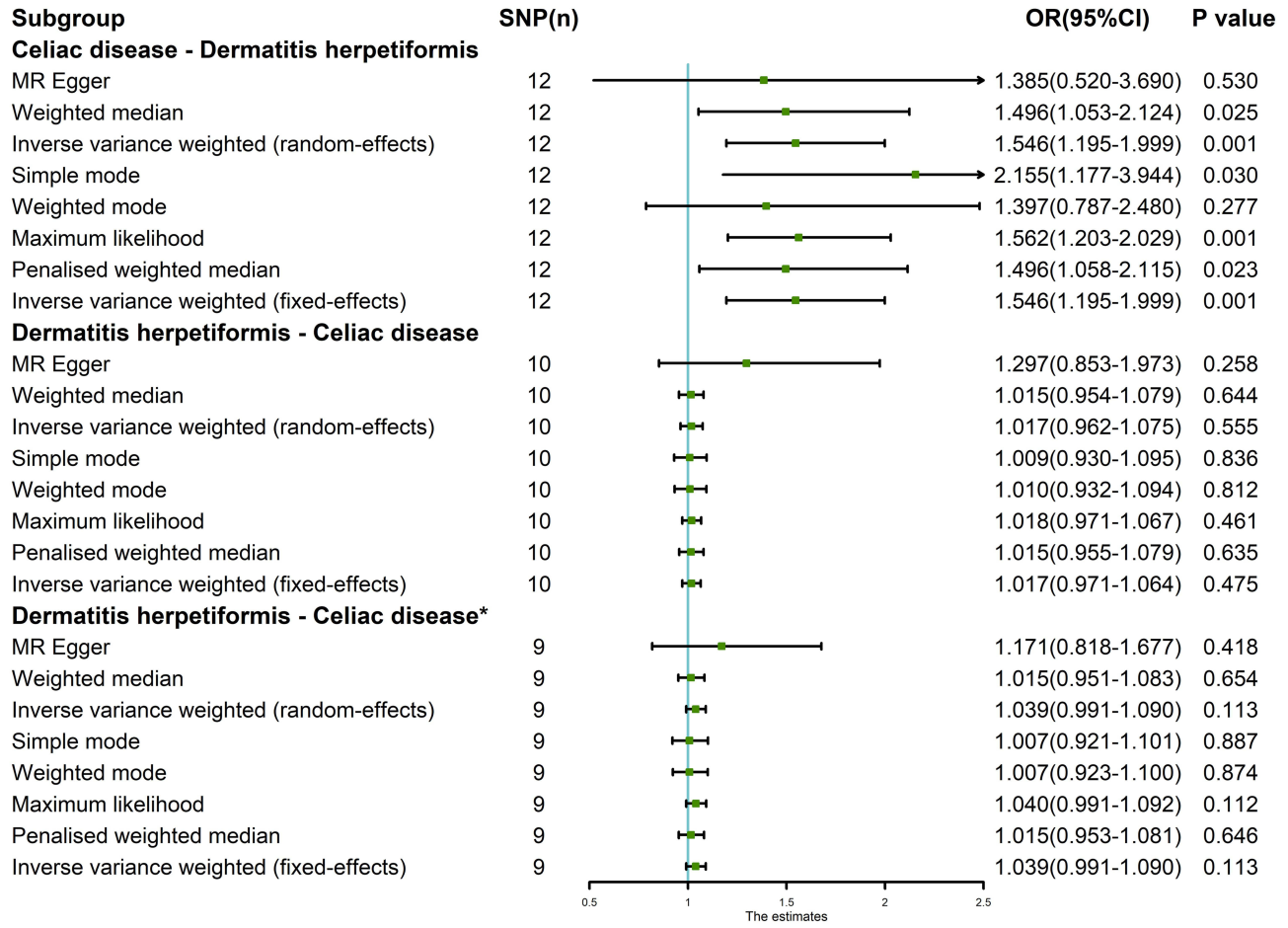

Figure 1 Genetic causal analysis of the relationship between celiac disease and dermatitis herpetiformis was conducted using eight distinct methods: MR Egger, random-effects IVW, weighted median, simple mode, weighted mode, maximum likelihood, penalized weighted median, and fixed-effects IVW. *Second round of genetic causal assessment of dermatitis herpetiformis to celiac disease after removing an outlier.

