Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

No Associations Between Genetically Predicted Chronotype, Insomnia, Daytime Sleepiness, or Physical Activity and Acne Vulgaris: A Two-Sample Mendelian Randomization Study

Chaoqun Tian

Department of Dermatology, Chongqing Yubei District People`s Hospital, Chongqing, 401120, People's Republic of China

Correspondence: Chaoqun Tian, Department of Dermatology, Chongqing Yubei District People`s Hospital, No. 23, Central Park North Road, Xiantao Street, Yubei District, Chongqing, 401120, People's Republic of China, Tel +86 15123948801, Email 609860051@qq.com

Purpose: The exact factors leading to the development of acne vulgaris are poorly understood. Besides diet, lifestyle habits like sleep and physical activity have received attention. This study explored the causal associations between genetically predicted sleep traits and exercise and acne vulgaris.

Patients and Methods: The genome-wide association study (GWAS) data for sleep, physical activity, and acne vulgaris were retrieved from the FinnGen Project (1092/211,139 patients/controls) to carry out a two-sample Mendelian randomization (MR) analysis. Validation was performed using a dataset from the Estonian Biobank (34,422/364,991 patients/controls). The inverse variance weighted (IVW) method was the primary analytical method, with robustness tested using the weighted median, weighted mode, and MR-Egger analyses. Heterogeneity was tested using Cochran's Q-test, horizontal pleiotropy using MR-Egger regression, outliers using MR-PRESSO, and driving SNPs using the leave-one-out method.

Results: The results revealed that genetically predicted chronotype (OR=1.021, 95% CI: 0.786–1.326, P=0.875), insomnia (OR=1.475, 95% CI: 0.676–3.216, P=0.329), daytime sleepiness (OR=0.466, 95% CI: 0.046–4.708, P=0.518), or physical activity (OR=0.990, 95% CI: 0.925–1.059, P=0.767) were not causally associated with acne vulgaris. Cochran's Q-test detected no heterogeneity (all P>0.05). No horizontal pleiotropy was detected (all P>0.05), indicating that the selected IVs met the third MR assumption. MR-PRESSO revealed no outliers. No single SNP drove the results according to the leave-one-out analysis. These results were validated through the use of additional datasets.

Conclusion: Our study found no causal associations between sleep traits and physical activity and acne vulgaris. However, further research is needed to explore other potential factors and validate these results in more diverse populations.

Keywords: acne vulgaris, sleep, physical activity, Mendelian randomization, causality

Introduction

Acne vulgaris is a chronic skin disease featuring noninflammatory open and/or closed comedones and lesions of an inflammatory nature (eg, papules, pustules, cysts, and nodules) found on the skin, particularly the face, neck, back, chest, and upper arms.[1,2] Acne poses no risk to physical health but can have significant psychosocial effects and impact quality of life.[3] Adults and adolescents with acne often have an increased risk of depression and anxiety.[4,5] Acne may also be linked to endocrinological disorders such as polycystic ovarian syndrome, precocious puberty, or rarely, late-onset congenital adrenal hyperplasia or Cushing syndrome. The exact factors contributing to the development of acne vulgaris remain poorly understood despite its high prevalence and significant impact on quality of life.[6] While diet has long been a focus of research, lifestyle habits such as sleep and physical activity have also gained attention in recent years as potential contributors to acne pathogenesis.[7]

Received: 7 January 2025
Accepted: 21 March 2025
Published: 6 April 2025

Indeed, there is evidence suggesting a relationship between sleep quality and acne. Studies have shown that the severity of acne is directly linked to insomnia and poor quality of life, highlighting the importance of addressing sleep disturbances in patients with acne.[8,9] Acne is also strongly associated with sleep deprivation and depressed mood, prompting physicians to consider the psychological burden of acne when managing their patients.[10] Nevertheless, it remains unclear whether sleep traits have a direct causal association with acne vulgaris. Additionally, poor sleep is often linked to depression and anxiety, which are well-documented factors that negatively impact sleep quality.[11,12] This relationship becomes even more complex when considering that acne itself can induce stress and contribute to sleep disorders.[13] On the other hand, physical activity possesses a plethora of beneficial effects on health, both physical and mental. Exercise has been shown to enhance skin health and promote anti-aging effects,[14] and it may even influence certain skin conditions, such as urticaria.[15] Given these benefits, it is worth investigating whether physical activity has an effect on acne vulgaris.

