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ORIGINAL RESEARCH

Association Between Specific Sleep Traits and Four Inflammatory Skin Diseases: A Mendelian Randomization Study

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Background: Sleep disturbances, including insomnia and abnormal sleep duration, are increasingly recognized for their role in various inflammatory processes, yet their causal impact on inflammatory skin diseases remains unclear.

Objective: This study aims to systematically explore the causal relationships between specific 8 sleep traits and 4 inflammatory skin diseases, including psoriasis, acne, atopic dermatitis, and urticaria.

Methods: We conducted a two-sample Mendelian randomization (MR) analysis using genetic data from the UK Biobank and FinnGen. Genetic variants associated with the sleep traits, such as insomnia, sleep duration, daytime sleepiness, daytime napping, snoring, and chronotype, were selected as instrumental variables. We employed methods including inverse variance weighting, weighted median estimation, and MR Egger regression to ensure robust causal inference. Sensitivity analyses were conducted to assess heterogeneity and pleiotropy.

Results: Notably, frequent insomnia was causally linked to an increased risk of psoriasis and atopic dermatitis, while longer sleep duration showed protective effects against acne and urticaria. Additionally, there was no strong evidence connecting other sleep traits like daytime sleepiness, napping, snoring, and chronotype to these skin conditions. Sensitivity analyses also confirmed the robustness and consistency of these findings across different methods.

Conclusion: This study provides evidence that specific sleep traits, especially insomnia and sleep duration, have a causal impact on inflammatory skin diseases. Addressing sleep disturbances in dermatological care could be crucial for reducing disease severity and enhancing patient outcomes.

Keywords: Mendelian randomization, inflammatory skin diseases, sleep traits, causal inference, GWAS

Introduction

Sleep is a fundamental physiological process that is critical in maintaining physical and mental health.[1] Sleep is a fundamental biological process that occupies one-third of a person's lifetime, with restful and sufficient sleep being a vital component of a healthy life, while sleep disturbances are linked to a range of physical and mental health problems. Beyond its well-established impact on cognitive function and metabolic regulation, emerging evidence also suggests that the disruption of sleep may influence immune responses and inflammatory processes.[2,3] Generally, frequent insomnia and snoring are categorized as sleep disorders, while chronotype, daytime napping, daytime sleepiness, long sleep duration, and short sleep duration are categorized as sleep disturbances. These sleep-related disorders and disturbances, such as insomnia and abnormal sleep duration, have been associated with systemic inflammation, oxidative stress, and immune dysregulation, which are key contributors to the pathogenesis of various chronic diseases, including cardiovascular, metabolic, and autoimmune conditions.[4,5] Despite these findings, the relationship between sleep traits and inflammatory skin diseases remains poorly understood, indicating a critical need to unravel their interconnected dynamics between sleep health and dermatological conditions.

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Inflammatory skin diseases, such as psoriasis, acne, atopic dermatitis, and urticaria, are complex disorders characterized by immune-mediated inflammation and impaired skin barrier function.[6] These conditions affect physical health and have profound psychological and social consequences, often disrupting patients' quality of life. Recent studies have highlighted the bidirectional relationship between skin inflammation and sleep disturbances, with inflammatory skin diseases frequently leading to impaired sleep quality through symptoms such as pruritus and pain.[7] Conversely, poor sleep may exacerbate skin inflammation by amplifying immune dysregulation and disrupting skin homeostasis.[8] However, whether sleep traits causally influence the risk of developing inflammatory skin diseases remains unclear, and the underlying mechanisms driving these associations have yet to be fully elucidated.

Traditional observational studies often struggle with confounding variables and reverse causation, limiting their ability to establish clear causal links. In contrast, Mendelian randomization (MR) offers a powerful approach to investigate causal relationships between exposures and outcomes by harnessing genetic variants as instrumental variables (IVs).[9] MR analysis minimizes confounding and reverse causation, making it particularly suited for exploring the complex interactions between sleep traits and inflammatory skin diseases.[10] By utilizing genetic data from large-scale genome-wide association studies (GWAS), MR enables researchers to disentangle causal effects from mere associations, providing robust evidence for biological pathways linking sleep disturbances to immune-mediated conditions.[11] Despite its potential, there has been a lack of MR studies specifically exploring these associations, highlighting a critical gap in the current research landscape.

To date, numerous genetic studies have preliminarily elucidated the complex interactions between sleep traits and inflammatory skin diseases. Atopic dermatitis, a prevalent chronic inflammatory skin condition, is linked to sleep disturbances affecting 47% to 80% of children and 33% to 90% of adults.[12] It is clear that both are influenced by genetic predispositions and immune-mediated pathways. The studies of GWAS have identified multiple genetic loci associated with sleep traits such as insomnia, sleep duration, and circadian rhythm, including gene variants that regulate circadian rhythm (such as core clock genes Bmal1, Clock, Per1/2) and stress responses (such as CRHR1, FKBP5). Similarly, inflammatory skin diseases like psoriasis and atopic dermatitis are associated with gene variants in immune-related pathways, including genes regulating cytokine signaling and skin barrier function, like TNFα, IL-1β, and IL-6.[13] These genetic factors may converge in influencing immune dysregulation and systemic inflammation, which are crucial for both sleep disorders and skin inflammation. For instance, the genetic predisposition to insomnia may exacerbate the production of pro-inflammatory cytokines and oxidative stress, thereby worsening skin barrier dysfunction and immune-mediated skin diseases, manifesting as increased signs of intrinsic aging, weakened skin barrier function, and decreased satisfaction with appearance.[14] Conversely, inflammation associated with skin diseases may disrupt sleep by activating nociceptive pathways and inducing pruritus.[15] By integrating genetic data from GWAS, MR can elucidate the associations between sleep traits and inflammatory skin diseases through epidemiologically relevant causal analyses.

