

Causal Relationships Between Popular Diets (Low-Calorie, Vegetarian, and Gluten-Free Diets) and Inflammatory Skin Diseases: A Mendelian Randomization Study

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Background: Inflammatory skin diseases including acne, atopic dermatitis, psoriasis, and psoriatic arthritis, and have become a major global public health concern. Diet's impact on inflammatory skin diseases has attracted significant attention. This study utilised the Mendelian randomization (MR) method to investigate the relationship between popular diets, such as low-calorie, vegetarian, and gluten-free diets, and several common inflammatory skin diseases.

Methods: Our study employed five MR methods, including the inverse variance weighted (IVW), MR-Egger, simple mode, weighted median, and weighted mode. Sensitivity analysis was conducted to confirm the accuracy and reliability of the research findings.

Results: The results revealed a positive causal relationship between low-calorie diets and the risk of psoriatic arthritis (odds ratio [OR]: 1.05; 95% confidence interval [CI]: 1.01–1.10; $p = 0.008$) but no significant association with other diseases. No significant association was observed between vegetarian or gluten-free diets and the diseases. The reliability of the conclusion was further validated through the MR-Egger regression, MR-PRESSO analysis.

Conclusion: This study offers preliminary insights into the links between diet and inflammatory skin conditions, with future large-scale, multi-method research needed to validate these findings and inform dietary recommendations.

Keywords: inflammatory skin diseases, low-calorie, vegetarian, gluten-free, Mendelian randomization

Introduction

Inflammatory skin diseases are a group of skin conditions characterised by inflammation, including acne, atopic dermatitis (AD), psoriasis, and psoriatic arthritis (PsA), among others. The pathological mechanisms of these diseases revolve around the excessive activation of the innate immune system and the imbalance of adaptive immune homeostasis. A common key factor is the dysfunction of T helper cell subsets, which can exacerbate the inflammatory cascade by secreting various inflammatory cytokines, leading to the persistent progression and recurrence of skin lesions.^{1–3} Inflammatory skin diseases led to a significant adverse effect on their quality of life and mental health, making them a global public health concern.

As per the World Health Organization's data, acne is a prevalent skin condition, impacting around 85% of teenagers and young adults.⁴ The adult population has a prevalence rate of 2–3% for AD.⁵ Psoriasis is a systemic inflammatory disease affecting approximately 1–2% of the global population, often leading to skin and joint involvement.⁶ Despite existing treatment methods being able to alleviate symptoms, many patients still face issues with recurrence and chronicity, highlighting the importance of finding new management strategies.

Diet as a modifiable lifestyle factor has received increasing attention in recent years. Analysis of global Google search data from 2004 to 2019 indicates that vegetarian and gluten-free diets rank among the most popular, while low-calorie diets have also emerged as a trend due to their high exposure on social media. Furthermore, the market share of products associated with these three diets has been steadily increasing.⁷

Low-calorie diets, which involve reduced daily caloric intake, have been shown to extend lifespan, induce autophagy, and alleviate symptoms of various diseases, including cardiovascular disease, type 2 diabetes, and neurodegenerative disorders.⁸ Vegetarian diets are plant-based and typically rich in fiber and antioxidants. A gluten-free diet excludes gluten, a protein found in wheat, rye, barley, and oats, and was initially developed for treating celiac disease but is now also used for gluten sensitivity and dermatitis herpetiformis. However, poorly balanced diets can lead to various nutritional deficiencies, including deficiencies in iron, zinc, calcium, vitamin B12, vitamin D, and omega-3 fatty acids.^{9,10} These deficiencies may subsequently trigger various skin issues, such as abnormal immune regulation, delayed wound healing, compromised barrier function, premature aging, and increased sensitivity to environmental irritants.^{11–14} Dermatologists often encounter patients with inflammatory skin diseases who follow these dietary patterns, especially those who are not gluten-sensitive but voluntarily adhere to a gluten-free diet.¹⁵ The internet and media have significantly promoted and advertised low-calorie, vegetarian, and gluten-free diets as part of a healthy lifestyle.