Establishing a causal relationship between sleep characteristics, physical activity, and acne vulgaris based solely on observational studies is challenging due to limitations such as measurement error, inherent bias, and reverse causality. To address these issues, Mendelian randomization (MR) offers a robust methodological approach.[16] Genome-wide association studies (GWASs) provided results for millions of single-nucleotide polymorphisms (SNPs) and their association with various phenotypes and diseases, revolutionizing the study of complex traits.[17] MR is based on the properties of the common genetic variations for different environmental exposures and allows the exploration of possible causal associations between exposures and diseases.[18] Two-sample MR combines the associations between SNPs and exposure and between SNPs and outcomes from different GWASs to estimate causality.

To better understand the role of sleep traits and physical activity in acne vulgaris, we applied MR analysis to investigate the causal associations between genetically predicted sleep traits and physical activity levels and the risk of developing acne vulgaris. These findings could provide valuable insights for improving the management and care of individuals affected by acne vulgaris.

Methods

Study Design

A two-sample MR was conducted in this study, with sleep traits (chronotype, insomnia, and daytime sleepiness) and physical activity as the exposure factors and acne vulgaris as the outcome (Figure 1). Publicly available data from GWASs were used for the analysis. Ethical approval was addressed in detail in the original studies from which the data were obtained. The MR methodology is based on three key assumptions: 1) the relevance assumption (ie, the SNPs being used as IVs for the exposure are associated with it), 2) the independence assumption (ie, no common causes between the SNPs and the outcome of interest), and 3) the no horizontal pleiotropy assumption (ie, no independent pathway between the SNPs and the outcome other than through the exposure).[19]

This study adhered to the "STrengthening the Reporting of OBservational studies in Epidemiology using Mendelian Randomization" (STROBE-MR) checklist guidelines to ensure comprehensive and transparent reporting standards.

Data Source

The exposure data were sourced from publicly available GWAS summary statistics obtained through the GWAS Catalog (https://www.ebi.ac.uk/gwas/). These data included the following traits within the European population: chronotype (morning person) (GCST007565; UK Biobank; 403,195 Europeans; 11,990,941 SNPs), insomnia (GCST007988; UK Biobank; 1,331,010 Europeans), daytime sleepiness (GCST012956; UK Biobank; 452,071 Europeans) and physical activity (ebi-a-GCST90093322; 89,983 individuals of European ancestry; 8,669,219 SNPs).

The GWAS summary data of acne vulgaris was obtained from the FinnGen Project (https://www.finngen.fi/en), a biobank comprising approximately 500,000 Finnish individuals of Finnish ancestry, with accessible health and SNP data. The dataset (finn-b-L12_ACNE_VULGARIS) included 1092 acne vulgaris cases and 211,139 controls, covering 16,380,453 SNPs. This dataset represents one of the most extensive collections of genetic data on acne vulgaris currently available.