Therefore, in this study, we utilized a two-sample MR analysis to systematically evaluate the causal relationships between 8 specific sleep traits, including sleep duration, short sleep duration, long sleep duration, chronotype, frequent insomnia, daytime napping, daytime sleepiness, snoring, and 4 common inflammatory skin diseases, including psoriasis, acne, atopic dermatitis, and urticaria. Using large-scale genome-wide association study data from the UK Biobank and FinnGen, genetic variants associated with sleep traits were selected as IVs. Multiple statistical approaches were employed to ensure the robustness of causal inference, including inverse variance weighting, weighted median estimation, and MR Egger regression. To further enhance the reliability of the results, we assessed heterogeneity and pleiotropy in the genetic instruments and conducted sensitivity analyses to minimize potential biases. Each sleep trait was individually analyzed to identify specific factors that may contribute to the onset or progression of these diseases. This study advances our understanding of the role of sleep in skin health and provides a theoretical basis for developing targeted interventions aimed at improving sleep quality and alleviating inflammatory skin conditions.

Materials and Methods

Study Overview

A two-sample MR analysis was employed to investigate causal associations between 8 sleep traits and 4 prevalent inflammatory skin diseases, including psoriasis, acne, atopic dermatitis, and urticaria. The analytical framework was outlined

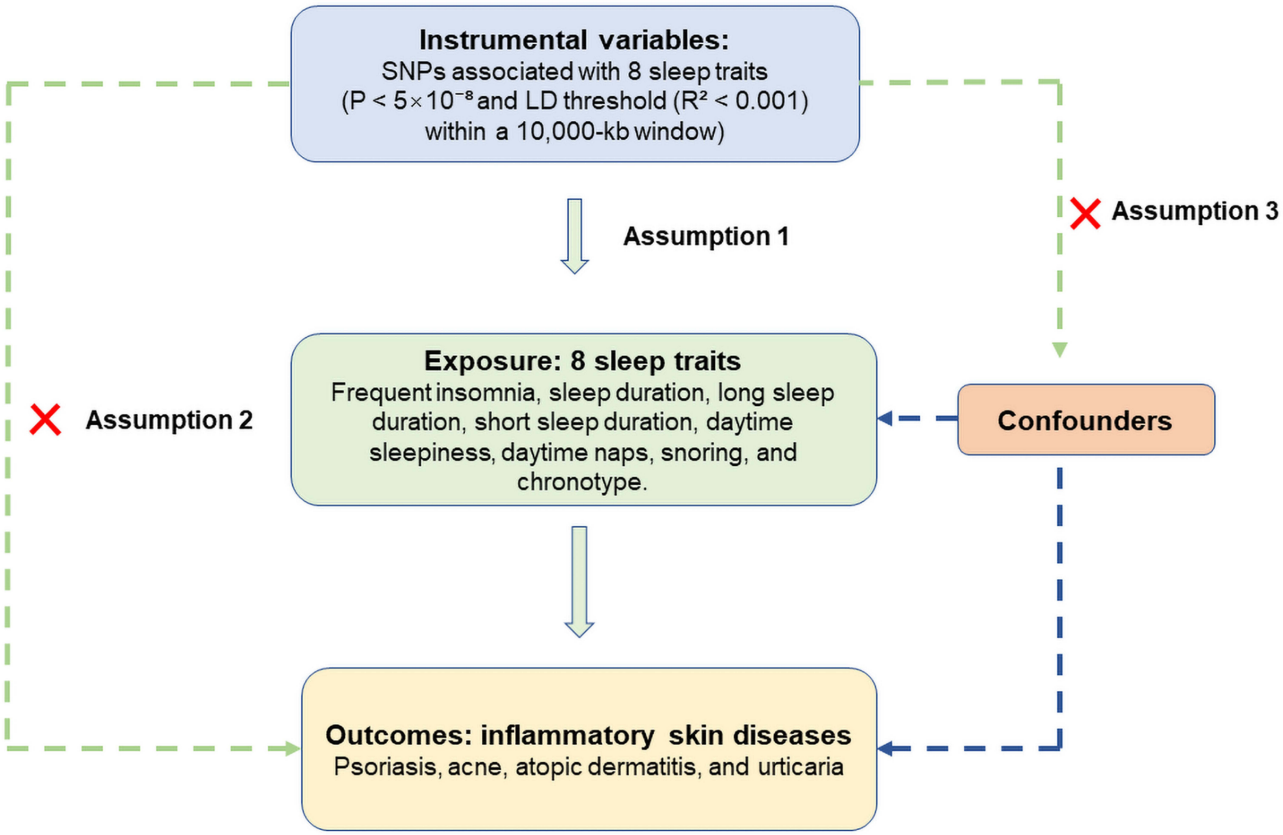

Figure 1 The design scheme for bidirectional MR analysis exploring the causal relationship between sleep traits and inflammatory skin diseases.

in Figure 1. Ensuring a valid causal interpretation in MR analysis relies on three fundamental assumptions: (1) Relevance assumption: Genetic IVs are robustly associated with sleep traits. (2) Independence assumption: IVs are independent of all confounding factors that influence both sleep traits and skin diseases. (3) Exclusivity assumption: IVs affect the outcome exclusively through the hypothesized exposure pathway, without direct effects. Since this is a research operated on databases and does not cause harm to the human body, does not involve sensitive personal information or commercial interests, this project can be exempted from ethical approval, according to the guidance of item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

GWAS Data Sources

The genetic data for inflammatory skin diseases were obtained from the FinnGen Release 12 database (https://www.finngen.fi/en/), a population-based biobank that includes genomic and health records from over 500,000 Finnish individuals. This study focused on 4 prevalent inflammatory skin diseases, including psoriasis (12,760 cases/482,181 controls), acne (4617 cases/476,404 controls), atopic dermatitis (31,245 cases/432,874 controls), and urticaria (13,990 cases/482,901 controls). Disease diagnoses were based on the 10th Revision of the International Classification of Diseases (ICD-10), ensuring standardized case definitions aligned with clinical practice. Table 1 summarizes median age at first event, diagnostic criteria, and sample size per disease category.

