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ORIGINAL RESEARCH

Celiac Disease and Skin Diseases: A Bidirectional Mendelian Randomization Study

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Background: Research as shown that celiac disease (CD) is associated with skin diseases, but their causality remains unclear. Therefore, this Mendelian randomization (MR) study evaluated the causality between CD and skin diseases.

Methods: Bidirectional MR analysis was performed on single nucleotide polymorphism (SNP) candidates identified from genome-wide association study (GWAS) datasets using inverse variance weighted (IVW), weighted median, MR-egger, weighted mode and simple mode. Multivariate MR (MVMR) analysis was subsequently conducted by adjusting for BMI, smoking, and alcohol use. Result reliability was assessed by horizontal pleiotropy and heterogeneity testing.

Results: IVW analysis revealed that CD increased the risk of atopic dermatitis (OR = 1.042, 95% CI: 1.018–1.067, $P = 5.75 \times 10^{-4}$) and cellulitis (OR = 1.026, 95% CI: 1.006–1.046, $P = 9.18 \times 10^{-3}$). Additionally, psoriasis had a suggestive association with CD (OR=0.836, 95% CI: 0.710–0.983, $P = 0.031$). MVMR analysis demonstrated that CD had a direct effect on atopic dermatitis and cellulitis.

Conclusion: CD contributes to higher risks of atopic dermatitis and cellulitis. Additionally, psoriasis is suggestively associated with CD. Nonetheless, further research is warranted to confirm these findings and to elucidate the underlying mechanisms.

Keywords: celiac disease, skin diseases, causality, Mendelian randomization

Introduction

Celiac disease (CD) is an autoimmune disease in which gluten ingestion triggers chronic inflammation of the small intestine in genetically susceptible individuals.[1,2] Patients with CD often present with recurrent abdominal pain, diarrhea, abdominal distension, and other gastrointestinal symptoms as a consequence of intestinal mucosal damage. These symptoms in turn lead to malnutrition, anemia and joint pain, which seriously impact quality of life and health.[3,4] Recent advancements in serology, histopathology and genetic testing has increased the detection rate of CD.[5] A clinical study by Lebwohl et al showed that CD patients have an elevated and persistent risk of skin diseases compared to healthy individuals.[6]

Skin is the human organ with the largest surface area, and its health directly impacts quality of life. Common skin diseases include atopic dermatitis, urticaria, psoriasis, cellulitis, and pruritus. Recent studies have revealed that these skin diseases may potentially be linked to CD. A meta-analysis showed that patients with atopic dermatitis have significantly higher prevalence of CD compared to healthy individuals.[7] Conversely, a high prevalence of atopic dermatitis has also been observed in a patient population with CD.[8] Follow-up data from Ludvigsson et al indicated that individuals with CD or genetic susceptibility to the condition had substantially elevated risks of developing urticaria.[9] The bidirectional meta-analysis by Acharya et al reported psoriasis and CD as mutual risk factors.[10] Current epidemiological data on the comorbidity of CD with cellulitis or pruritus remain limited, though case reports suggest potential associations. Eren et al documented resolution of cellulitis symptoms following a gluten-free diet, while Sedlack et al reported similar improvement in unexplained pruritus after gluten restriction.[11,12] Although these observational studies have provided valuable insights, they have some limitations such as

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confounding effects, reverse causation, and selection bias.[13,14] Additionally, existing research has only demonstrated an association between CD and skin diseases without establishing causality.

Mendelian randomization (MR) is an analytical technique that utilizes genetic variations, such as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to investigate whether an exposure directly influences an outcome.[15] Since alleles are randomly passed to the next generation during meiosis and are not influenced by late environmental factors, confounding factors can be minimized.[16] This study explored the potential causality and strength of association between CD and five skin diseases through a two-sample MR (2SMR) analysis. Our findings not only revealed the complex interactions among diseases but also provided support for the development of more effective screening methods and early diagnostic tools, thereby enhancing patient outcomes and disease management.

Materials and Methods

Study Design

The causality between CD and five skin diseases, including atopic dermatitis, urticaria, psoriasis, cellulitis, and pruritus, was assessed by bidirectional 2SMR analysis. To ensure the validity of the MR analysis, the selected IVs must satisfy the following 3 conditions[17,18] (Figure 1A): (I) Relevance assumption: The IVs are strongly correlated with the exposures; (II) Independence assumption: The IVs are not influenced by any potential confounders; (III) Exclusion-restriction assumption: The IVs should only affect the outcome through exposure, with no other independent pathways. Specifically, forward MR analysis investigated the impact of CD on the onset risks of the five skin diseases, while reverse MR analysis evaluated the potential causal link between the five skin diseases and the risk of CD. A schematic diagram of the study design is depicted in Figure 1B. Since body mass index (BMI), smoking, and alcohol use may be confounders for the exposure and outcome, an multivariate MR (MVMR)analysis was performed to further explore the direct effect of the exposure on the outcome.