Genetic Causality Between DH to CD (Reverse MR Analysis)

Given the stringent significance threshold of $P < 5 \times 10^{-8}$, the number of SNPs identified for MR analysis was insufficient. To address this limitation, we relaxed the significance threshold to $P < 6 \times 10^{-5}$, following established methodologies.[30,31] This adjustment resulted in the identification of 86 SNPs significantly associated with DH, all meeting the criteria of $P < 6 \times 10^{-5}$ and demonstrating F-statistics greater than 10. Subsequent matching of these SNPs to the GWAS summary data for CD yielded 13 SNPs suitable for further analysis. A thorough examination revealed no proxy SNPs and no associations of these SNPs with either CD or potential confounding factors. Additionally, three palindromic SNPs (rs1012753, rs12515176, rs312026) were excluded to ensure the robustness of the analysis. As a result, a final set of 10 SNPs was identified and selected as IVs for subsequent causal inference studies (Supplementary Table 3).

The random-effects IVW analysis revealed no significant evidence of a genetic causal relationship between DH and CD (P = 0.555, OR 95% CI: 1.017 [0.962–1.075]). Similarly, the fixed-effects IVW analysis did not identify a genetic causal association between these conditions (P = 0.475, OR 95% CI: 1.017 [0.971–1.064]). These findings were consistent across six additional MR methods, further corroborating the lack of genetic causality between DH and CD (Figures 1 and 3A). Assessments of heterogeneity using Cochran's Q statistic (IVW) and Rucker's Q statistic (MR-Egger) demonstrated no significant heterogeneity (P > 0.05). While MR-Egger's intercept test showed no indication of horizontal pleiotropy (P > 0.05), the global test from MR-PRESSO did detect evidence of horizontal pleiotropy (P < 0.05) (Table 1). Detailed examination using radial MR methods (IVW and MR-Egger) identified one outlier (Figures 3B), which was confirmed by MR-PRESSO's distortion test as SNP rs7674113 (Table 1). Despite these findings, leave-one-

Table 1 Sensitivity Analysis of the MR Analysis Results of Celiac Disease and Dermatitis Herpetiformis

Exposure	Outcome	Heterogeneity		Pleiotropy		Outliers	Normal Distribution
		Cochran's Q test (IVW)	Rucker's Q test (MR-Egger)	Egger Intercept (MR-Egger)	Global test (MR-PRESSO)	Distortion test (MR-PRESSO)	Shapiro–Wilk Normality test (MR-RAPS)
		P value	P value	P value	P value	Number	P value
Celiac disease	Dermatitis herpetiformis	0.665	0.582	0.824	0.692	0	0.142
Dermatitis herpetiformis	Celiac disease	0.153	0.182	0.284	0.036	1	0.695
Dermatitis herpetiformis	Celiac disease *	0.844	0.812	0.533	0.367	0	0.223

Notes: *Second round of genetic causal assessment of dermatitis herpetiformis to celiac disease after removing an outlier.
Abbreviations: IVW, inverse variance weighted; MR-PRESSO, R Pleiotropy Residual Sum and Outlier; MR-RAPS, MR Robust Adjusted Profile Score.

out analysis revealed that the results of the reverse MR analysis between DH and CD were not substantially influenced by any single SNP, supporting the overall stability of the analysis (Figure 3C). Additionally, the Shapiro–Wilk normality test within the MR-RAPS framework indicated that the causal effect estimates followed a normal distribution, ensuring the validity of the analysis assumptions (Figure 3D and Table 1).