Table 1 The Basic Clinical Characteristics of the Sample in the FinnGen Database

Inflammatory Skin Diseases	Diagnostic Criteria	Cases	Controls	Median Age at First Event (Years)
Psoriasis	ICD10-L40	12,760	482,181	51.41
Acne	ICD10-L70	4617	476,404	24.57
Atopic dermatitis	ICD10-L20	31,245	432,874	34.24
Urticaria	ICD10-L50	13,990	482,901	41.23

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Table 2 Description of the Sleep Genome-Wide Association Studies (GWAS) Data Included in the MR Analyses

Variable Factors	Phenotype Definition	Sample Size	Data Source	Population
Sleep duration	Average duration of sleeping in 24 h, including naps (continuous variable, hours)	446,118	UKB	European
Short sleep duration	Average sleep duration of 24 h is 6 h or less vs 7–8 h (binary variable of yes/no)	411,934	UKB	European
Long sleep duration	Average sleep duration of 24 h is 9 h or more vs 7–8 h (binary variable of yes/no)	339,926	UKB	European
Chronotype	Considering yourself as morning/evening person (ordered categorical variable of definitely a morning person, more a morning than an evening person, do not know, more an evening than morning person and definitely an evening person)	449,734	UKB	European
Frequent insomnia	Difficulty falling asleep at night or waking up in the middle of the night (binary variable of "usually" vs "never/rarely")	453,379	UKB	European
Daytime napping	Having a nap during the day (ordered categorical variable of never/rarely, sometimes, usually)	452,633	UKB	European
Daytime sleepiness	Unconsciously dozing off or falling asleep during the day (ordered categorical variable of never, sometimes, often and all the time)	452,071	UKB	European
Snoring	Creating noise while sleeping (binary variable of yes/no)	408,317	UKB	European

Exposure data were sourced from the UK Biobank, which is a large-scale prospective cohort study involving 500,000 adults recruited across 22 centers in the United Kingdom. The UK Biobank captures detailed phenotypic, genotypic, and health outcome data, making it ideal for investigating complex trait-disease relationships. Sleep phenotypes were operationalized using self-reported measures and objective assessments. GWAS were conducted in individuals of European ancestry for frequent insomnia,[16] sleep duration,[17] daytime sleepiness,[18] daytime naps,[19] snoring,[20] and chronotype.[21] Summary statistics were obtained from the Sleep Disorders Genetics Consortium (http://sleepdisordergenetics.org/). Table 2 summarizes the data sources, sample sizes, and key parameters for each sleep phenotype.

In the FinnGen cohort, the median age at biobank sample donation was 53 years, with participants comprising a broad population including hospital biobank patients, blood donors, and individuals from national studies. The age distribution of the Finnish database covers almost every age group, with the majority concentrated among those aged 40–69, accounting for 56%. In the UK Biobank, participants were aged between 40 and 69 at recruitment, with 24% aged 40–49, 34% aged 50–59, and 42% aged 60–69.

Instrumental Variables (IVs) Selection

To establish robust IVs for MR analysis, we systematically curated single-nucleotide polymorphisms (SNPs) associated with sleep traits following established epidemiological and statistical guidelines. First, we extracted all genome-wide significant SNPs ($P < 5\times10^{-8}$) from GWAS data for sleep traits, adhering to the stringent significance threshold recommended for GWAS-based MR studies. Subsequently, linkage disequilibrium (LD) clumping was performed using PLINK software to ensure independence among selected SNPs. This process applied a strict LD threshold ($R^2 < 0.001$) within a 10,000-kb window, ensuring genetic independence to meet MR's key instrumental variable assumption of no horizontal pleiotropy. To address weak instrument bias, we calculated the F-statistic for each SNP-exposure association, a standard metric for IV strength. SNPs with F-statistics < 10 were excluded, as values below this threshold indicate weak relevance to the exposure and increase susceptibility to bias. Palindromic SNPs were then removed to eliminate potential errors in allele coding or strand directionality, which could distort effect estimates in cross-study harmonization. Finally, we employed the MR-PRESSO algorithm to mitigate pleiotropic effects. This method uses a global test to identify and exclude SNPs with significant pleiotropic deviations, enhancing the validity of causal inference by ensuring IVs act exclusively through the hypothesized exposure pathway.

Statistical Analysis

In this study, all data analysis was conducted using R4.4.1 software, primarily using the TwoSampleMR and MR-PRESSO packages. Following harmonization of the selected IVs from the exposure GWAS dataset, two-sample MR

analysis was performed using the TwoSampleMR package, incorporating methods such as inverse-variance weighted (IVW), MR Egger regression, simple median, simple mode, and weighted mode approaches. The IVW method served as the primary analytical framework to investigate causal associations between sleep traits and inflammatory skin diseases. IVW method integrates effect estimates from all valid IVs under the assumption of no horizontal pleiotropy, providing a precise summary of causal effects. To enhance result reliability, the MR-PRESSO method was employed to detect and correct potential outlier genetic variants. This approach uses a global test to identify SNPs with significant pleiotropic effects and recalculates causal estimates after outlier removal, improving robustness against influential variants. Additionally, MR Egger regression was applied to assess horizontal pleiotropy, with its intercept term testing for systematic pleiotropic bias. Cochrane's Q test was used to evaluate heterogeneity among SNPs associated with sleep traits, determining whether variations in causal estimates across genetic variants exceed chance expectations ($P < 0.05$). Significant heterogeneity indicates potential inconsistencies in underlying causal relationships, prompting consideration of random-effects models or subgroup analyses. Finally, the leave-one-out sensitivity analysis was performed by iteratively excluding each SNP to evaluate its influence on the overall MR estimate.