Currently, there is limited research on the relationship between these three diets and skin diseases. Moreover, traditional clinical studies often face challenges such as heterogeneity, selection bias, and confounding factors, making it difficult to draw definitive conclusions. For instance, some studies suggest that a vegetarian diet may improve symptoms of AD, while others find no association between vegetarianism and the occurrence or severity of AD.^{16,17} Mendelian randomization (MR) employs genetic variations as instrumental variables (IVs) and is widely used for causal inference to analyze the relationship between exposures and outcomes. Since alleles are randomly assigned at conception, MR effectively reduces residual confounding and eliminates the possibility of reverse causation. Compared to randomized controlled trials, MR is more resource-efficient and does not require long-term follow-up.^{18,19} Currently, MR studies primarily focus on the relationship between individual dietary components, such as vitamin E, tea, beef, and milk, and specific diseases.^{20–24} However, there remains a significant gap in research regarding the associations between these three complex dietary patterns and inflammatory skin diseases.

Therefore, this study aims to explore the potential causal relationships between low-calorie, vegetarian, and gluten-free diets and conditions such as acne, AD, psoriasis, and PsA by analyzing large-scale genome-wide association study (GWAS) data. This research seeks to provide certain insights for genetic epidemiology in this field.

Methods

Study Design

Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines ([Table S1](#)). MR studies are built on three fundamental assumptions: first, the IVs are closely associated with the exposure factor. Second, genetic variations are unrelated to any confounding factors. Lastly, genetic variations cannot directly influence the outcome but only through the specific exposure selected, as illustrated in [Figure 1A](#) outlining the overall study design. Our study designated three specific diets (low-calorie, vegetarian, gluten-free) as exposure factors and conducted MR analyses with four skin diseases (psoriasis, PsA, AD, acne) as outcomes ([Figure 1B](#)).

Data Sources and Participants

The datasets for the three specific diets (gluten-free, low-calorie, vegetarian) were obtained from a cohort within the UK Biobank, consisting of 64,949 samples and 9,851,867 single nucleotide polymorphisms (SNPs). The psoriasis data was also sourced from the UK Biobank, comprising 462,933 samples and 9,851,867 SNPs. We accessed the data from <https://gwas.mrcieu.ac.uk> on August 9, 2024. In addition, we retrieved PsA data with 325,181 samples and 9,419,702 SNPs, AD data with 18,896 samples and 7,433,555 SNPs, and acne data with 399,413 samples and 6,438,339 SNPs from the GWAS catalog, available at <https://www.ebi.ac.uk> ([Table 1](#)).