Data Sources

Raw data were acquired from the GWAS database (https://gwas.mrcieu.ac.uk/). The GWAS ID was ieu-a-1058 for CD (12,041 cases and 12,228 healthy controls),[19] ebi-a-GCST90027161 for atopic dermatitis (22,474 cases and

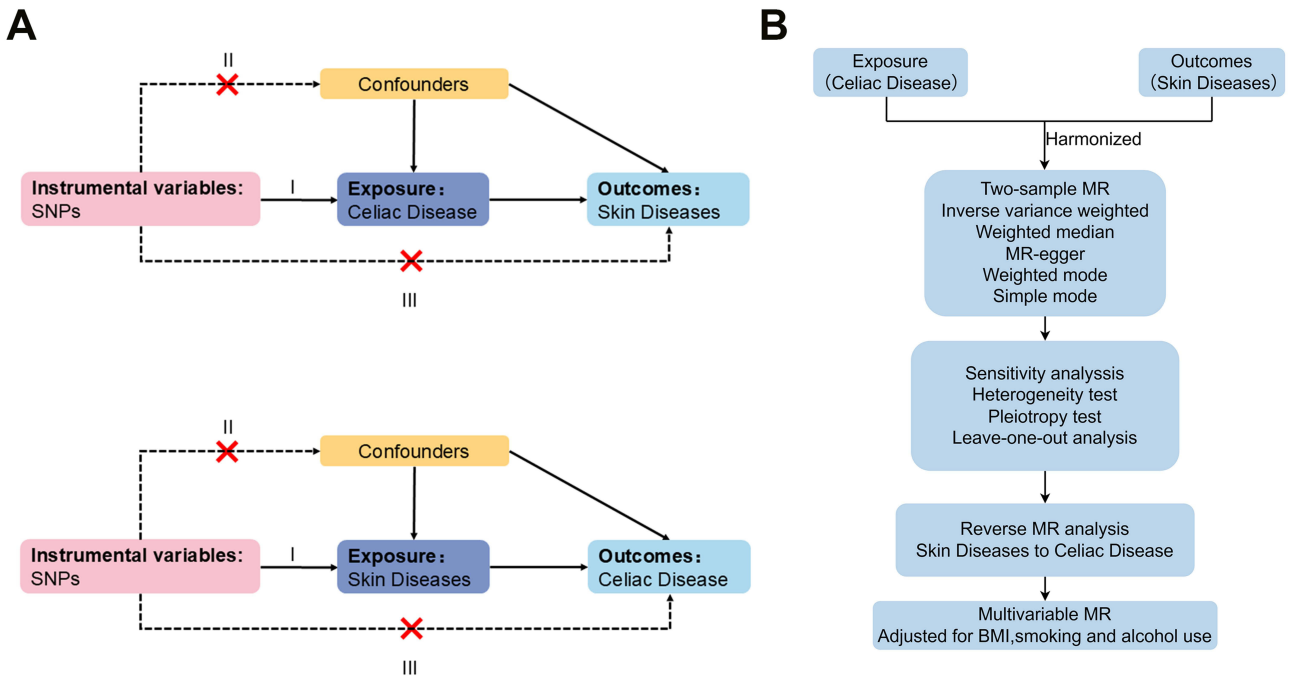

Figure 1 Overview of study design. (**A**) Principles of this 2SMR study. Three principle assumptions in MR design: (I) Relevance assumption: The IVs are strongly correlated with the exposures; (II) Independence assumption: The IVs are not influenced by any potential confounders; (III) Exclusion-restriction assumption: The IVs should only affect the outcome through exposure, with no other independent pathways. (**B**) Flowchart of MR study.

774,187 healthy controls),[20] ebi-a-GCST90018936 for urticaria (1,057 cases and 482,892 healthy controls),[21] ebi-a-GCST90019016 for psoriasis (15,967 cases and 28,194 healthy controls),[22] ieu-b-4970 for cellulitis (12,196 cases and 474,288 healthy controls; adjusted by age and gender),[23] and finn-b-L12_PRURITUS for pruritus (1,370 cases and 198,740 healthy controls). GWAS data on BMI (ieu-a-835: 322,154 subjects),[24] current smoking status (ukb-a-225: 33,928 smokers and 302,096 non-smokers),[23] and alcoholic drinks per week (ieu-b-73: 335,394 subjects)[25] were also retrieved. All of the above datasets originated from the European population (Table S1).