Results

Effect of Sleep Traits on Psoriasis

Table S1 presented the IVs that demonstrated significant associations with the 8 sleep traits. A two-sample MR analysis was conducted to evaluate the impact of sleep traits on psoriasis. Findings from the IVW method indicated that frequent insomnia was significantly and positively associated with an elevated risk of psoriasis, with an odds ratio (OR) of 1.114 (95% confidence interval [CI]: 1.011–1.227; p = 0.029). Although the results of the other four analytical methods did not reach statistical significance, they aligned with the IVW method in terms of the direction of association. The IVW analysis further suggested that no significant associations were observed between the remaining seven sleep traits and psoriasis. Additionally, the MR Egger analysis revealed that short sleep duration was positively associated with psoriasis risk, with an OR of 7.698 (95% CI: 1.306–45.365; p = 0.034). Similar to the previous findings, while the other four analytical methods did not achieve statistical significance, they exhibited the same direction of association as the MR Egger analysis (Figure 2). The results of the MR Egger intercept test indicated that the IVs did not show evidence of horizontal pleiotropy (Table S2). Cochran's Q test, however, suggested the presence of potential heterogeneity for daytime napping, sleep duration, chronotype, daytime sleepiness, short sleep duration, and snoring (Table S3). Visualized through scatter plots, funnel plots, and forest plots, the stability of the relationship between insomnia and psoriasis was emphasized. The "leave-one-out" analysis plot for the MR analysis further indicated that no single SNP substantially impacted the overall estimates of the causal effect (Figure S1).

Effect of Sleep Traits on Acne

A two-sample MR analysis was also carried out to assess the influence of sleep traits on acne. The IVW results indicated that there were no significant associations between the 8 sleep traits and acne. Notably, the MR Egger analysis revealed that sleep duration exerted a protective effect against acne, with an OR of 0.972 (95% CI: 0.948–0.996; p = 0.029). Despite the lack of statistical significance in the other four analytical methods, their results were consistent with the direction of the MR Egger analysis (Figure 3). The MR Egger intercept test results demonstrated that, except for sleep duration, the IVs did not exhibit horizontal pleiotropy (Table S2). Cochran's Q test suggested the presence of potential heterogeneity for daytime napping, sleep duration, and snoring (Table S3).

Effect of Sleep Traits on Atopic Dermatitis

For the genetic predisposition to atopic dermatitis, the IVW results showed that frequent insomnia was positively associated with an increased risk of atopic dermatitis, with an OR of 1.081 (95% CI: 1.003–1.164; p = 0.042). The results of the Simple mode, Weighted median, and Weighted mode analyses were consistent with the IVW method in terms of the direction of association. The IVW analysis further indicated that no significant associations were found between the other 7 sleep traits and atopic dermatitis (Figure 4). The MR Egger intercept test results suggested that,

exposure	outcome	nsnp	method	pval	OR(95% CI)
Chronotype	Psoriasis	141	Inverse variance weighted	0.642	1.033 (0.900 to 1.187)
		141	MR Egger	0.199	0.769 (0.516 to 1.146)
		141	Simple mode	0.509	0.875 (0.589 to 1.300)
		141	Weighted median	0.335	0.920 (0.777 to 1.089)
		141	Weighted mode	0.501	0.903 (0.672 to 1.214)
Daytime napping	Psoriasis	104	Inverse variance weighted	0.138	1.294 (0.921 to 1.819)
		104	MR Egger	0.082	2.980 (0.881 to 10.083)
		104	Simple mode	0.940	1.055 (0.263 to 4.222)
		104	Weighted median	0.455	1.204 (0.740 to 1.960)
		104	Weighted mode	0.770	1.193 (0.366 to 3.887)
Daytime sleepiness	Psoriasis	35	Inverse variance weighted	0.210	0.568 (0.235 to 1.376)
		35	MR Egger	0.165	0.062 (0.001 to 2.872)
		35	Simple mode	0.466	0.474 (0.065 to 3.440)
		35	Weighted median	0.152	0.484 (0.180 to 1.306)
		35	Weighted mode	0.314	0.424 (0.082 to 2.197)
Frequent insomnia	Psoriasis	44	Inverse variance weighted	**0.029**	1.114 (1.011 to 1.227)
		44	MR Egger	0.790	1.038 (0.790 to 1.365)
		44	Simple mode	0.188	1.238 (0.905 to 1.692)
		44	Weighted median	0.352	1.075 (0.923 to 1.253)
		44	Weighted mode	0.454	1.093 (0.868 to 1.375)
Long sleep duration	Psoriasis	7	Inverse variance weighted	0.841	1.026 (0.798 to 1.320)
		7	MR Egger	0.351	1.444 (0.717 to 2.907)
		7	Simple mode	0.531	0.861 (0.553 to 1.339)
		7	Weighted median	0.471	0.898 (0.670 to 1.204)
		7	Weighted mode	0.407	0.825 (0.541 to 1.259)
Short sleep duration	Psoriasis	25	Inverse variance weighted	0.248	1.303 (0.832 to 2.039)
		25	MR Egger	**0.034**	7.698 (1.306 to 45.365)
		25	Simple mode	0.257	1.377 (0.802 to 2.364)
		25	Weighted median	0.103	1.250 (0.956 to 1.634)
		25	Weighted mode	0.131	1.377 (0.923 to 2.055)
Sleep duration	Psoriasis	72	Inverse variance weighted	0.591	1.001 (0.997 to 1.006)
		72	MR Egger	0.643	0.996 (0.979 to 1.013)
		72	Simple mode	0.981	1.000 (0.987 to 1.014)
		72	Weighted median	0.941	1.000 (0.994 to 1.005)
		72	Weighted mode	0.554	0.997 (0.985 to 1.008)
Snoring	Psoriasis	29	Inverse variance weighted	0.975	0.983 (0.324 to 2.977)
		29	MR Egger	0.356	0.066 (0.000 to 19.283)
		29	Simple mode	0.620	0.582 (0.070 to 4.829)
		29	Weighted median	0.954	1.032 (0.354 to 3.011)
		29	Weighted mode	0.931	1.081 (0.187 to 6.251)