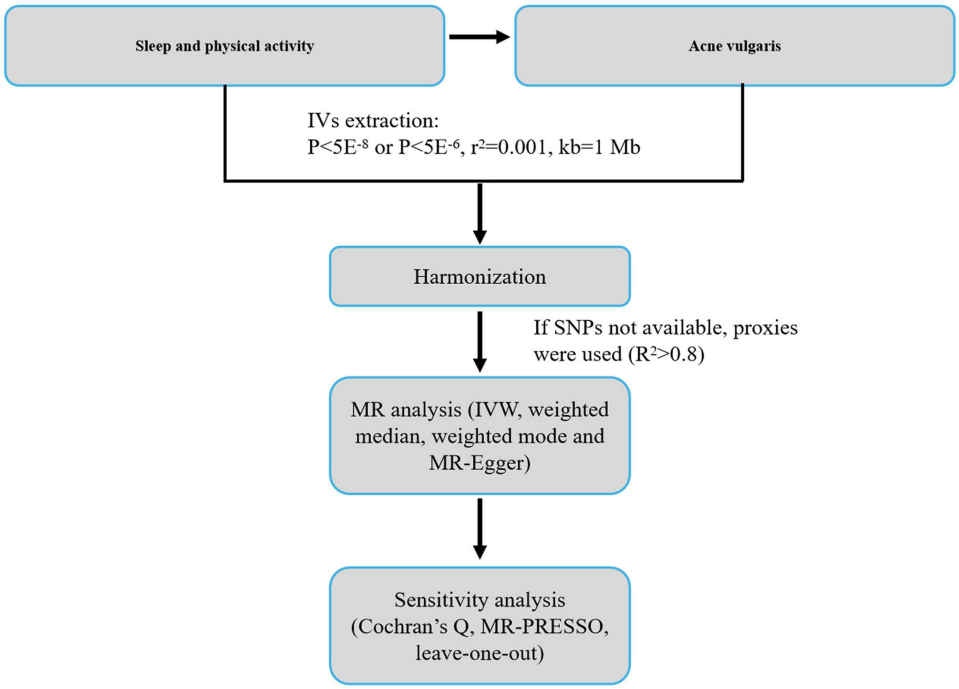

Figure 1 Schematic representation of the Mendelian randomization study.

To further validate our findings, we conducted an additional analysis using the GCST90245818 dataset from the Estonia Biobank (EsB), which includes 34,422 cases and 364,991 controls.[20] This supplementary analysis provided robust support for the reliability and consistency of our results across different populations.

Instrumental Variable Selection

The IVs were included based on the following criteria. 1) The significant SNPs related to sleep traits were selected based on $P<5\times10^{-8}$.[21] For physical activity, given the limitation of obtaining an insufficient number of SNPs when applying the conventional threshold, we adopted a less stringent threshold of $P < 5\times10^{-6}$. This method has been widely utilized in MR studies to balance the need for sufficient IVs with the requirement for robust statistical inference, as demonstrated in prior research.[22,23] 2) The SNPs were retained if they displayed a minor allele frequency (MAF) >0.01. 3) The SNPs were pruned based on the presence of linkage disequilibrium (LD) between SNPs according to $R^2<0.001$ and a window size of 10,000 kb. 4) When an IV was absent in the summary data for the outcome, a SNP with a high LD ($R^2>0.8$) was sought as a proxy and used for replacement. The F-value for each SNP within the IV was computed to assess the IV strength, thereby mitigating potential weak instrument bias between the IV and the exposure factor. The formula for F is $F=R^2\times(N-2)/(1-R^2)$. The IVs were retained if they exhibited no weak instrument bias, as indicated by F-values greater than 10.[24]

Mendelian Randomization Analysis

The primary MR method was the inverse variance weighted (IVW) analysis. The results were presented as odds ratios (OR) and 95% confidence intervals (CIs).[25] The robustness of the IVW analysis was tested using the MR-Egger, weighted median, and weighted mode methods. All analyses were conducted using the "TwoSampleMR" package (version R 4.3.3). The results were visualized using scatter and sensitivity plots.

Sensitivity Analysis

Heterogeneity among IVs can affect the results of MR studies. Heterogeneity was detected using Cochran's Q-test, where P>0.05 indicated low heterogeneity, meaning that the estimates among IVs were randomly distributed and had little impact on the IVW results.[26] Funnel plots were drawn to illustrate heterogeneity. The third MR assumption requires the

absence of horizontal pleiotropy. The MR-Egger regression method was applied to detect the presence of horizontal pleiotropy. An intercept of the MR-Egger regression approaching zero or P>0.05 suggested the absence of pleiotropy.[26] The MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to identify outliers (based on P<0.05) and re-estimate causal associations after their removal to correct for horizontal pleiotropy A leave-one-out analysis was performed to assess robustness and consistency by sequentially excluding each SNP.[27]