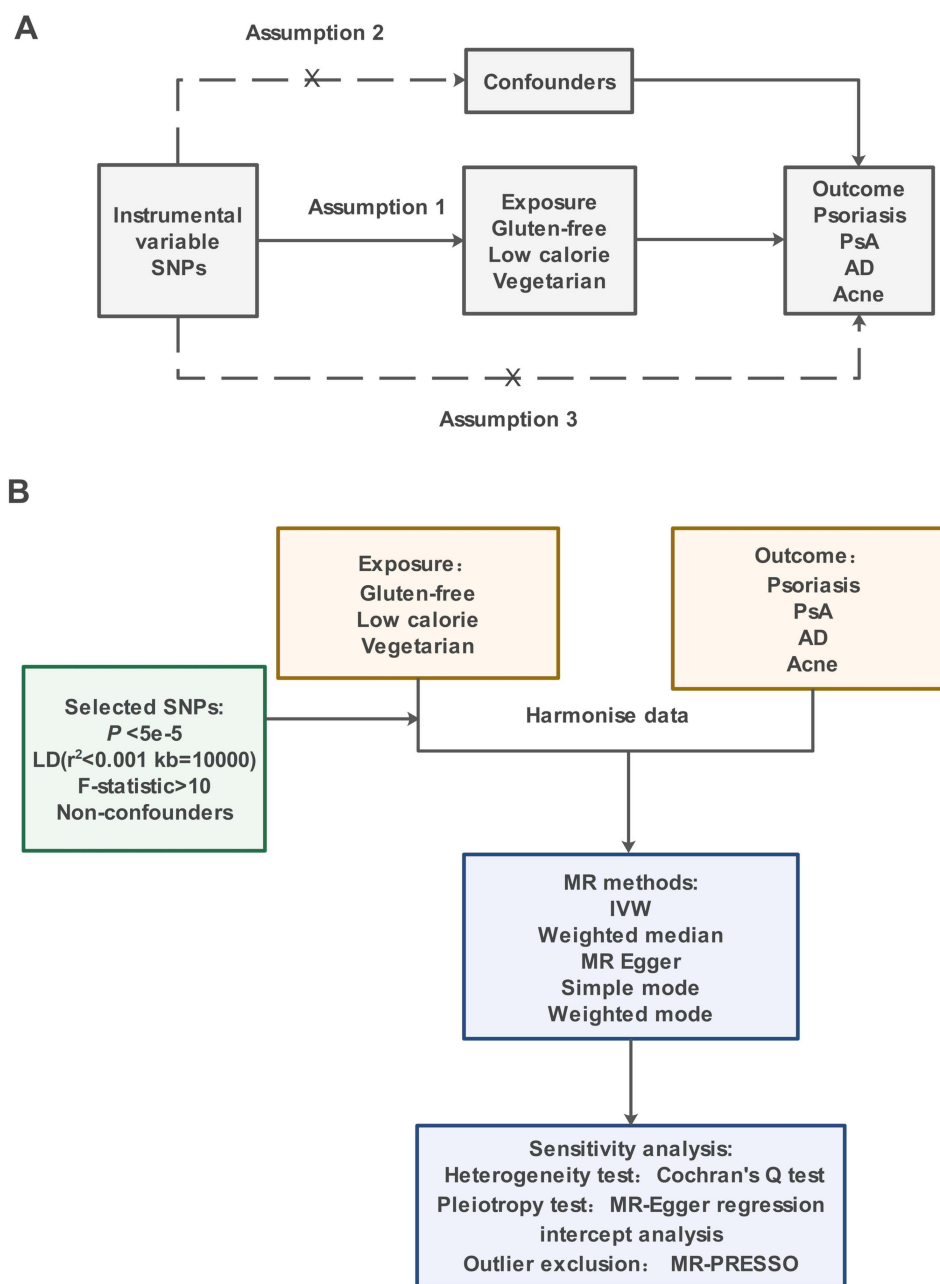


Figure 1 The hypothesis diagram for the MR analysis (A) and the analysis flowchart (B).

Abbreviations: SNPs, single nucleotide polymorphisms; AD, atopic dermatitis; PsA, psoriatic arthritis; LD, linkage disequilibrium; MR, Mendelian randomization; IVW, Inverse variance weighted.

Selection of IVs

To select effective IVs, we chose SNPs with a significance level of $p < 5 \times 10^{-8}$ and applied stringent linkage disequilibrium (LD) clumping thresholds ($R^2 < 0.001$; $kb = 10,000$) to exclude SNPs in LD. Since there were fewer than 5 SNPs that met the stringent threshold ($p < 5 \times 10^{-8}$) in the vegetarian, low-calorie, and gluten-free diets, we used a relaxed threshold ($p < 5 \times 10^{-5}$; $R^2 < 0.001$; $kb = 10,000$) to select SNPs for these specific diets. We utilised the F statistic to assess SNPs with minimal instrumental variable bias, and only SNPs with an F statistic $> 10^{25}$ were deemed eligible for analysis. All selected SNPs were evaluated using the PhenoScanner database to satisfy the second and third assumptions and exclude SNPs associated with confounding factors or directly linked to the outcome.

Table 1 Summary of Genetic Data Information for Phenotypes

Phenotypes	GWAS ID	Sample size	SNP
Gluten-free	ukb-b-11189	64949	9851867
Vegetarian	ukb-b-11679	64949	9851867
Low-calorie	ukb-b-15768	64949	9851867
Psoriasis	ukb-b-10537	462933	9851867
PsA	GCST90014454	325181	9419702
Acne	GCST90245818	399413	6438339
AD	GCST90429798	18896	7433555

Abbreviations: AD, atopic dermatitis; PsA, psoriatic arthritis; GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms.

Statistical Analysis

In our MR analysis, we used five MR methods to investigate the causal effects of three specific diets on four diseases (psoriasis, PsA, AD, and acne): IVW, MR-Egger, simple mode, weighted median, and weighted mode. The primary technique used in this experiment was the IVW method, which is a conventional approach for meta-analysis that can estimate causal effects without requiring individual-level data, with other methods used as supplements. MR analysis outcomes were expressed using p-values, odds ratios (OR), and 95% confidence intervals (CI) to interpret the results better.

Heterogeneity was evaluated using Cochran's Q statistic in the MR-Egger and IVW methods, with a p-value greater than 0.05 indicating no significant heterogeneity. Horizontal pleiotropy was tested using MR Egger to assume no pleiotropy, ie, the IVs solely influence the outcome through exposure.