Following the removal of an outlier, a second round of MR analysis was conducted. The random-effects IVW analysis revealed no significant genetic causal relationship between DH and celiac CD (P = 0.113, OR 95% CI: 1.039 [0.991–1.090]). Similarly, the fixed-effects IVW analysis yielded consistent results, showing no evidence of a genetic causal association between these traits (P = 0.113, OR 95% CI: 1.039 [0.991–1.090]). Six additional MR methods provided results consistent with both the random- and fixed-effects IVW analyses, further confirming the absence of a causal relationship (Figures 1 and 4A). Tests for heterogeneity, including Cochran's Q statistic (IVW) and Rucker's Q statistic (MR-Egger), indicated no significant heterogeneity (P > 0.05). Furthermore, no evidence of horizontal pleiotropy was detected through either MR-Egger's intercept test or MR-PRESSO's global test (P > 0.05) (Table 1). Detailed examination using the radial MR radial method (IVW and MR-Egger) demonstrated the absence of outliers in the genetic analyses between DH and CD (Figures 4B), a finding corroborated by MR-PRESSO's distortion test, which also identified no outliers (Table 1). Leave-one-out sensitivity analysis confirmed the stability of the reverse MR results, showing that no single SNP significantly influenced the findings (Figure 4C). The Shapiro–Wilk normality test conducted within the MR-RAPS framework further validated that the genetic causal effect estimates adhered to a normal distribution, supporting the robustness of the analysis (Figure 4D and Table 1). In summary, both random- and fixed-effects IVW analyses consistently demonstrated no significant genetic causal relationship between DH and CD. The comprehensive sensitivity analyses, showing no heterogeneity, pleiotropy, or undue SNP influence, underscore the reliability of these findings. Based on the fixed-effects IVW analysis and the absence of confounding factors, the results strongly support the conclusion that there is no genetic causal association between DH and CD.

Discussion

We conducted a bidirectional two-sample MR analysis to investigate the potential genetic causality between CD and DH. Our findings demonstrate robust evidence supporting a positive genetic causal association, indicating that genetic predisposition may play a pivotal role in the pathophysiology of CD-induced DH. This highlights the influence of genetic determinants in shaping the underlying mechanisms through which CD contributes to the development of DH. Conversely, results from the reverse MR analysis did not reveal any significant genetic causal effect of DH on CD, either in a positive or negative direction. This asymmetry reinforces the predominant influence of CD on DH while minimizing