Results

Instrument Variable Selection

In this study, 122, 33, 13, and 48 SNPs were selected for chronotype, daytime sleepiness, insomnia, and physical activity, respectively. The mean (min-max) F-values were 45.67 (29.02–168.52), 42.45 (29.51–118.15), 41.19 (30.36–94.70), and 25.09 (20.90–45.75), respectively. All F-values were >10, indicating the absence of weak instrumental bias. Thirteen SNPs were not found in the acne vulgaris dataset; proxy SNPs could not be found for two SNPs, while the others had proxies: rs9365769 was replaced by rs9356270, rs78095690 by rs6043841, rs4241964 by rs1283044, rs34719019 by rs12356674, rs2668658 by rs2732630, rs186056728 by rs117833456, rs1668835 by rs1786150, rs13059636 by rs13062430, rs12460611 by rs17599450, rs12055234 by rs60271, and rs11078398 by rs11868035. The SNPs are presented in Tables S1-S8.

Mendelian Randomization Analysis Results

The IVW method in the main analysis showed that genetically predicted chronotype (OR=1.021, 95% CI: 0.786–1.326, P=0.875), insomnia (OR=1.475, 95% CI: 0.676–3.216, P=0.329), daytime sleepiness (OR=0.466, 95% CI: 0.046–4.708, P=0.518), or physical activity (OR=0.990, 95% CI: 0.925–1.059, P=0.767) were not causally associated with acne vulgaris in the FinnGen database (Table 1, Figures 2, and S1). The results from three additional analytical methods were consistent with those of the IVW approach (Table S9).

To ensure the robustness of our results, we conducted a validation analysis using data from the EsB study. The IVW method in the validation analysis showed that genetically predicted chronotype (OR=0.993, 95% CI: 0.937–1.051, P=0.796), insomnia (OR=1.016, 95% CI: 0.869–1.187, P=0.843), daytime sleepiness (OR=1.045, 95% CI: 0.573–1.903, P=0.887), or physical activity (OR=0.994, 95% CI: 0.974–1.015, P=0.575) were not causally associated with acne vulgaris in the EsB Database (Table 1), supported by the other MR analyses (Table S10). These findings provide comprehensive evidence supporting the reliability of our initial screening results and strengthen the validity of the conclusions drawn from this study.

Sensitivity Analyses

Heterogeneity can affect the MR results, but Cochran's Q-test detected no heterogeneity (all P>0.05) (Table 2 and Figure S2). No horizontal pleiotropy was detected (all P>0.05), indicating that the selected IVs met the third MR assumption (Table 2). The MR-PRESSO analysis revealed no outliers (Tables S11 and S12). The leave-one-out analysis did not show a single SNP

Table 1 MR Analysis of Sleep Trait and Acne Vulgaris (IVW Results Only)

Exposure	Outcome	SNP Significance Threshold	SNPs	Methods	OR (95% CI)	P
Physical activity	Acne vulgaris (FinnGen)	5×10^{-6}	46	IVW	0.99 (0.925, 1.059)	0.767
Daytime sleepiness	Acne vulgaris (FinnGen)	5×10^{-8}	33	IVW	0.466 (0.046, 4.708)	0.518
Insomnia	Acne vulgaris (FinnGen)	5×10^{-8}	13	IVW	1.475 (0.676, 3.216)	0.329
Chronotype	Acne vulgaris (FinnGen)	5×10^{-8}	118	IVW	1.021 (0.786, 1.326)	0.875
Physical activity	Acne vulgaris (EsB)	5×10^{-6}	46	IVW	0.994 (0.974, 1.015)	0.575
Daytime sleepiness	Acne vulgaris (EsB)	5×10^{-8}	33	IVW	1.045 (0.573, 1.903	0.887
Insomnia	Acne vulgaris (EsB)	5×10^{-8}	13	IVW	1.016 (0.869, 1.187)	0.843
Chronotype	Acne vulgaris (EsB)	5×10^{-8}	114	IVW	0.993 (0.937, 1.051)	0.796

Abbreviations: MR, Mendelian randomization; IVW, inverse variance weighted; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; EsB, Estonian Biobank.