A result with $p > 0.05$ suggests no statistically significant difference from zero for the intercept, indicating the absence of horizontal pleiotropy. The MR-PRESSO method was employed for a global test to assess horizontal pleiotropy and outliers, comparing results before and after removing outliers (with the number of iterations set to 10,000). To assess the statistical power of our MR analyses, we used the online tool Power calculations for MR (<https://shiny.cnsgenomics.com/mRnd/>), which is designed for power estimation in MR studies with continuous or binary outcomes. We utilised the TwoSampleMR package to create forest and scatter plots, illustrating the relationship between the three specific diets and the risk of the four diseases. In this analysis, we used the TwoSampleMR package (v0.6.5) in R (v4.4.1) for statistical analysis.

Results

MR Analysis Results

In this analysis, the IVW method was used as the primary approach, and the results showed that among the three specific diets and four diseases examined, only the low-calorie diet was associated with a modest increase in PsA risk (OR=1.05, 95% CI 1.01–1.10, $p=0.008$) (Figure 2). The scatter plot further illustrates the results of this group of studies (Figure 3A), showing the magnitude of the effect for each MR method and depicting the relationship with the outcome. For the other combinations of specific diets and diseases (gluten-free diet with psoriasis, PsA, acne, and AD; low-calorie diet with psoriasis, acne, and AD; vegetarian diet with psoriasis, PsA, acne, and AD), the IVW did not show a significant causal relationship between exposure and outcome (Figure 2).

In the study of the relationship between a vegetarian diet and psoriasis, heterogeneity was observed ($p < 0.05$), leading us to use the IVW (multiplicative random effects) method instead of the IVW method for testing, which also yielded non-significant results ($p > 0.05$). However, for the other study groups, we did not observe heterogeneity. The detailed results of these analyses are listed in Table 2. The statistical power of MR analyses may be insufficient (see Table S2).

Sensitivity Analysis Results

The study used the MR-Egger regression intercept analysis to test for horizontal pleiotropy. The results showed that all p-values exceeded 0.05, suggesting the absence of significant indications of horizontal pleiotropy in our study. This shows that our findings are not only dependable but also robust. Table 2 presents detailed information on these analyses.

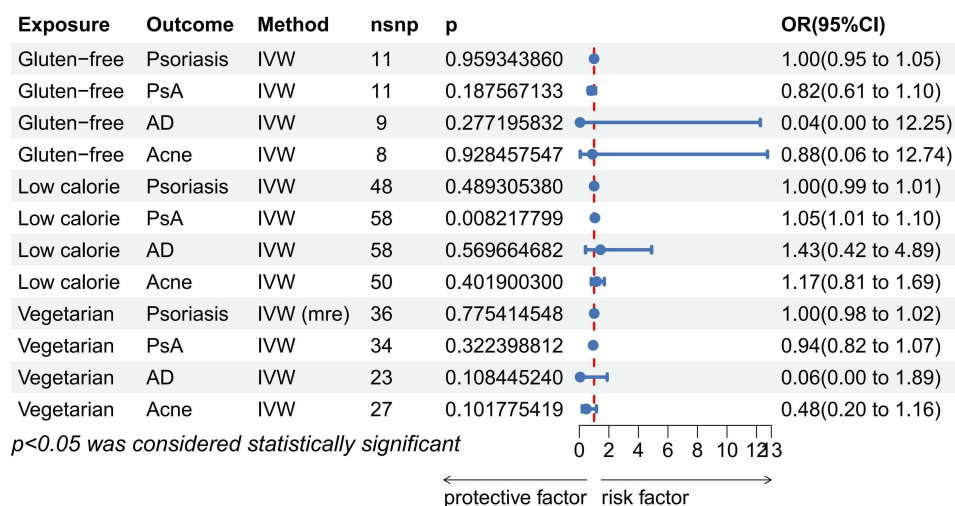


Figure 2 MR analysis results on the causal relationships between different types of specialised diets and various disease outcomes.

We also conducted a leave-one-out plot in the sensitivity analysis of the association between a low-calorie diet and PsA (Figure 3B). After sequentially removing each SNP, the results showed no significant changes. Therefore, the sensitivity analysis confirms the reliability of the MR analysis results, indicating no influence from heterogeneity or pleiotropy. Additionally, the funnel plot presented a symmetrical shape (Figure 3C), suggesting minimal significant bias in the causal estimates. The sensitivity analysis results from other research groups can be found in the [supplementary Figures 1–11](#).