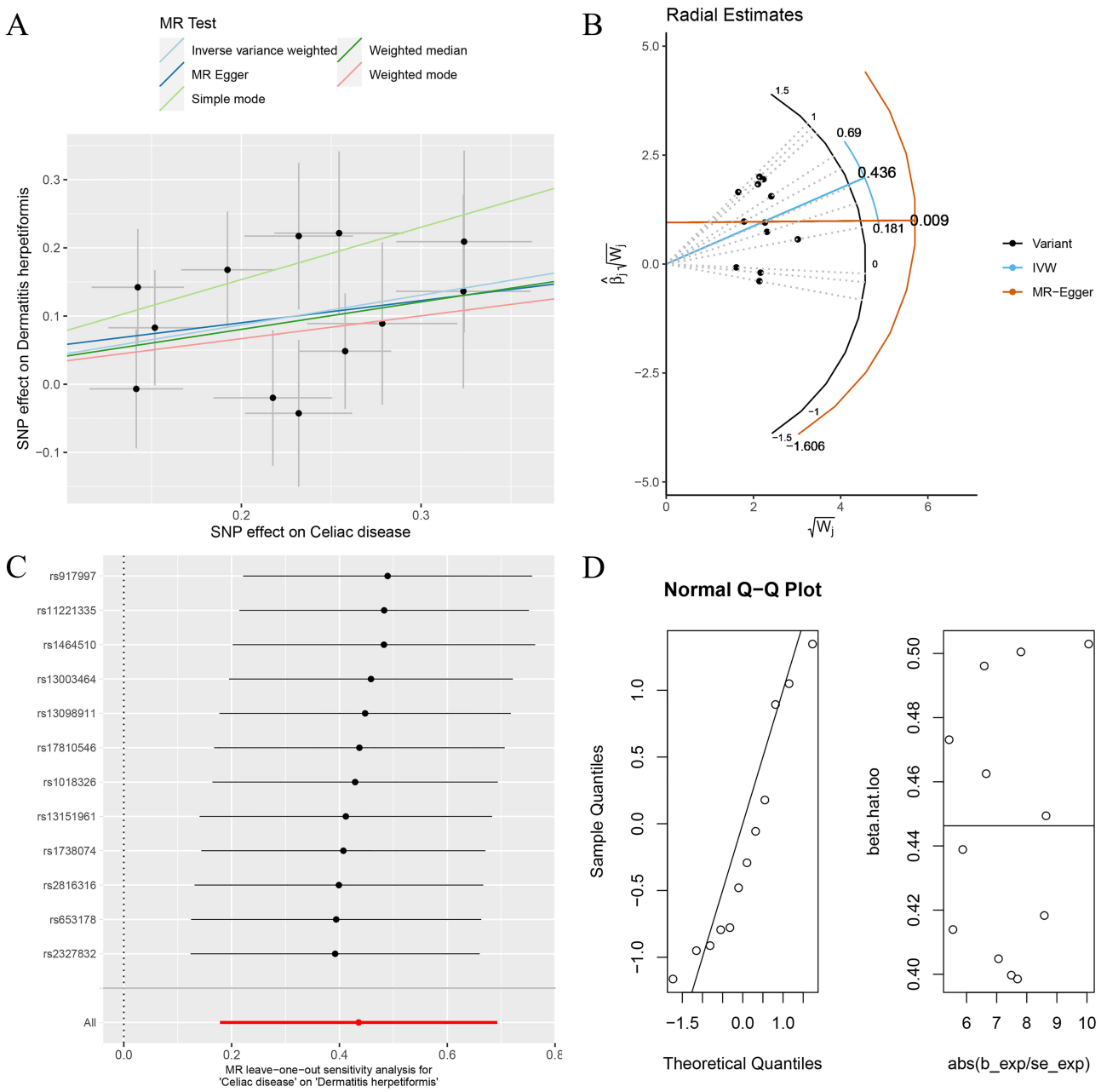

Figure 2 Genetic causal assessment of celiac disease to dermatitis herpetiformis. (**A**) scatter plot; (**B**) radial plot; (**C**) leave-one-out analysis; (**D**) normal distribution.

the likelihood of reciprocal causation. Together, these results offer valuable genetic insights into the intricate interplay between CD and DH, advancing our understanding of their shared pathogenesis. Furthermore, these findings hold clinical relevance, potentially guiding more targeted prevention and therapeutic strategies aimed at mitigating DH in the context of CD.

DH is a chronic inflammatory skin disorder traditionally regarded as a specific dermatological manifestation of CD. Both conditions predominantly occur in individuals with gluten sensitivity and demonstrate significant clinical improvement following adherence to a strict gluten-free diet. However, observations from studies on Japanese and Chinese populations indicate that DH can, in some cases, manifest independently of CD.[32–34] These findings have prompted speculation regarding the existence of a subset of DH that may not be attributable to gluten sensitivity, despite exhibiting clinicopathological features typically associated with gluten-related DH. The majority of individuals diagnosed with DH