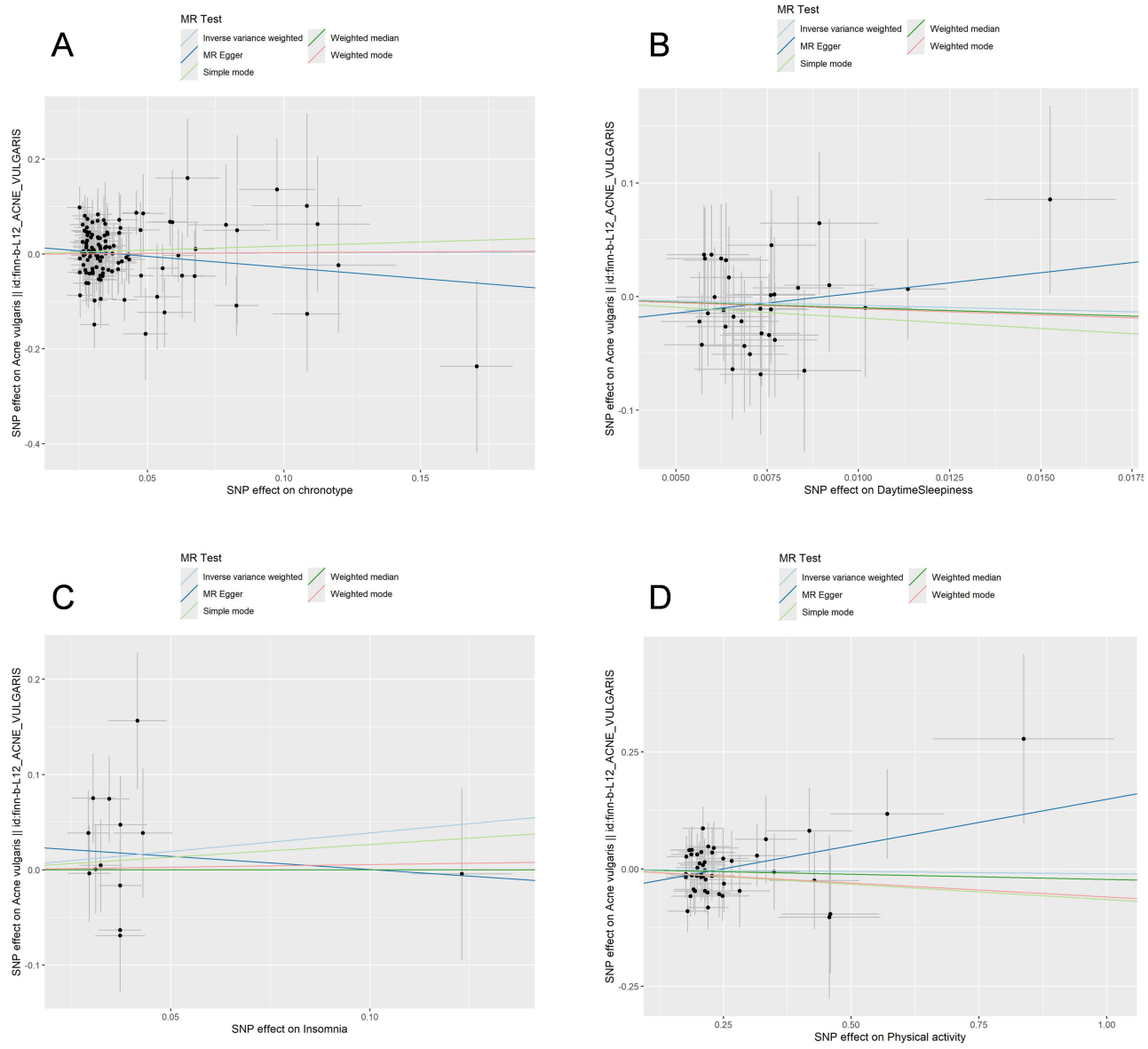

Figure 2 Scatter plots for the Mendelian randomization of acne vulgaris as the outcome and (**A**) chronicity, (**B**) daytime sleepiness, (**C**) insomnia, and (**D**) physical activity as the exposures.

driving the results (Figure S3). Those results are also supported by the validation analysis from the EsB (Tables 2 and S6), except for physical activity, for which heterogeneity and one outlier were detected. After removing the outlier, the results remained similar (Tables S13–S15).