Although sensitivity analyses, which accounted for horizontal pleiotropy, assessed the stability and symmetry of the results, support the reliability and robustness of the current findings, it is important to note that the results are influenced by factors such as small effect sizes, potential uncontrolled confounding, and limited definitions of dietary patterns. Therefore, these findings should not be interpreted as definitive causal evidence.

Discussion

To our knowledge, this study represents the first attempt to explore the potential causal effects between popular diets and common inflammatory skin diseases at the genetic level. Through MR analysis, this study suggests that a low-calorie diet may moderately increase the risk of PsA, while no association was found with acne, AD, or psoriasis. The study also found no significant potential causal effects between vegetarian and gluten-free diets with acne, AD, psoriasis, and PsA. These findings provide preliminary insights into the relationship between diet and inflammatory skin diseases, opening new avenues for further exploration in this field.

Based on our knowledge, overweight and obesity are considered important risk factors for the development of psoriasis, AD, and acne. Obesity can lead to chronic low-grade inflammation, characterised by elevated levels of adipokines and pro-inflammatory cytokines, which may exacerbate the development of skin diseases.²⁶ Low-calorie and vegetarian diets are considered among the most effective interventions for weight reduction and lowering chronic inflammatory markers. A randomised controlled trial (n = 303) found that a low-calorie diet combined with exercise positively impacted the severity of psoriasis in patients with a recent-onset BMI increase.²⁷ Other studies have indicated that a 12-week low-calorie diet intervention can control BMI in psoriasis patients with non-alcoholic fatty liver disease, improve response to medication, and enhance quality of life. Additionally, a 5% reduction in body weight through a low-calorie diet can improve the response to TNF inhibitors in PsA patients, and further weight reduction can lead to an even more significant improvement in response.²⁸ Furthermore, an 8-week low-calorie diet with additional nutrients for 19 AD patients showed a relationship between weight loss and improvement in dermatitis.²⁹ Additionally, a study involving 31 untreated moderate acne class I obese women showed overall improvements in body measurements and body composition parameters following a very low-calorie intervention.³⁰