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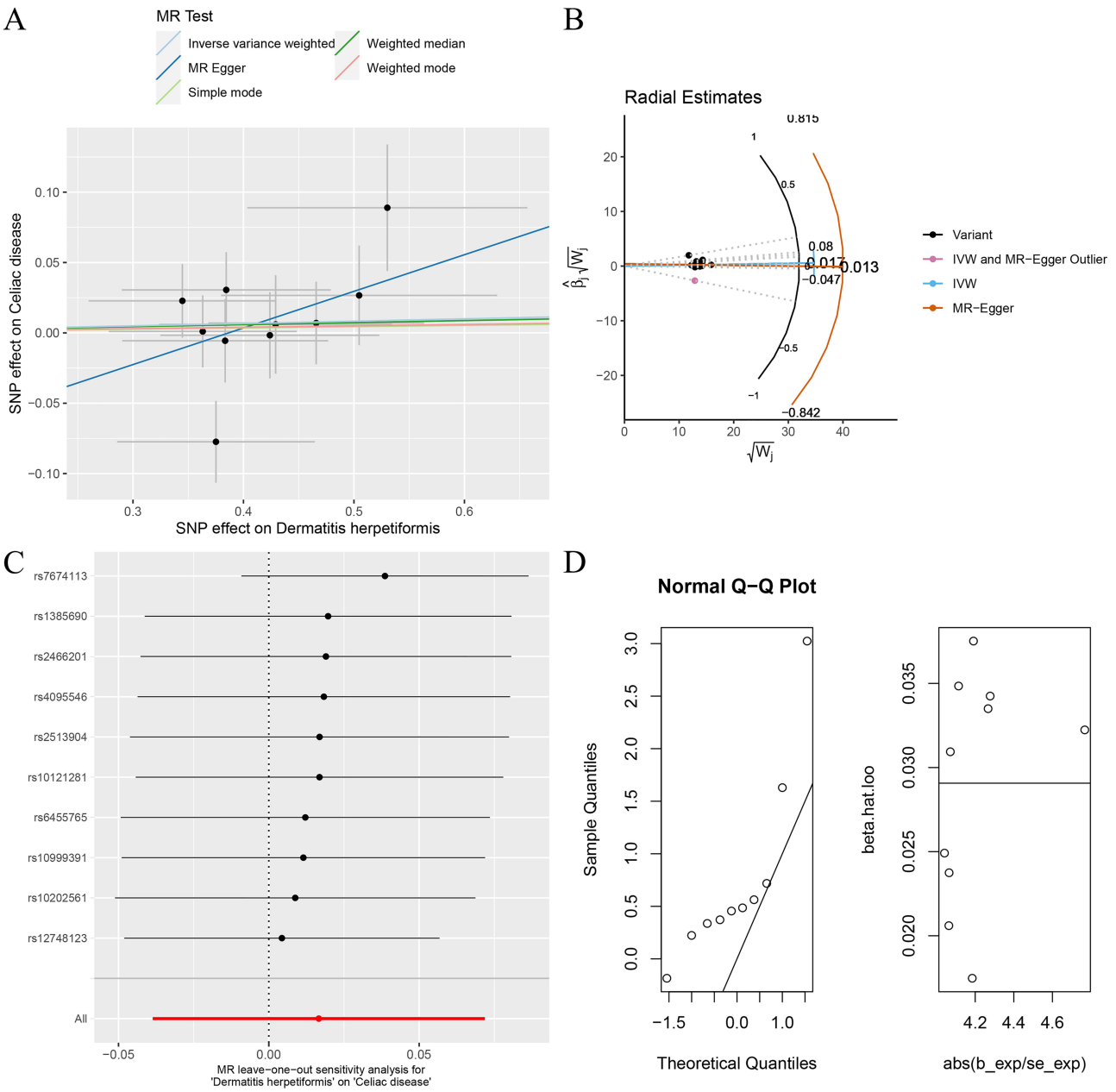

Figure 3 Genetic causal assessment of dermatitis herpetiformis to celiac disease. (**A**) scatter plot; (**B**) radial plot; (**C**) leave-one-out analysis; (**D**) normal distribution.

present with characteristic CD-associated changes in small intestinal biopsies, including varying degrees of villus atrophy, increased intraepithelial lymphocyte counts, and elevated circulating autoantibodies targeting tissue transglutaminase (tTG). Notably, some researchers have reported a declining incidence of DH, potentially attributable to the earlier diagnosis and management of CD, thereby reducing the timeframe required for DH to develop.[24] Contrasting evidence from Japanese literature underscores a distinctive pattern in DH cases among Japanese patients. Unlike the majority of cases observed in Western populations, these patients often lack the hallmark intestinal involvement and fail to exhibit typical serological markers of CD, such as anti-tTG antibodies. Intriguingly, similar atypical presentations have also been documented in some Caucasian patients, adding complexity to the accurate diagnosis and understanding of DH.[24] These findings underscore the heterogeneity of the relationship between CD and DH, suggesting potential differences in disease pathogenesis and manifestation across diverse ethnic and genetic backgrounds.