Selection of IVs

SNPs associated with the exposures were selected as IVs using the "TwoSampleMR" R package:[26] (1) SNPs that are significantly associated with the exposure were screened using a genome-wide significance threshold $P < 5\times10^{-8}$. However, due to the insufficient number of SNPs reaching the significance threshold for atopic dermatitis, urticaria, cellulitis, and pruritus, the threshold was lowered to $P < 5 \times 10^{-5}$;[27] (2) Avoidance of linkage disequilibrium (LD): Each IV is independent of each other ($R^2 < 0.001$, cluster distance=10,000kb);[28] (3) Strength of IVs: Strong IVs ($F \geq 10$) were retained, while weak IVs ($F < 10$) were eliminated. The F-statistic was calculated by $F = R^2(N-K-1)/K(1-R^2)$, where N = exposure sample size, K = number of IVs, and R^2 = percent of variation in exposure explained by the IVs.[29]

Statistical Analysis

A standardized approach was applied to ensure that the direction of SNPs was consistent between the exposure and outcome. MR analysis was performed using inverse variation weighted (IVW), weighted median, MR-egger, weighted mode, and simple mode. In particular, IVW was selected as the primary approach due to its high statistical power and low tolerance for bias in horizontal pleiotropy. Other methods were used as supplementary assessments of MR effect size to assess data robustness. The results were visualized in scatter plots, and statistical significance threshold was determined by the Bonferroni correction method. Specifically, a $P < 0.01$ (ie, 0.05/5) was defined as statistically significant. A $0.01 \leq P < 0.05$ indicates evidence of suggestive association.[30] For bidirectional MR analysis showing statistical significance, an IVW-based MVMR analysis was performed, with adjustments for confounders such as BMI, smoking, and alcohol use.

Sensitivity analyses were performed by testing for heterogeneity and horizontal pleiotropy. For heterogeneity, a $P > 0.05$ in the Cochran's Q test indicates absence of heterogeneity (Table 1). Horizontal pleiotropy was evaluated through the MR-Egger intercept and MR-PRESSO test, with a near-zero intercept and a $P > 0.05$ indicating absence of pleiotropy. In the case where $P < 0.05$ for horizontal pleiotropy, the corresponding outliers must be identified, and the horizontal pleiotropy test and MR analysis should be repeated after removing the outliers. In addition, the leave-one-out (LOO) analysis was carried out to evaluate data robustness. All analyses were performed using the "TwoSample MR", "MVMR", "MR-PRESSO" packages in R (version 4.2.1).[31]

Results

Effects of CD on Skin Diseases

In the forward MR analysis, SNPs strongly associated with CD ($P < 5\times10^{-8}$) were extracted from the GWAS, followed by the removal of LD SNPs ($R^2 < 0.001$, cluster distance = 10,000 kb) and palindromic sequences. Finally, 11 SNPs, 15 SNPs, 8 SNPs, 15 SNPs, and 15 SNPs were used for MR analysis of CD in relation to atopic dermatitis, urticaria, psoriasis, cellulitis and pruritus, respectively. There was no weak deviation in all IVs ($F > 10$, Table 1). Details of the final IVs used are summarized in Table S2. IVW analysis showed a significant causal effect of CD on atopic dermatitis (OR=1.042, 95% CI: 1.018–1.067, $P = 5.75\times10^{-4}$). The weighted median, simple mode and weighted mode results were directionally consistent with the IVW findings, indicating that genetically determined CD can increase the risk of atopic dermatitis (Table 1 and Figure 2A). Similarly, IVW analysis demonstrated that the genetic proxy for CD increased the risk of cellulitis (OR=1.026, 95% CI: 1.006–1.046, $P = 9.18\times10^{-3}$), suggesting that CD may increase susceptibility to cellulitis. The directions of the weighted median and weighted mode results were in line with those of IVW (Table 1 and Figure 2D). No causal relationship was identified between CD and urticaria (OR = 0.994, 95% CI: 0.971–1.019, $P = 0.645$), psoriasis (OR = 0.968, 95% CI: 0.900–1.040, $P = 0.370$) or pruritus (OR = 1.047, 95% CI: 0.984–1.114, $P = 0.145$) (Table 1, Figure 2B, C and E). The analysis

Table 1 MR Results for the Relationship Between CD and Skin Diseases

Exposure	Outcomes	No. of SNPs	MR Method	OR (95% CI)	*P*	Heterogeneity Test		Horizontal Pleiotropy Test		F
						Cochran's Q	*P*	Egger-Intercept	*P*	
CD	Atopic dermatitis	11	IVW	1.042(1.018–1.067)	5.75×10^{-4}	4.124	0.942	0.004	0.466	199.59
			Weighted median	1.046 (1.016–1.077)	2.38×10^{-3}					
			MR-Egger	1.032 (0.998–1.068)	0.102					
			Simple mode	1.056(1.012–1.103)	0.032					
			Weighted mode	1.038(1.009–1.069)	0.029					
CD	Urticaria	15	IVW	0.994(0.971–1.019)	0.645	15.661	0.335	−0.006	0.462	333.83
			Weighted median	1.003 (0.971–1.036)	0.859					
			MR-Egger	1.005(0.969–1.042)	0.805					
			Simple mode	1.013(0.952–1.077)	0.699					
			Weighted mode	1.003(0.977–1.029)	0.850					
CD	Psoriasis	8	IVW	0.968(0.900–1.040)	0.370	8.731	0.273	0.006	0.648	69.54
			Weighted median	0.963 (0.889–1.044)	0.362					
			MR-Egger	0.946 (0.840–1.066)	0.398					
			Simple mode	0.928(0.812–1.060)	0.306					
			Weighted mode	0.958(0.884–1.038)	0.329					
CD	Cellulitis	15	IVW	1.026 (1.006–1.046)	9.18×10^{-3}	7.570	0.910	0.0003	0.958	333.83
			Weighted median	1.028 (1.004–1.052)	0.024					
			MR-Egger	1.026 (0.996–1.056)	0.112					
			Simple mode	1.017(0.984–1.051)	0.341					
			Weighted mode	1.027(1.004–1.051)	0.039					
CD	Pruritus	15	IVW	1.047 (0.984–1.114)	0.145	6.789	0.943	−0.003	0.875	333.83
			Weighted median	1.039 (0.957–1.128)	0.358					
			MR-Egger	1.053 (0.961–1.154)	0.290					
			Simple mode	1.046(0.930–1.177)	0.465					
			Weighted mode	1.046(0.971–1.127)	0.255					