Discussion

Previous MR studies (searched on PubMed on February 11, 2025) examined acne vulgaris as an outcome of various exposures such as gut microbiota,[28–34] serum metabolites,[31,35,36] proteomics,[37,38] lipid-lowering drugs,[39] circulating cytokines,[40,41] lactase persistence and milk intake,[42] and mineral deficiencies,[43] but none used sleep traits and physical activity as exposures. Enriching the literature using different exposures is important to better understand the pathogenesis and pathophysiology of acne vulgaris. Epidemiological studies support links between sleep traits[8–10] and physical activity[14,15] and acne (or common skin diseases). However, these studies struggled to establish causal relationships due to potential confounding factors and reverse causality. By applying MR, our study reveals no causal links between

Table 2 Heterogeneity and Pleiotropy Analyses

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q Statistic (IVW)	P	MR-Egger Intercept	P
Physical activity	Acne vulgaris (FinnGen)	31.997	0.928	−0.04866	0.116
Daytime sleepiness	Acne vulgaris (FinnGen)	15.686	0.993	−0.03219	0.432
Insomnia	Acne vulgaris (FinnGen)	14.424	0.274	0.02812	0.533
Chronotype	Acne vulgaris (FinnGen)	103.473	0.810	0.01849	0.226
Physical activity	Acne vulgaris (EsB)	74.415	<0.001	0.01154	0.258
Daytime sleepiness	Acne vulgaris (EsB)	44.616	0.053	−0.00522	0.677
Insomnia	Acne vulgaris (EsB)	10.141	0.604	0.01388	0.164
Chronotype	Acne vulgaris (EsB)	106.218	0.661	−0.00043	0.900

Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization.

genetically predicted chronotype, insomnia, daytime sleepiness, physical activity, and acne vulgaris. Supported by sensitivity analyses and validation, these findings suggest that observed correlations may result from confounding factors or indirect pathways rather than direct causation. Clinically, this provides important insights into the etiology of acne vulgaris, helping to refine preventive strategies and focus future research on more relevant causal factors.

Several studies reported associations between sleep characteristics and acne. Still, cross-sectional and observational studies cannot determine causality. Guler et al[9] reported that acne severity is directly correlated with insomnia and poor quality of life. Indeed, acne vulgaris is well-known to lead to image and self-esteem issues that can lead to depression and anxiety,[44,45] which in turn can lead to sleep disorders.[46,47] Sleep disorders can also lead to depression and anxiety in a vicious circle.[46,47] Still, the present study showed that the chronotype, insomnia, and daytime sleepiness were not associated with acne vulgaris. The relationship between sleep and acne may be indirect and mediated by negative emotions, but well-designed studies are necessary to examine that hypothesis.

The benefits of physical activity on physical and mental health are well known, including sleep.[48] Two previous studies reported no associations between physical activity and acne.[49,50] On the other hand, sweating can exacerbate acne due to bacteria and debris being entrapped in the pores that enlarge during physical activity and sweating.[51] Still, the available evidence between physical activity and acne is scarce. Of note, physical activity is behavior influenced by one's occupation, available time left after accounting for work and familial responsibilities, physical fitness, and willingness to exercise. Therefore, several factors besides genetics influence physical activity, while MR studies only consider the genetic component. It is a well-known limitation of the MR methodology, especially when the genetic predictability is weaker than the other factors. In addition, several environmental factors can influence the acne vulgaris risk and could not be considered because they were not included in the available datasets. Furthermore, several drugs are associated with acne and acneiform lesions, including anabolic steroids, bromides, corticosteroids, isoniazid, phenytoin, azathioprine, cyclosporine, disulfiram, phenobarbital, quinidine, tetracycline, vitamins B1, B2, B6, B12, and D2, progestin-only containing contraceptives, lithium, epidermal growth factor inhibitors (eg, erlotinib and gefitinib), and Janus kinase inhibitors (eg, abrocitinib, baricitinib, deucravacitinib, deuruxolitinib, and upadacitinib).[52]

MR studies mimic the design of randomized controlled trials and use genetic variants as naturally occurring IVs to provide strong evidence that sleep characteristics and physical activity are not causally associated with acne vulgaris. Subsequent clinical studies need to pay attention to this point, not only focusing on sleep itself but also focusing on the impact of potential factors leading to sleep disorders on acne vulgaris, such as life stress and dietary habits.