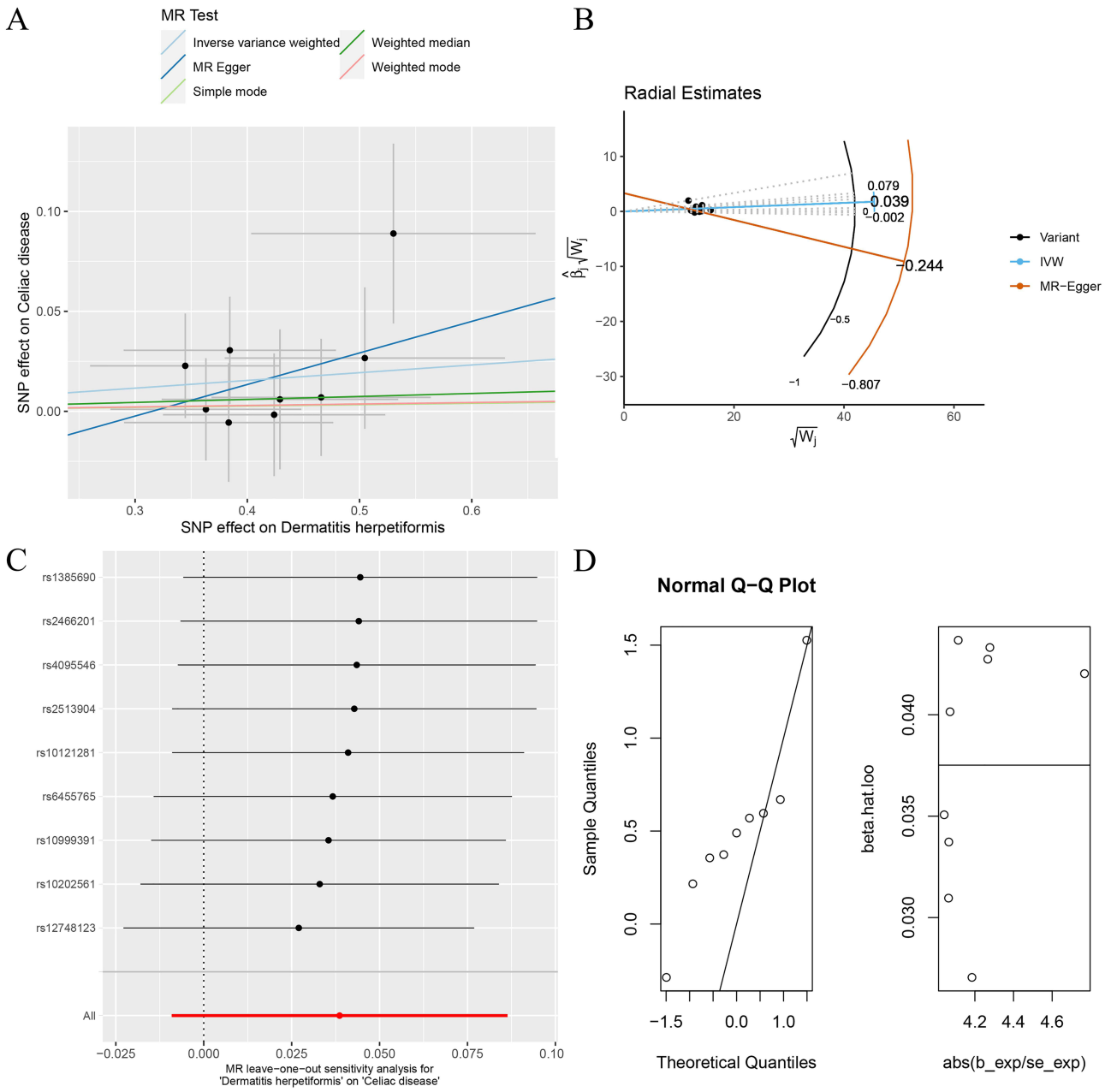

Figure 4 Second round of genetic causal assessment of dermatitis herpetiformis to celiac disease after removing an outlier. (**A**) scatter plot; (**B**) radial plot; (**C**) leave-one-out analysis; (**D**) normal distribution.

Nearly all patients with DH have an underlying diagnosis of CD, which places them at an elevated risk for developing non-Hodgkin's lymphoma and other gastrointestinal malignancies.[35] Nevertheless, unlike CD, DH does not appear to be associated with increased overall mortality.[36,37] A large-scale population-based study involving 476 individuals with DH revealed a lower all-cause mortality rate compared to the general population, with a notably reduced mortality from cerebrovascular diseases. While an increased risk of mortality due to non-Hodgkin's lymphoma was observed, this risk was confined to the initial five years post-diagnosis and diminished thereafter. Interestingly, patients with DH exhibited healthier profiles compared to controls, with lower prevalence rates of hypercholesterolemia and tobacco use.[38] It has been hypothesized that smoking may exert a protective effect against DH by inhibiting natural killer (NK) lymphocyte activity and suppressing intestinal IgA secretion, though this potential mechanism warrants further investigation.[24,39] Additionally, socioeconomic factors may influence these outcomes. Evidence suggests that a higher proportion of DH

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patients belong to higher social strata, which correlates with better health behaviors, access to healthcare, and living conditions. This association may partially explain the reduced mortality observed in DH, reflecting the multifaceted benefits associated with elevated socioeconomic status and its impact on overall quality of life.[39]