Abbreviations: CD, celiac disease; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

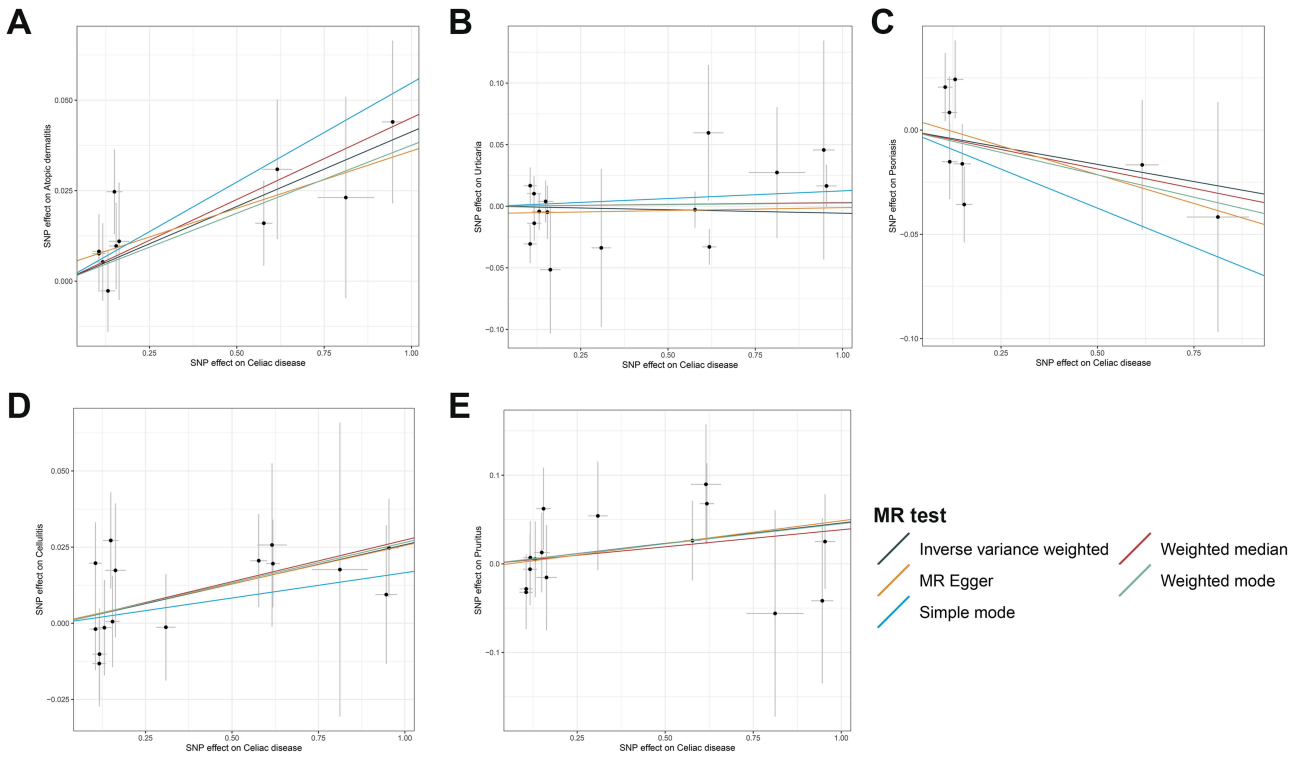

Figure 2 Scatter plots of the effect of CD on skin diseases. (**A**) CD and atopic dermatitis. (**B**) CD and urticaria. (**C**) CD and psoriasis. (**D**) CD and cellulitis. (**E**) CD and pruritus.

was reliable, as no outliers, heterogeneity or horizontal pleiotropy were identified (Table 1 and Figure 2). LOO sensitivity analysis revealed no significant impact on the overall findings by any single SNP (Figure 3).