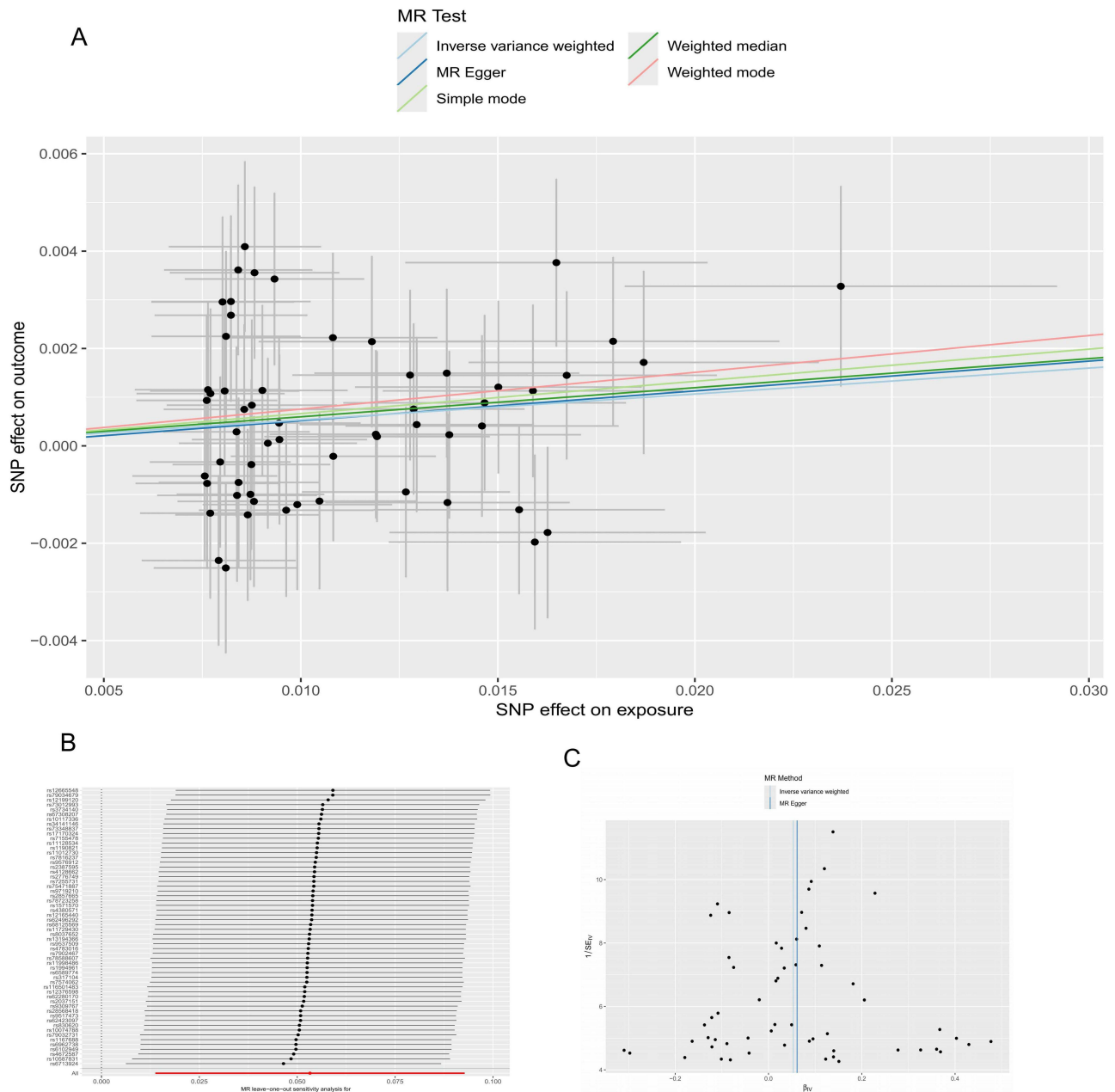


Figure 3 Scatter plot (A), leave-one-out plot (B) and funnel plot (C) of the MR analysis on the association between low-calorie diet and PsA.

Our study found that low-calorie diets are not associated with psoriasis, AD, and acne but may increase the modest risk of PsA. However, due to the lenient threshold for selecting SNPs and the suboptimal statistical power, these results should be interpreted with caution. Previous observational studies have primarily been conducted on populations of obese psoriasis or PsA patients, and it is currently unclear whether low-calorie diets can directly improve the inflammatory status of these patients. A large retrospective cohort study found no association between pro-inflammatory diets and the risk of psoriasis, PsA, or AD. In age-adjusted models, a pro-inflammatory dietary pattern was associated with PsA, but once critical confounding factors, especially BMI, were adjusted, the correlation weakened and was no longer statistically significant.³¹

Prolonged excessive low-calorie diets can lead to malnutrition. A deficiency in key nutrients such as proteins, vitamins, and minerals may directly impair the function and activity of immune cells, resulting in an imbalance in immune regulation. For example, vitamin D deficiency can affect the anti-inflammatory activity of innate immune cells and the regulation of

Table 2 Pleiotropy and Heterogeneity Analysis

		Pleiotropy Test			Heterogeneity Test					
		MR-Egger			MR-Egger			IVW		
Exposure	Outcome	Intercept	SE	p	Q	Q (df)	p	Q	Q (df)	p
Gluten-free	Psoriasis	-2.39E-03	1.90E-03	0.240	16.13	9	0.064	18.97	10	0.041
Gluten-free	PsA	4.58E-03	1.08E-02	0.683	5.36	9	0.802	5.54	10	0.852
Gluten-free	AD	4.18E-02	3.06E-02	0.215	2.51	7	0.926	4.37	8	0.822
Gluten-free	Acne	-9.15E-02	9.96E-02	0.394	11.96	6	0.063	13.64	7	0.058
Low-calorie	Psoriasis	-8.08E-05	2.12E-04	0.705	41.14	46	0.676	41.29	47	0.707
Low-calorie	PsA	-9.63E-05	7.74E-04	0.902	50.60	56	0.679	50.62	57	0.712
Low-calorie	AD	2.83E-03	2.47E-02	0.909	53.42	56	0.573	53.43	57	0.610
Low-calorie	Acne	-1.29E-02	7.85E-03	0.107	54.72	48	0.235	57.78	49	0.183
Vegetarian	Psoriasis	1.33E-05	5.78E-04	0.982	52.63	34	0.022	52.63	35	0.028
Vegetarian	PsA	4.37E-03	3.69E-03	0.244	36.36	32	0.273	37.96	33	0.253
Vegetarian	AD	-1.10E-01	9.86E-02	0.279	13.76	21	0.880	14.99	22	0.863
Vegetarian	Acne	4.09E-02	2.50E-02	0.115	26.02	25	0.406	28.80	26	0.320