Epidemiological studies indicate that approximately 5–10% of individuals diagnosed with DH have first-degree relatives who also present with DH or CD, underscoring the significant contribution of genetic factors to disease susceptibility.[24] Genetic associations between DH and specific HLA Class I and Class II molecules, such as HLA A1, B8, DR3, and DPB1, have been well-documented.[24] Among these, the strongest correlations are observed in HLA-DQ2 and HLA-DQ8. Approximately 85% of patients with DH express the HLA-DQ2 haplotype, which consists of the DQA10501 and DQB102 alleles, while 15% exhibit HLA-DQ8, defined by the DQA103 and DQB10302 alleles.[24] Both haplotypes, located on chromosome 6, are pivotal for gluten antigen presentation. HLA-DQ2 and DQ8 molecules are critically involved in the immune response to gluten, particularly its antigenic component glutenin, which is implicated in DH and CD pathogenesis.[24,40] In CD, tTG enzymatically deamidates glutenin, creating epitopes with enhanced binding affinity for HLA-DQ2 and DQ8 on antigen-presenting cells. This interaction activates an adaptive immune response against glutenin and tTG, further triggering innate immune mechanisms. Consequently, characteristic histopathological changes, such as reversible villous atrophy, crypt hyperplasia in the small intestinal mucosa, and intraepithelial lymphocytosis, become evident in CD.[41,42] Nearly all DH patients exhibit subclinical or mild CD, supporting the hypothesis that DH represents a specific cutaneous manifestation of gluten sensitivity, linked to the same genetic predisposition seen in CD.[43] Further studies substantiate the causative interplay between HLA-DQ haplotypes and dietary gluten in DH. Unlike other autoimmune blistering skin conditions, passive transfer of DH sera into thymectomized mice grafted with human skin fails to reproduce DH-like lesions. However, approximately 17% of HLA-DQ8-positive autoimmune-susceptible nodular mice exposed to gluten through regular intraperitoneal injections develop DH lesions. These findings provide compelling evidence that DH arises uniquely in the context of a dual requirement: HLA-DQ-mediated antigen presentation and environmental exposure to gluten.[44,45]