Effects of Skin Diseases on CD

In the reverse MR analysis, SNPs closely associated with the five skin diseases were extracted from GWAS (threshold of $P < 5\times10^{-8}$ for psoriasis, and $P < 5\times10^{-5}$ for the other four skin diseases), followed by the removal of LD SNPs (R^2 <0.001, cluster distance=10,000 kb) and palindromic sequences.[27] Since outcome data for SNPs related to urticaria and pruritus could not be extracted from the target datasets, the final MR analyses were performed using 6 SNPs, 5 SNPs, and 5 SNPs for atopic dermatitis, psoriasis, and cellulitis in relation to CD, respectively. All of the selected IVs were strong (F >10, Table 2). Details of the final IVs selected are summarized in Table S3. Psoriasis was suggestively associated with CD (OR=0.836, 95% CI: 0.710–0.983, P=0.031; Table 2 and Figure 4B), indicating that psoriasis may have a potential protective effect on CD. No causal relationship was found between atopic dermatitis (OR=1.180, 95% CI: 0.915–1.522, P = 0.202) or cellulitis (0.969, 95% CI: 0.729–1.289, P =0.830) and CD (Table 2, Figure 4A and C). The absence of outliers in the MR-PRESSO analysis and $P > 0.05$ in the Cochran's Q test confirmed that the results were reliable without significant heterogeneity. The MR-Egger intercept test indicated that the MR results were not influenced by horizontal pleiotropy (Table 2 and Figure 4A–C). Furthermore, none of the individual SNPs significantly influenced the causality between skin diseases and CD (Figure 4D–F).

MVMR

Considering the confounding effects of BMI, smoking, alcohol use, we conducted an MVMR analysis to further assess the direct impact of CD on atopic dermatitis and cellulitis. The effect of CD on atopic dermatitis and cellulitis remained statistically significant after adjusting for these confounders (Table 3). These findings suggest that CD directly influences the risk of atopic dermatitis and cellulitis, highlighting the importance of its active management to reduce the risks of these comorbidities.

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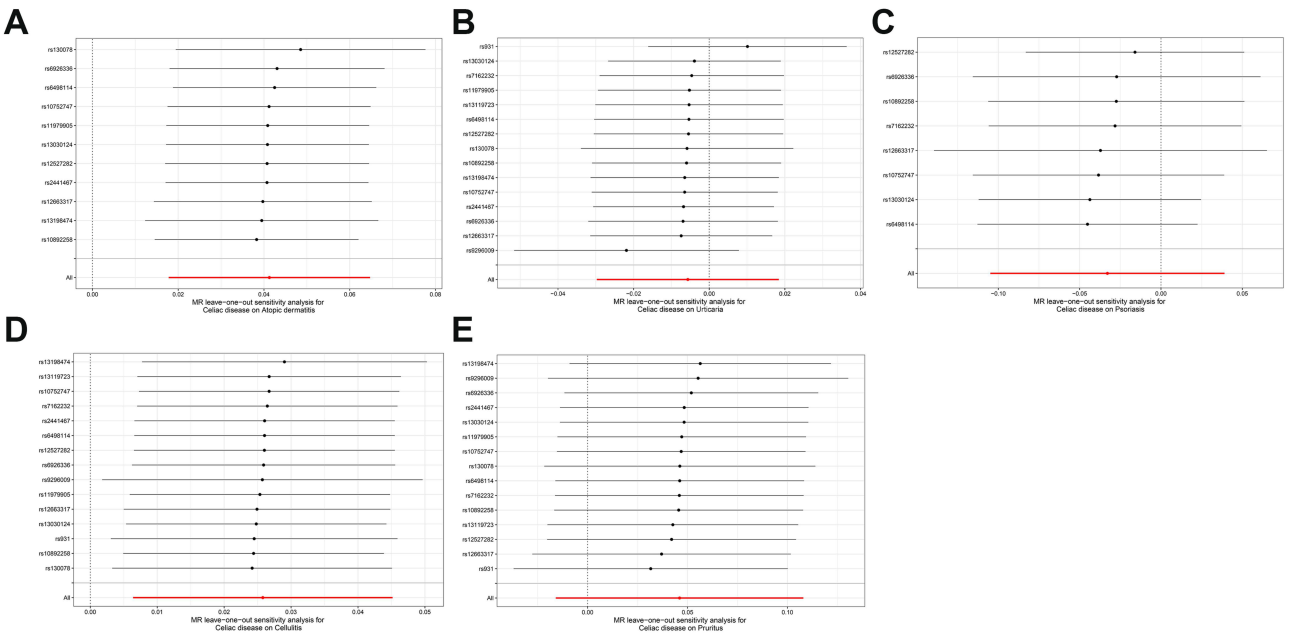

Figure 3 LOO plots for the causal relationship between CD and skin diseases. (**A**) CD and atopic dermatitis. (**B**) CD and urticaria. (**C**) CD and psoriasis. (**D**) CD and cellulitis. (**E**) CD and pruritus.