Abbreviations: AD, atopic dermatitis; PsA, psoriatic arthritis; IVW, Inverse variance weighted; SE, Standard Error.

immune homeostasis. This immune imbalance may further trigger autoimmune responses, exacerbating inflammation.^{32,33} At the same time, malnutrition can impair the ability of immune cells to recognize and eliminate pathogens, potentially triggering or exacerbating joint inflammation.⁸ This effect may create a compounded risk, particularly for patients with psoriatic arthritis, who are already more susceptible to bone health issues such as osteoporosis and brittle fractures.^{34,35} The specific phenotypes of low-energy diets have not yet been clearly defined, and there is a lack of direct and conclusive evidence supporting their underlying biological mechanisms. Further rigorous studies, including multivariable Mendelian randomization and targeted intervention trials, are needed to elucidate the associated pathways.

Research has indicated that female and male vegetarians tend to weigh 3.3 kg and 7.6 kg less, respectively, compared to meat eaters.³⁶ Due to a vegetarian diet's anti-inflammatory and antioxidant properties and its association with lower BMI, research suggests it may help improve the clinical conditions of acne, psoriasis, and AD patients.³⁷ Psoriasis patients undergoing vegetarian treatment have been found to have fewer and less severe skin lesions compared to those not undergoing such treatment.³⁸ A vegetarian diet can improve AD symptoms by reducing the number of peripheral eosinophils and monocyte PGE2 synthesis, although the study involved only 20 subjects.¹⁷ Additionally, an MR study found that beef intake may be associated with a reduced risk of AD when excluding beef allergy, but no causal relationship was found between vegetable or fruit intake and AD.²⁰ A recent cross-sectional study (n = 56,896) investigated the relationship between lifestyle factors (such as alcohol consumption, obesity, sleep duration, and diet) and AD in adults. In this study, no association was found between a vegetarian diet and the presence or severity of AD.¹⁶ Literature reports a significantly lower proportion of acne patients adhering to a vegetarian diet than the control group. In contrast, the normal control group was more inclined to follow a vegetarian diet.³⁷

Our MR analysis indicates that the relationship between a vegetarian diet and these inflammatory diseases is not significant. If vegetarians do not maintain a balanced diet, they may lack essential nutrients such as vitamin B12, iron, zinc, and omega-3 fatty acids. This deficiency can weaken immune function, slow skin barrier repair, and reduce anti-inflammatory capacity, ultimately affecting immune homeostasis and skin health. Furthermore, an over-reliance on refined carbohydrates or processed plant proteins may lead to a lack of dietary fiber, resulting in decreased gut microbiome diversity.³⁹⁻⁴¹ Therefore, adhering to a carefully planned dietary pattern is crucial to meet all necessary nutritional requirements and avoid any potential health risks.

Gluten is a protein found in barley, wheat, and rye. It can trigger abnormal immune responses in individuals with gluten sensitivity, leading to celiac disease, intestinal atrophy, and impaired nutrient absorption. In recent years, a gluten-free diet has become a popular trend for treating chronic diseases, although the evidence is limited and controversial. However, some research has found that some patients have independently adopted a gluten-free diet to manage their conditions.⁴²