The pathophysiology of DH is thought to involve intricate interactions among autoimmune mechanisms, genetic predispositions, and environmental influences, with HLA susceptibility playing a central role.[46] Evidence from previous studies highlights the substantial contribution of genetic factors to DH pathogenesis. While DH has predominantly been regarded as a specific cutaneous manifestation of CD, some reports suggest that DH may, in certain cases, occur independently of CD. This raises questions about the precise nature of their relationship. Although significant overlap exists in the genetic underpinnings of CD and DH—most notably within the HLA-DQ2 and HLA-DQ8 haplotypes—it remains unclear whether their shared genetic basis directly translates into a causal relationship. In this study, we employed a suite of MR analysis techniques to disentangle the genetic causality between CD and DH. MR analysis, which leverages genetic variants as instrumental variables, offers a robust framework to infer causal relationships at the heritable level while minimizing confounding by environmental factors. Our findings provide strong evidence that CD acts as a genetic predisposing factor for DH, suggesting that the pathogenesis of DH is, at least in part, driven by genetic determinants associated with CD. These results not only confirm the genetic interdependence of the two conditions but also shed light on their complex etiological linkage, offering valuable insights for future research and potential therapeutic interventions.

This study is not without limitations, which should be considered when interpreting the findings. First, the sample population is exclusively of European descent. As a result, caution is warranted when extrapolating these results to other ethnic groups or populations with different genetic and environmental backgrounds. Future research involving more diverse cohorts is essential to assess the generalizability and broader applicability of these findings. Second, the MR analysis employed in this study relied on a relatively limited number of IVs. This constraint may reduce the robustness of causal inference, as fewer IVs could lead to less precise estimates and reduced statistical power. While the selected IVs provide valuable preliminary insights, incorporating a more extensive set of robust genetic instruments in future analyses would likely enhance the reliability, accuracy, and resolution of causal effect estimates. Addressing these limitations through expanded datasets and refined methodologies will be critical to strengthening the validity of the conclusions and deepening our understanding of the genetic interplay underlying the studied associations.

Conclusion

This study investigates the genetic causal relationship between CD and DH. By employing a comprehensive bidirectional two-sample MR analysis, we provide robust evidence supporting a significant genetic causal association between these two conditions. Our findings strongly indicate that CD serves as a genetic predisposing factor for DH, suggesting that the manifestation of DH in individuals with a history of CD may be attributable to a direct causal relationship at the genetic level. The pathogenesis of DH is multifactorial, involving a complex interplay between genetic predisposition and environmental influences. While this study offers valuable insights into the genetic contributions to DH development, it also highlights the need for further research at other biological and environmental levels to unravel the intricate mechanisms linking CD and DH. Investigating these interactions may provide deeper insights into disease progression and comorbidity. By offering detailed genetic insights into the relationship between CD and DH, this study seeks to establish a foundation for more integrated and targeted clinical approaches. Future studies expanding upon these findings may contribute to the development of personalized therapeutic strategies and more effective management frameworks for individuals affected by these interrelated conditions.

Data Sharing Statement

This study utilized publicly available datasets, which were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) and FinnGen consortium (https://www.finngen.fi/).

Ethics Approval

The design and implementation of this study followed the relevant regulations and ethical guidelines of China. According to Article 32 of the "Ethical Review Measures for Human Life Sciences and Medical Research" jointly issued by relevant Chinese departments on February 18, 2023, the following two types of studies can be exempted from ethical review: (1): Non-intrusive observational studies conducted in public places, and those that do not involve the collection of private behaviors and information that cannot identify individual identities; (2): Studies using legally available database data or information collected through anonymous methods, and those that cannot be traced back to specific individuals and will not pose any risks to the subjects. After assessment, this study falls under the circumstances stipulated in the second item of the above-mentioned provisions. Therefore, this study is exempt from the review and approval of the institutional ethics committee.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors of this article declare that they have no conflicts of interest to disclose.

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