Discussion

Our MR analysis revealed that genetic predisposition to CD is positively linked to risks of atopic dermatitis and cellulitis, which is further supported by the MVMR results. Though, no reverse causality was observed. In addition, CD was not causally associated with urticaria, psoriasis or pruritus. Furthermore, a suggestive association was noted between psoriasis and CD, but not between atopic dermatitis or cellulitis and CD.

Atopic dermatitis is a persistent or recurrent inflammatory skin disease characterized by severe itching and recurrent eczematous lesions.[32] Although the exact etiology and pathogenesis of atopic dermatitis are still not well understood, its pathogenesis is associated with skin barrier dysfunction, aberrant immune responses, and skin microbial dysbiosis. Notably, aberrant immune responses play an important role in driving atopic dermatitis.[32,33] CD is an autoimmune disease in which 90%–95% of patients carry the HLA-DQ molecule. HLA-DQ presents gluten peptide heterodimers to T cells, promoting T cell activation and the release of a large array of cytokines. These processes in turn damage the intestinal wall, leading to increased intestinal permeability.[34,35] Using a MR-based genetics approach, we uncovered that CD increased the likelihood of atopic dermatitis onset. The mechanism by which CD increases atopic dermatitis risk is currently unclear, but numerous potential mechanisms have been proposed. In patients with CD, increased intestinal wall damage and permeability allow macromolecules and particles to interact with intestinal lymphoid tissue, triggering allergic reactions in extraintestinal sites.[36,37] The onset of atopic dermatitis is associated with mucosal damage, which is considered the pathological basis for the increased prevalence of allergic symptoms.[38] When mucosal permeability increases, autoantigens can enter into circulation through the intestinal wall, facilitating immune hyperactivation and disease progression.[39] Studies have shown that $FOXP3^+$ regulatory T cells are increased in CD and atopic dermatitis, playing a key role in their pathogeneses.[40–43] Therefore, impaired $FOXP3^+$ Treg function may lead to immune hyperactivation, potentially contributing to the coexistence of atopic dermatitis and CD. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) gene polymorphisms are linked to atopic dermatitis and CD and have been shown to regulate immune responses in these diseases.[44–46] This finding suggests that variations in the CTLA-4 gene may influence the susceptibility, progression, and severity of both diseases.

Cellulitis is an infection of the dermis and subcutaneous tissues, and can be classified as suppurative and non-suppurative. Common pathogens of cellulitis are β-hemolytic streptococci, Gram-negative bacteria, and *Staphylococcus aureus*.[47] The colonization density of *S. aureus* and/or β-hemolytic streptococci on the skin, edema, hypoproteinemia,

Table 2 MR Results for the Relationship Between Skin Diseases and CD

Exposures	Outcome	No. of SNPs	MR Method	OR(95% CI)	*P*	Heterogeneity Test		Horizontal Pleiotropy Test		F
						Cochran's Q	*P*	Egger-Intercept	*P*	
Atopic dermatitis	CD	6	IVW	1.180(0.915–1.522)	0.202	2.122	0.832	-1.95×10^{-2}	0.513	37.327
			Weighted median	1.253(0.922–1.702)	0.150					
			MR-egger	1.542(0.711–3.344)	0.335					
			Simple mode	1.191(0.762–1.864)	0.478					
			Weighted mode	1.295(0.874–1.919)	0.253					
Urticaria	CD	NA	NA	NA	NA	NA	NA	NA	NA	NA
Psoriasis	CD	5	IVW	0.836(0.710–0.983)	0.031	1.635	0.803	-1.96×10^{-2}	0.860	39.906
			Weighted median	0.833(0.685–1.012)	0.066					
			MR-egger	0.985(0.181–5.368)	0.987					
			Simple mode	0.865(0.662–1.129)	0.346					
			Weighted mode	0.832(0.643–1.076)	0.234					
Cellulitis	CD	5	IVW	0.969(0.729–1.289)	0.830	3.382	0.496	0.013	0.774	19.605
			Weighted median	0.968(0.656–1.429)	0.871					
			MR-egger	0.823(0.283–2.388)	0.744					
			Simple mode	1.061(0.613–1.835)	0.843					
			Weighted mode	1.065(0.624–1.818)	0.829					
Pruritus	CD	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CD, celiac disease; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