In cases with no gastrointestinal disease present, the marker for celiac disease, anti-gliadin antibodies, may hold autoimmune significance. However, studies have found that positive anti-gliadin antibodies are not significantly correlated with the severity of psoriasis, age of onset, joint involvement, or arthritis.⁴³ It is currently unclear whether gluten intake contributes to the development of psoriasis.⁴⁴ Reports have confirmed that psoriasis lesions improved in patients who eliminated gluten from their diets. This improvement applies to individuals who have both celiac disease and those who have wheat protein antibodies but do not have celiac disease.^{45,46} However, in patients without antibodies, the lesions did not improve.⁴⁴ A survey indicated that over half of the AD patients (n=169) who removed gluten from their diets reported an improvement in their eczema symptoms.⁴⁷ Nonetheless, other studies have found that dietary gluten intake is not a risk factor for adult female psoriasis (n= 85,185), PsA (n=85,324), or AD (n= 63,443).⁴⁸ A study on the skin disease burden reported that the risk of psoriasis, acne, AD, and rosacea did not significantly increase in patients with celiac disease, and the severity did not differ between the study groups.⁴⁹ A multicenter cross-sectional study involving 1571 patients found that 50% of acne patients believed that a gluten-free diet had no benefit in alleviating acne.⁵⁰ Therefore, most studies or guidelines do not recommend systematic screening for gluten sensitivity in these inflammatory skin diseases unless patients have clinical or serological evidence of gluten sensitivity.^{35,44,51,52} Adopting a gluten-free diet without proper guidance may lead to insufficient intake of dietary fiber, B vitamins, and magnesium. This deficiency can weaken intracellular anti-inflammatory signaling and increase oxidative stress, along with the release of pro-inflammatory factors such as TNF- α and IL-6. Additionally, some gluten-free processed foods are often high in sugar and fat, which may exacerbate insulin resistance and activate pro-inflammatory pathways, indirectly promoting excessive proliferation of keratinocytes or inflammation in the synovial membrane.^{10,53}

Although this study is the first MR study to explore the relationship between popular diets and multiple inflammatory skin diseases, some limitations still require careful interpretation of the MR results. First, while using a relaxed SNP threshold helps balance sample size and ensures the feasibility of the analysis, it may introduce bias and result in insufficient statistical power, thereby limiting the precision of association identification. Future work should focus on optimizing selection strategies to enhance the strength and efficacy of the tools used. Second, the overlap of dietary exposure and psoriasis data may confound genetic signals, and self-reported dietary data are prone to classification errors. To mitigate overlapping biases, individual-level data should be utilized, and precise assessment methods such as metabolomics or food frequency questionnaires linked with biomarkers should be employed to reduce errors. Third, the small effect sizes, lack of adjustments for multiple testing, and reliance on univariate Mendelian randomization only reflect overall effects. Future studies should validate findings with larger samples, apply multiple corrections, and use multivariable Mendelian randomization to control for confounding factors. Additionally, mediation analysis should clarify mechanisms, and subgroup analyses should explore potential interactions. Finally, the study population predominantly consists of individuals of European ancestry, which limits the generalizability of the results. Expanding the sample to include diverse racial and ethnic groups is essential for validation.

Conclusions

In conclusion, this study provides preliminary insights into the association between diet and inflammatory skin diseases, revealing a potential link between low-calorie diets and the modest risk of PsA. This finding contrasts with common perceptions, suggesting that the relationship may be more nuanced than typically assumed and highlighting the need for targeted dietary research in this population. Although the study is grounded in scientific methodology, limitations such as small effect sizes and constraints related to instrumental variables prevent it from directly informing clinical practice at this time. Future large-scale studies, including multivariable Mendelian randomization, mediation analysis, or targeted intervention trials, are essential for further validation and exploration of underlying mechanisms. We encourage the public to stay informed about ongoing research developments and to avoid making health behavior adjustments based solely on isolated findings.

Abbreviations

MR, Mendelian randomization; IVW, Inverse variance weighted; AD, atopic dermatitis; PsA, psoriatic arthritis; GWAS, genome-wide association study; IVs, instrumental variables; STROBE-MR, Strengthening the Reporting of

Observational Studies in Epidemiology using Mendelian Randomization; SNPs, single nucleotide polymorphisms; LD, linkage disequilibrium; OR, odds ratios; CI, confidence intervals.

Data Sharing Statement

The entirety of the data generated or analyzed in this research is presented within this published article.

Ethics Statement

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects approved by the National Ethics Committee for Science and Technology of the People's Republic of China, this study is exempt from ethical review as the data used poses no harm to individuals, does not involve any sensitive personal information or commercial interests, and the selected database is publicly accessible and legally obtained.

Acknowledgments

We want to acknowledge the participants and investigators of the UK biobank and the GWAS catalog database.

Funding

This work was supported by the Tianjin Key Medical Discipline (Specialty) Construction Project (No: TJYXZDXK-057B) and Tianjin Health Research Project (Grant No.TJWJ2023XK006).

Disclosure

The authors declare that they have no competing interests in this work.

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