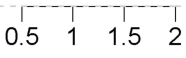

Figure 2 Associations of sleep-related phenotypes with psoriasis risk. p-values less than 0.05 are marked in red.
Abbreviations: nsnp, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

except for frequent insomnia, the IVs did not show evidence of horizontal pleiotropy (Table S2). Cochran's Q test indicated the potential presence of heterogeneity for daytime napping, sleep duration, chronotype, daytime sleepiness, and long sleep duration (Table S3). The stability of the relationship between insomnia and atopic dermatitis was further illustrated by scatter plots, funnel plots, and forest plots. The "leave-one-out" analysis plot for the MR analysis suggested that no single SNP significantly affected the overall estimates of the causal effect (Figure S2).

exposure	outcome	nsnp	method	pval	OR(95% CI)
Chronotype	Acne	141	Inverse variance weighted	0.609	0.948 (0.774 to 1.162)
		141	MR Egger	0.211	0.685 (0.380 to 1.236)
		141	Simple mode	0.219	0.661 (0.343 to 1.275)
		141	Weighted median	0.177	0.827 (0.628 to 1.090)
		141	Weighted mode	0.187	0.729 (0.457 to 1.163)
Daytime napping	Acne	104	Inverse variance weighted	0.132	1.540 (0.878 to 2.702)
		104	MR Egger	0.361	2.586 (0.340 to 19.653)
		104	Simple mode	0.827	0.813 (0.128 to 5.164)
		104	Weighted median	0.423	1.373 (0.632 to 2.987)
		104	Weighted mode	0.865	1.135 (0.264 to 4.884)
Daytime sleepiness	Acne	35	Inverse variance weighted	0.081	0.352 (0.109 to 1.138)
		35	MR Egger	0.480	0.153 (0.001 to 26.507)
		35	Simple mode	0.264	0.170 (0.008 to 3.624)
		35	Weighted median	0.126	0.294 (0.061 to 1.412)
		35	Weighted mode	0.356	0.283 (0.020 to 3.973)
Frequent insomnia	Acne	44	Inverse variance weighted	0.306	1.087 (0.926 to 1.277)
		44	MR Egger	0.274	0.774 (0.492 to 1.218)
		44	Simple mode	0.850	0.950 (0.558 to 1.617)
		44	Weighted median	0.544	0.929 (0.734 to 1.177)
		44	Weighted mode	0.469	0.862 (0.580 to 1.283)
Long sleep duration	Acne	7	Inverse variance weighted	0.762	0.942 (0.641 to 1.385)
		7	MR Egger	0.582	0.710 (0.227 to 2.222)
		7	Simple mode	0.672	0.855 (0.429 to 1.703)
		7	Weighted median	0.212	0.757 (0.489 to 1.172)
		7	Weighted mode	0.385	0.769 (0.444 to 1.332)
Short sleep duration	Acne	25	Inverse variance weighted	0.547	1.110 (0.791 to 1.557)
		25	MR Egger	0.352	2.115 (0.451 to 9.914)
		25	Simple mode	0.362	0.642 (0.252 to 1.635)
		25	Weighted median	0.404	0.829 (0.534 to 1.288)
		25	Weighted mode	0.339	0.642 (0.263 to 1.564)
Sleep duration	Acne	72	Inverse variance weighted	0.763	0.999 (0.992 to 1.006)
		72	MR Egger	**0.029**	0.972 (0.948 to 0.996)
		72	Simple mode	0.233	0.988 (0.968 to 1.008)
		72	Weighted median	0.071	0.992 (0.983 to 1.001)
		72	Weighted mode	0.086	0.987 (0.972 to 1.002)
Snoring	Acne	29	Inverse variance weighted	0.378	0.514 (0.117 to 2.258)
		29	MR Egger	0.106	0.002 (0.000 to 2.955)
		29	Simple mode	0.212	0.096 (0.003 to 3.495)
		29	Weighted median	0.288	0.388 (0.068 to 2.220)
		29	Weighted mode	0.463	0.289 (0.011 to 7.632)

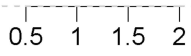

Figure 3 Associations of sleep-related phenotypes with acne risk. p-values less than 0.05 are marked in red.
Abbreviations: nsnp, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Effect of Sleep Traits on Urticaria

The IVW results suggested that there was no compelling evidence to suggest any causal relationship between any of the sleep-related phenotypes and the risk of urticaria. However, sleep duration showed a protective effect on urticaria in Simple mode analysis (OR = 0.988, 95% CI: 0.976–1.000; p = 0.0497). Although the other four analytical methods did