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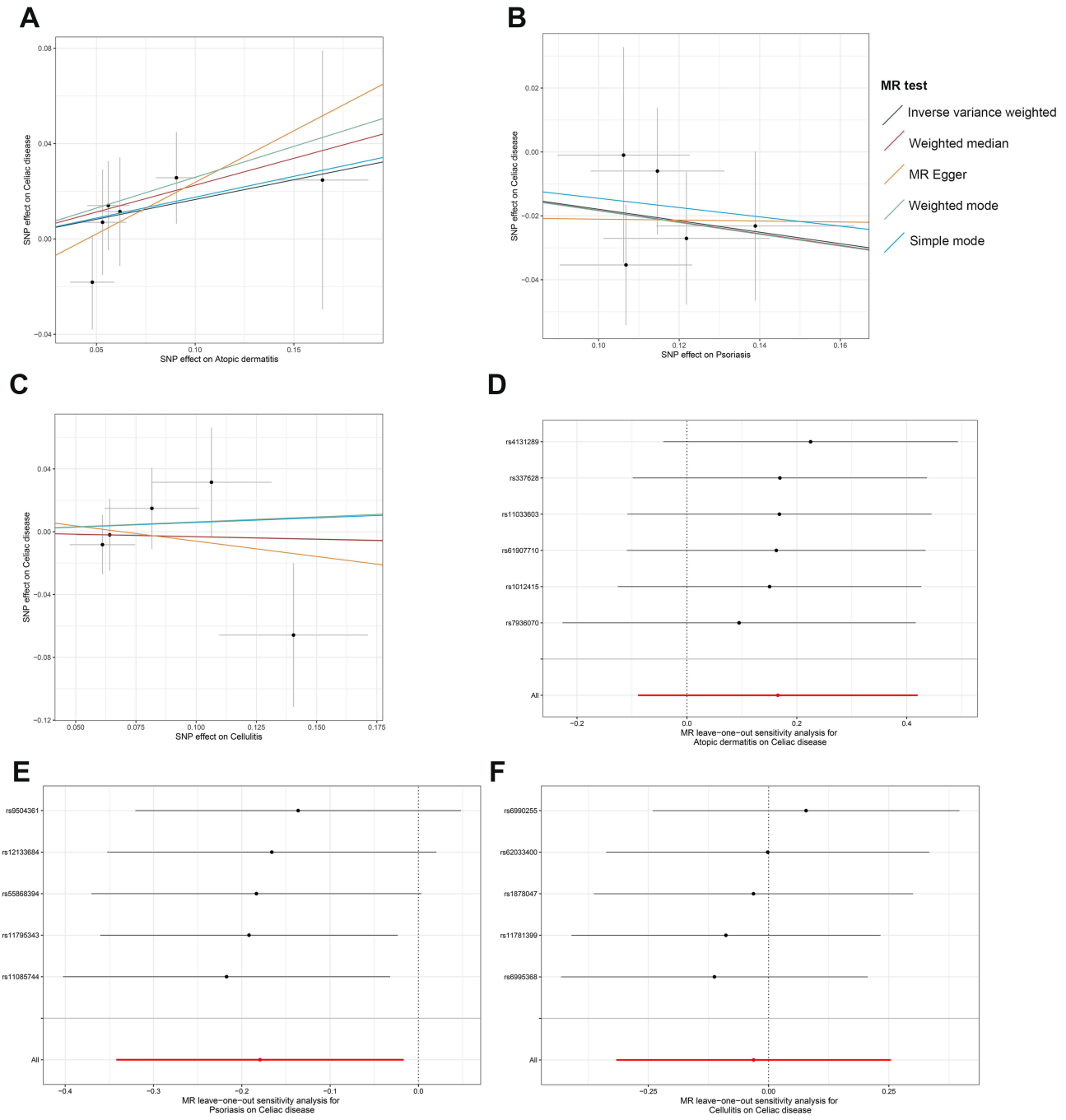

Figure 4 Effects of skin diseases on CD. (**A**–**C**) Scatter plots of the effect of atopic dermatitis, psoriasis, and cellulitis on CD. (**D**–**F**) LOO plots for the causal relationship between atopic dermatitis, psoriasis, or cellulitis and CD.

and barrier dysfunction have been reported as risk factors for cellulitis.[48,49] Our UVMR and MVMR analyses showed a significantly increased risk of cellulitis in patients with CD. Villi damage and long-term gluten-free diet in CD patients can lead to nutrient deficiencies and imbalances characterized by inadequate levels of trace minerals (iron, copper, zinc), water-soluble vitamins (B6, B12, folic acid), and fat-soluble vitamins (A, D, E, K).[50] These nutrients are essential for the maintenance and repair of skin barrier function, and their long-term deficiency can lead to compromised immune responses and an increased risk of skin infection. *S. aureus* and β-hemolytic streptococci are ubiquitously found in nature and on the skin, in the nasal cavity, and in the throat of humans. These bacteria are non-pathogenic under normal conditions but can become opportunistic pathogens and cause cellulitis when the immune system or skin barrier becomes

Table 3 MVMR Analyses of Common Risk Factors for Atopic Dermatitis and Cellulitis

Confounders	No. of SNPs	MR Method	OR (95% CI)	*P*
MVMR for the effect of celiac disease on atopic dermatitis				
BMI	14	IVW	1.037 (1.013–1.060)	2.01×10^{-3}
Smoking status: Current	15	IVW	1.037 (1.014–1.061)	1.27×10^{-3}
Alcoholic drinks per week	14	IVW	1.037 (1.014–1.060)	1.25×10^{-3}
MVMR for the effect of CD on cellulitis				
BMI	14	IVW	1.027 (1.013–1.042)	1.80×10^{-4}
Smoking status: Current	15	IVW	1.025 (1.011–1.040)	5.23×10^{-4}
Alcoholic drinks per week	14	IVW	1.027 (1.012–1.042)	4.48×10^{-4}

compromised. Impaired protein absorption in the small intestine of CD patients reduces plasma albumin levels, leading hypoproteinemia and edema, both of which have been reported as risk factors for cellulitis.[51] Of note, up to 30% of patients with CD have concomitant splenic insufficiency, which further increases the risk of developing cellulitis.[52]

Psoriasis is a chronic autoimmune disease that clinically presents with focal inflammatory plaque formation in the skin and persistent scaling.[53] Our bidirectional 2SMR study revealed that while CD was not associated with psoriasis, psoriasis had a suggestive association with CD. During the pathogenesis of psoriasis, T cells differentiate into TH17 cells and secrete key pathogenic cytokines such as IL-17, IFN-γ, and IL-22, which drive skin inflammation and abnormal keratinocyte proliferation.[54] On the other hand, IL-17 promotes the formation of tight junctions in the intestinal epithelium and increases transepithelial electrical resistance, while IL-22 induces mucin secretion by goblet cells and upregulates tight junction protein expression. Together, these mechanisms enhance intestinal barrier integrity, which may contribute to the suggestive association between psoriasis and CD.[55,56] Although both CD and psoriasis are immune-mediated diseases, our forward MR analysis did not indicate an association between CD and risk of psoriasis.[1,53] Future studies should explore the potential associations between these conditions across diverse populations. Of note, the bidirectional 2SMR analysis by Li et al revealed a forward causality between CD and psoriasis, but no reverse effect of psoriasis on CD.[57] The discrepancy between our findings and previous studies may be attributed to the heterogeneity in the datasets analyzed. MR analysis identifies statistical associations but the relationship between these diseases warrants further investigation through molecular and experimental validation. Murdaca et al found some associations between urticaria and CD.[58] However, our MR analysis did not identify a causal link between CD and urticaria. HLA-DQ was reported to be genetically associated with the development of urticaria and drives CD pathogenesis.[59,60] Therefore, the possibility that HLA-DQ mediates the association of CD with urticaria cannot be excluded.

Moderate-to-severe atopic dermatitis was found to be associated with smoking >15 packs of cigarettes per year, >2 alcoholic drinks per day, and obesity.[61] In particular, moderate-to-severe atopic dermatitis exhibited a dose-response relationship with the number of packs of cigarettes smoked per year.[61] Children of mothers with high BMI before pregnancy are at increased risk of atopic dermatitis.[62] An observational cross-sectional study found that smoking, alcohol consumption, and obesity were risk factors for cellulitis.[63] Hu et al reported an association of BMI with an elevated risk of cellulitis, but no causal relationship was identified after adjusting for type 2 diabetes and peripheral vascular disease.[64] A meta-analysis found that CD patients who consumed a gluten-free diet had significantly increased weight and body fat.[65] Marild et al observed that continuous maternal smoking during pregnancy was associated with a reduced likelihood of CD diagnosis in offspring.[66] Additionally, an MR study examining tobacco and alcohol use in relation to upper and lower gastrointestinal diseases found a negative correlation between smoking and CD.[67] While previous observational studies did not account for the effects of BMI, smoking, and alcohol use, our MVMR analysis effectively controlled for these confounders, providing more reliable evidence for our results.

Several limitations should be considered for this study. First, since horizontal pleiotropy could not be completely eliminated in this study, the presence of some confounders would likely impact exposure and outcomes. However, it is important to note that we have obtained consistent and reliable results by multiple MR methods and sensitivity analyses,

which could minimize potential bias introduced by horizontal pleiotropy. Second, data from the European population were utilized in our analyses, limiting the generalizability of our findings. Given the genetic variations among different races, further studies in other racial populations are warranted. Finally, while our MR analysis, using publicly available data, provides valuable statistical insights to guide future research, additional basic and clinical studies are essential to fully clarify the relationships between these diseases.

Conclusion

CD contributes to the risk of atopic dermatitis and cellulitis onset. Furthermore, psoriasis is suggestively associated with CD. However, the mechanisms underlying the relationship between these diseases warrant further investigation.

Data Sharing Statement

All data generated in the present study are available in the main text and supplementary materials. The raw data are available from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/).

Ethics Statement

This study is a secondary analysis utilizing publicly available GWAS data, and no original data was collected. According to Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023), research utilizing legally obtained, non-interventional public or observational data, or anonymized information, is exempt from institutional ethics review. Therefore, the Hebei Medical University Third Hospital ethics committee exempted the ethical review requirements for this study.

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Author Contributions

All authors significantly contributed to the conception, design, execution, data acquisition, analysis, and interpretation of the study; participated in drafting, revising, or critically reviewing the manuscript; approved the final version for publication; agreed on the target journal; and accept responsibility for all aspects of the work.

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Disclosure

Authors declare no conflict of interests for this article.

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