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exposure	outcome	nsnp	method	pval	OR(95% CI)
Chronotype	Atopic dermatitis	141	Inverse variance weighted	0.907	0.994 (0.903 to 1.095)
		141	MR Egger	0.995	0.999 (0.755 to 1.322)
		141	Simple mode	0.270	1.222 (0.857 to 1.743)
		141	Weighted median	0.146	1.092 (0.970 to 1.230)
		141	Weighted mode	0.252	1.162 (0.900 to 1.500)
Daytime napping	Atopic dermatitis	104	Inverse variance weighted	0.733	1.051 (0.792 to 1.394)
		104	MR Egger	0.531	1.387 (0.500 to 3.846)
		104	Simple mode	0.724	0.867 (0.395 to 1.904)
		104	Weighted median	0.914	1.017 (0.748 to 1.384)
		104	Weighted mode	0.984	1.007 (0.520 to 1.951)
Daytime sleepiness	Atopic dermatitis	35	Inverse variance weighted	0.349	0.777 (0.458 to 1.318)
		35	MR Egger	0.302	0.292 (0.029 to 2.918)
		35	Simple mode	0.579	0.705 (0.208 to 2.395)
		35	Weighted median	0.590	0.837 (0.437 to 1.603)
		35	Weighted mode	0.512	0.705 (0.251 to 1.980)
Frequent insomnia	Atopic dermatitis	44	Inverse variance weighted	**0.042**	1.081 (1.003 to 1.164)
		44	MR Egger	0.247	0.885 (0.722 to 1.085)
		44	Simple mode	0.192	1.160 (0.931 to 1.444)
		44	Weighted median	0.300	1.054 (0.954 to 1.164)
		44	Weighted mode	0.752	1.024 (0.886 to 1.184)
Long sleep duration	Atopic dermatitis	7	Inverse variance weighted	0.924	1.015 (0.743 to 1.387)
		7	MR Egger	0.799	0.879 (0.343 to 2.252)
		7	Simple mode	0.252	1.185 (0.911 to 1.541)
		7	Weighted median	0.269	1.110 (0.923 to 1.335)
		7	Weighted mode	0.303	1.118 (0.920 to 1.359)
Short sleep duration	Atopic dermatitis	25	Inverse variance weighted	0.831	0.985 (0.862 to 1.127)
		25	MR Egger	0.936	1.026 (0.551 to 1.912)
		25	Simple mode	0.458	1.130 (0.822 to 1.553)
		25	Weighted median	0.887	1.012 (0.855 to 1.198)
		25	Weighted mode	0.557	0.919 (0.697 to 1.213)
Sleep duration	Atopic dermatitis	72	Inverse variance weighted	0.293	1.002 (0.999 to 1.005)
		72	MR Egger	0.769	1.002 (0.990 to 1.013)
		72	Simple mode	0.727	0.998 (0.990 to 1.007)
		72	Weighted median	0.785	0.999 (0.996 to 1.003)
		72	Weighted mode	0.783	0.999 (0.992 to 1.006)
Snoring	Atopic dermatitis	29	Inverse variance weighted	0.171	1.465 (0.848 to 2.531)
		29	MR Egger	0.311	4.409 (0.264 to 73.614)
		29	Simple mode	0.280	2.232 (0.535 to 9.314)
		29	Weighted median	0.203	1.556 (0.788 to 3.072)
		29	Weighted mode	0.271	2.093 (0.577 to 7.584)

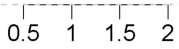

Figure 4 Associations of sleep-related phenotypes with atopic dermatitis risk. p-values less than 0.05 are marked in red.
Abbreviations: nsnp, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

not reach statistical significance, they showed the same direction as the Simple mode analysis (Figure 5). The MR Egger intercept test results revealed that the IVs did not exhibit horizontal pleiotropy (Table S2). Cochran's Q test revealed that there was no significant heterogeneity except for chronotype (Table S3).

Discussion

Sleep disturbances have been increasingly recognized as potential risk factors for various inflammatory and autoimmune conditions.[22] This study employed MR to investigate the causal relationships between sleep characteristics and 4 common

exposure	outcome	nsnp	method	pval	OR(95% CI)
Chronotype	Urticaria	141	Inverse variance weighted	0.844	1.013 (0.889 to 1.154)
		141	MR Egger	0.921	1.020 (0.697 to 1.491)
		141	Simple mode	0.643	1.103 (0.729 to 1.669)
		141	Weighted median	0.548	1.050 (0.895 to 1.233)
		141	Weighted mode	0.503	1.118 (0.808 to 1.547)
Daytime napping	Urticaria	104	Inverse variance weighted	0.713	1.060 (0.778 to 1.444)
		104	MR Egger	0.235	1.966 (0.648 to 5.964)
		104	Simple mode	0.808	0.869 (0.282 to 2.682)
		104	Weighted median	0.897	1.029 (0.671 to 1.578)
		104	Weighted mode	0.897	1.058 (0.453 to 2.470)
Daytime sleepiness	Urticaria	35	Inverse variance weighted	0.433	0.781 (0.420 to 1.450)
		35	MR Egger	0.266	0.213 (0.015 to 3.112)
		35	Simple mode	0.388	0.452 (0.076 to 2.675)
		35	Weighted median	0.347	0.659 (0.277 to 1.572)
		35	Weighted mode	0.259	0.418 (0.095 to 1.851)
Frequent insomnia	Urticaria	44	Inverse variance weighted	0.119	1.086 (0.979 to 1.204)
		44	MR Egger	0.212	0.833 (0.627 to 1.105)
		44	Simple mode	0.846	1.031 (0.760 to 1.398)
		44	Weighted median	0.928	1.007 (0.869 to 1.166)
		44	Weighted mode	0.877	0.983 (0.798 to 1.213)
Long sleep duration	Urticaria	7	Inverse variance weighted	0.163	0.870 (0.716 to 1.058)
		7	MR Egger	0.656	0.877 (0.508 to 1.512)
		7	Simple mode	0.238	0.793 (0.561 to 1.122)
		7	Weighted median	0.146	0.833 (0.651 to 1.065)
		7	Weighted mode	0.278	0.809 (0.572 to 1.146)
Short sleep duration	Urticaria	25	Inverse variance weighted	0.175	1.156 (0.938 to 1.425)
		25	MR Egger	0.539	0.735 (0.280 to 1.931)
		25	Simple mode	0.804	0.932 (0.536 to 1.620)
		25	Weighted median	0.209	1.182 (0.910 to 1.535)
		25	Weighted mode	0.723	1.081 (0.705 to 1.658)
Sleep duration	Urticaria	72	Inverse variance weighted	0.103	0.997 (0.994 to 1.001)
		72	MR Egger	0.974	1.000 (0.987 to 1.013)
		72	Simple mode	**0.050**	0.988 (0.976 to 1.000)
		72	Weighted median	0.080	0.995 (0.990 to 1.001)
		72	Weighted mode	0.056	0.990 (0.980 to 1.000)
Snoring	Urticaria	29	Inverse variance weighted	0.067	1.972 (0.953 to 4.081)
		29	MR Egger	0.866	0.721 (0.017 to 31.242)
		29	Simple mode	0.149	5.497 (0.580 to 52.097)
		29	Weighted median	0.080	2.430 (0.901 to 6.555)
		29	Weighted mode	0.312	3.243 (0.345 to 30.467)

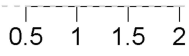

Figure 5 Associations of sleep-related phenotypes with urticaria risk. p-values less than 0.05 are marked in red.
Abbreviations: nsnp, nonsynonymous single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

inflammatory skin diseases, including psoriasis, acne, atopic dermatitis, and urticaria. The findings revealed that frequent insomnia was significantly associated with an increased risk of both psoriasis and atopic dermatitis, while longer sleep duration demonstrated protective effects against acne and urticaria. No strong evidence was found linking other sleep traits, such as snoring, daytime napping, or chronotype, with the risk of these skin conditions. Thus, we provide novel insights into the complex links between sleep traits and skin inflammation, highlighting potential therapeutic implications.

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The first major finding of this study is the observed positive association between frequent insomnia and the heightened risk of psoriasis and atopic dermatitis. Insomnia is a well-documented stressor that disrupts the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels and systemic inflammation.[23] Chronic inflammation is a hallmark of both psoriasis and atopic dermatitis, and sleep deprivation may exacerbate immune dysregulation by amplifying pro-inflammatory cytokine production, such as IL-6 and tumor necrosis factor-alpha (TNF-α). Psychological stress, represented by Insomnia, disrupts epidermal barrier function by activating the HPA axis, leading to increased production of stress hormones.[24] These hormones impair the barrier by reducing epidermal lipids and structural proteins, decreasing stratum corneum hydration, and increasing transepidermal water loss. Identifying stressors and promoting stress-reduction strategies may help preserve epidermal integrity and prevent stress-related dermatological conditions. In another aspect, patients with inflammatory skin disorders, such as psoriasis, experience significantly higher fatigue levels and greater odds of insomnia compared to those with noninflammatory skin disorders like nonmelanoma skin cancers.[25] Interestingly, A US population-based study showed that psoriasis is independently associated with a 1.88-fold increased risk of trouble sleeping, particularly in older adults, females, and those with a history of sleep disorders.[26] Atopic dermatitis in children is consistently associated with impaired sleep quality throughout childhood.[27] Meanwhile, two weeks of intensive topical corticosteroid and emollient therapy significantly improved insomnia severity, deep sleep, and overall sleep architecture in psoriasis and atopic dermatitis patients, alongside reductions in disease activity and pruritus, highlighting the strong link between skin inflammation and sleep disturbances.[28] Therefore, addressing sleep disturbances in individuals with these conditions may be a viable strategy to reduce inflammatory severity or progression, while mitigating skin inflammation may, in turn, improve sleep quality.

The second key observation is the protective role of longer sleep duration against acne and urticaria. Adequate sleep is essential for maintaining skin barrier integrity and promoting tissue repair processes. Sleep deprivation has been linked to increased oxidative stress and impaired immune function, both of which are implicated in acne pathogenesis and histamine-mediated urticaria.[29] And, Type 2 inflammation regulates chronic pruritus in various skin diseases, including atopic dermatitis and acne, through key cytokines that activate sensory neurons or amplify itch sensitivity, significantly affecting quality of life.[30] As Besedovsky reported, sleep modulates immune function by influencing inflammatory responses, infection risk, vaccination outcomes, and maintaining inflammatory homeostasis, while chronic sleep deficiency promotes systemic low-grade inflammation linked to inflammatory diseases.[31] Chronic poor sleep quality is linked to accelerated intrinsic skin ageing, impaired barrier recovery, delayed erythema resolution, and reduced self-perceived attractiveness, highlighting the critical role of sleep in maintaining skin health and appearance.[14] Besides, the observed protective effects of sleep duration may reflect the importance of restorative sleep in regulating immune responses and maintaining skin homeostasis. These findings highlight the critical importance of promoting healthy sleep habits in dermatological care, particularly for patients susceptible to inflammatory skin conditions, as restorative sleep serves as a fundamental pillar of immune regulation and skin homeostasis.

Another noteworthy finding is the lack of significant associations between other sleep traits, such as snoring, daytime napping, and chronotype, with the risk of inflammatory skin diseases. While these sleep traits may influence general health and well-being, their effects on skin-specific inflammatory pathways appear to be limited based on the current evidence.[32] Importantly, early sensitization to both food and inhalant allergens significantly elevates the risk of habitual snoring in childhood, likely due to ongoing upper airway inflammation from allergic triggers.[33] This highlights the importance of focusing on specific sleep disturbances, such as insomnia and sleep duration, which may have more direct impacts on immune-mediated skin disorders. Further research is warranted to elucidate the underlying mechanisms and explore whether certain subgroups may exhibit differential susceptibility to these sleep traits.

Obstructive sleep apnea (OSA) involves repeated full or partial blockages of the upper airway, leading to intermittent low oxygen levels, fluctuations in autonomic function, and disrupted sleep.[34] OSA is linked to skin disease both epidemiologically and mechanistically. Chronic inflammation plays a central role in the pathophysiology of OSA, contributing to its associated comorbidities, such as cardiovascular, metabolic diseases, and skin diseases.[35] Overall sleep quality and sleep disorders, including OSA, sleep deprivation, and sleep fragmentation, are closely associated with chronic low-grade inflammation, oxidative stress, and the regulation of pro-inflammatory cytokines. Poor sleep quality elevates levels of pro-inflammatory cytokines, which are crucial in the pathogenesis of psoriasis and atopic dermatitis. As

reported, OSA is linked to skin diseases through shared mechanisms involving inflammatory pathways, obesity, upper airway mechanical obstruction, and hypoxia. Additionally, sleep disturbances activate the HPA axis, increasing cortisol secretion and impairing skin barrier function, while sleep deprivation can compromise immune function and exacerbate inflammatory responses. Cameron et al reported that atopic dermatitis (AD) and sleep disturbance share a bidirectional relationship driven by inflammation, immune dysregulation, and itch, with systemic and neuropsychiatric impacts significantly affecting patient quality of life.[36] Overall, addressing the broader impact of sleep disorders like OSA and general sleep quality, provides valuable consideration into the complex interplay between sleep, inflammation, and skin health, paving the way for novel therapeutic interventions.

Acne is a complex, multifactorial condition characterized by papules, pustules, comedones, and nodules, affecting individuals across various age groups, with underlying mechanisms differing by age. In adolescents, acne is primarily triggered by hormonal changes during puberty, particularly elevated androgen levels, which enhance sebaceous gland activity and lead to follicular hyperkeratinization. Adolescent acne typically occurs between the ages of 10 and 19. In contrast, adult acne, more common in individuals over 25, exhibits distinct clinical features and etiological factors, with inflammatory papules and pustules primarily concentrated around the jawline and chin. Adult acne is often influenced by chronic inflammation, psychological stress, increased sebaceous gland sensitivity to androgens, and endocrine fluctuations, such as those related to the menstrual cycle in women.[37] Given that the FinnGen biobank predominantly includes middle-aged and older individuals aged 40–69, the findings of this study may better reflect mechanisms of adult acne and may not fully capture the pathophysiology of adolescent acne. To better understand the relationship between sleep characteristics and acne, it is essential to include younger populations in MR analyses and assess how these associations vary across different age groups.

The fourth point of discussion pertains to the heterogeneity identified in certain MR analyses. Although the MR framework is designed to mitigate confounding and reverse causation, the observed heterogeneity in sleep traits, such as daytime napping and chronotype, highlights potential variability in the underlying genetic instruments or unresolved pleiotropic effects.[38] This heterogeneity may be caused by differences in genetic architecture, environmental exposures, or gene-environment interactions, which could influence the causal estimates derived from MR analyses.[39] Addressing this issue requires the application of advanced statistical techniques, such as MR-PRESSO, Cochran's Q test, and detailed sensitivity analyses, to detect and correct for pleiotropy, as well as to assess the stability and reliability of causal estimates.[40] Stratified analyses and multi-trait approaches offer valuable insights into subgroup-specific effects and overlapping genetic pathways, helping to untangle the complex relationships between sleep traits and inflammatory skin diseases. Refining analytical methods and integrating genetic and environmental data can significantly enhance the reliability of causal estimates and deepen our understanding of these interactions.

While this study offers valuable insights, several limitations should be acknowledged. The MR approach assumes that genetic instruments influence the outcome exclusively through the exposure, without horizontal pleiotropy. Although sensitivity analyses, including MR Egger and MR-PRESSO, were conducted to detect and correct for pleiotropy, the possibility of residual pleiotropy affecting the results cannot be entirely ruled out, especially given the complex genetic architecture of sleep traits and inflammatory skin diseases. Second, the study focused exclusively on European populations, limiting the generalizability of the findings to other ethnic groups. Furthermore, sleep traits were assessed using self-reported data, which may introduce measurement bias. For instance, Bawany et al posed that sleep disturbances affect 47%-80% of children and 33%-90% of adults with atopic dermatitis, with most studies relying on subjective measures and limited objective data.[12] Objective sleep measures, such as actigraphy or polysomnography, could provide more accurate insights into the relationships between sleep and skin diseases. Lastly, while MR provides evidence for causality, it does not account for environmental factors or lifestyle influences that may interact with genetic predispositions. Future studies should incorporate multi-ethnic cohorts and longitudinal designs to validate the causal links between sleep disturbances and inflammatory skin diseases, and to explore how these associations may vary across different populations.

Conclusion

In conclusion, this study reveals potential causal links between sleep traits and inflammatory skin diseases, emphasizing the role of sleep in modulating inflammatory pathways. Especially, we confirm that frequent insomnia and sleep duration,

but not other sleep traits, have distinct causal effects on inflammatory skin diseases. Insomnia increased the risk of psoriasis and atopic dermatitis, while longer sleep duration reduced the risk of acne and urticaria. Insomnia and sleep duration may influence skin inflammation through immune dysregulation, as supported by prior mechanistic studies. These findings add to the growing evidence connecting sleep health with immune-related skin diseases, providing a foundation for future research and potential therapeutic strategies. Future research should incorporate severity metrics such as scoring atopic dermatitis (SCORAD) and psoriasis area and severity index (PASI), to determine whether sleep interventions could inhibit inflammatory skin disease progression.

Abbreviations

GWAS, genome-wide association studies; HPA, hypothalamic-pituitary-adrenal; IVs, instrumental variables; IVW, inverse-variance weighted; LD, linkage disequilibrium; MR, Mendelian randomization; OR, odds ratio; SNPs, single nucleotide polymorphisms; TNF-α, tumor necrosis factor-alpha.

Data Sharing Statement

All data are publicly available.

Consent for Publication

All patients in this study provided their consent for publication.

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Disclosure

Peiquan Yang and Yongyou Huang are co-first authors for this study. The authors declare no competing interests in this work.

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