The major advantage of this study lies in its MR design, which effectively minimizes reverse causality and confounding effects. However, several limitations warrant consideration. First, the available GWAS datasets are predominantly European, raising uncertainty about the generalizability of the findings to other populations, such as Asians. Second, GWAS participants are typically adults, whereas acne is more prevalent in children and adolescents, potentially introducing age-related biases into the analysis. Third, while MR reduces confounding, residual biases from unmeasured factors such as environmental exposures or medication use cannot be entirely ruled out. Future studies

incorporating such data would enhance the robustness of causal inference. In addition, this study focused on common forms of acne vulgaris as defined by the FinnGen database and did not differentiate between subtypes due to data limitations. Future research should aim to analyze various acne subtypes, including rare forms like acne tropica and acne conglobata, to provide a more comprehensive understanding of the disease. Longitudinal datasets tracking acne severity over time would also offer valuable insights.

Conclusion

In summary, our MR study found no significant causal associations between sleep traits (chronotype, insomnia, daytime sleepiness), physical activity, and acne vulgaris. Our findings clarify previously observed associations suggesting these factors may not directly influence acne development. Future studies should explore additional genetic markers, diverse populations, and longitudinal data to validate findings and identify other causal factors for acne vulgaris.

Data Sharing Statement

All data generated or analyzed during this study are included in this article and Supplementary information files.

Ethics Approval and Consent to Participate

This study used publicly available data from GWASs. The local Research Ethics Board (REB) ruled that no ethical review was required because the study relied exclusively on the secondary use of anonymous data and because it was impossible to generate identifiable information during the process of data linkage or recording or dissemination of results.

Funding

There is no funding to report.

Disclosure

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

References

1. Zaenglein AL. Acne vulgaris. *N Engl J Med*. 2018;379(14):1343–1352. doi:10.1056/NEJMcp1702493
2. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet*. 2012;379(9813):361–372. doi:10.1016/S0140-6736(11)60321-8
3. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2024;90(5):1006e1–1006e30. doi:10.1016/j.jaad.2023.12.017
4. Samuels DV, Rosenthal R, Lin R, Chaudhari S, Natsuaki MN. Acne vulgaris and risk of depression and anxiety: a meta-analytic review. *J Am Acad Dermatol*. 2020;83(2):532–541. doi:10.1016/j.jaad.2020.02.040
5. Uhlenhake E, Yentzer BA, Feldman SR. Acne vulgaris and depression: a retrospective examination. *J Cosmet Dermatol*. 2010;9(1):59–63. doi:10.1111/j.1473-2165.2010.00478.x
6. Say YH, Heng AHS, Reginald K, et al. Modifiable and non-modifiable epidemiological risk factors for acne, acne severity and acne scarring among Malaysian Chinese: a cross-sectional study. *BMC Public Health*. 2021;21(1):601. doi:10.1186/s12889-021-10681-4
7. Khormi G, Aldubayyan N, Hakami M, Daghriri S, Aqeel S. Impact of lifestyle and dietary habits on the prevalence of acne vulgaris: a cross-sectional study from Saudi Arabia. *Cureus*. 2024;16(3):e57200. doi:10.7759/cureus.57200
8. Chaudhary S, Ameer A, Sarwar MZ, Naqi SA, Butt AI. A cross-sectional study of body mass index and sleep quality as risk factors to severity of acne. *J Pak Med Assoc*. 2021;71(9):2148–2150. doi:10.47391/JPMA.404
9. Guler D, Soylu S, Guler HA. The relationship of quality of life and acne severity with chronotype and insomnia in patients with acne vulgaris. *Arch Dermatol Res*. 2023;315(6):1689–1695. doi:10.1007/s00403-023-02569-7
10. Zhu J, Peng K, Zhang Y, et al. Sleep quality, circadian preferences, and mood among patients with acne vulgaris: a case-control study. *Sleep Breath*. 2023;27(5):1997–2003. doi:10.1007/s11325-023-02777-5
11. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*. 2008;10(3):329–336. doi:10.31887/DCNS.2008.10.3/dnutt
12. Oh CM, Kim HY, Na HK, Cho KH, Chu MK. The effect of anxiety and depression on sleep quality of individuals with high risk for insomnia: a population-based study. *Front Neurol*. 2019;10:849. doi:10.3389/fneur.2019.00849
13. Misery L, Wolkenstein P, Amici JM, et al. Consequences of acne on stress, fatigue, sleep disorders and sexual activity: a population-based study. *Acta Derm Venereol*. 2015;95(4):485–488. doi:10.2340/00015555-1998
14. Nishikori S, Yasuda J, Murata K, et al. Resistance training rejuvenates aging skin by reducing circulating inflammatory factors and enhancing dermal extracellular matrices. *Sci Rep*. 2023;13(1):10214. doi:10.1038/s41598-023-37207-9
15. Ertas R, Turk M, Yucel MB, et al. Eating increases and exercise decreases disease activity in patients with symptomatic dermographism. *J Allergy Clin Immunol Pract*. 2023;11(3):932–940. doi:10.1016/j.jaip.2022.11.041

16. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. *JAMA*. 2017;318(19):1925–1926. doi:10.1001/jama.2017.17219
17. Visscher PM, Wray NR, Zhang Q, et al. 10 years of GWAS discovery: biology, function, and translation. *Am J Hum Genet*. 2017;101(1):5–22. doi:10.1016/j.ajhg.2017.06.005
18. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. *J Am Soc Nephrol*. 2016;27(11):3253–3265. doi:10.1681/asn.2016010098
19. Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Davey Smith G. Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. *Am J Clin Nutr*. 2016;103(4):965–978. doi:10.3945/ajcn.115.118216
20. Teder-Laving M, Kals M, Reigo A, et al. Genome-wide meta-analysis identifies novel loci conferring risk of acne vulgaris. *Eur J Hum Genet*. 2024;32(9):1136–1143. doi:10.1038/s41431-023-01326-8
21. Li Y, Guo J, Cao Z, Wu J. Causal association between inflammatory bowel disease and psoriasis: a two-sample bidirectional Mendelian randomization study. *Front Immunol*. 2022;13:916645. doi:10.3389/fimmu.2022.916645
22. Lu Y, Wang P, Liu H, et al. Coffee and risk of pancreatic cancer: insights from two-sample and multivariable Mendelian randomization analyses. *Nutrients*. 2024;16(21). doi:10.3390/nu16213723
23. Qu S, Zhu Y, Pfeiffer N, Grus FH. Serum iron status and retinal degenerative diseases: a Mendelian randomization study on AMD, RP, and DR. *Nutrients*. 2024;16(21):3747. doi:10.3390/nu16213747
24. Wang Y, Liu S, Wu C, Yu H, Ji X. Association between circulating unsaturated fatty acid and preeclampsia: a two-sample Mendelian randomization study. *J Matern Fetal Neonatal Med*. 2024;37(1):2294691. doi:10.1080/14767058.2023.2294691
25. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
26. Bowden J, Del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. 2017;36(11):1783–1802. doi:10.1002/sim.7221
27. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology*. 2017;28(1):30–42. doi:10.1097/EDE.0000000000000559
28. Mao R, Yu Q, Li J. The causal relationship between gut microbiota and inflammatory dermatoses: a Mendelian randomization study. *Front Immunol*. 2023;14:1231848. doi:10.3389/fimmu.2023.1231848
29. Wu Y, Wang X, Wu W, Yang J. Mendelian randomization analysis reveals an independent causal relationship between four gut microbes and acne vulgaris. *Front Microbiol*. 2024;15:1326339. doi:10.3389/fmicb.2024.1326339
30. Cao Q, Guo J, Chang S, Huang Z, Luo Q. Gut microbiota and acne: a Mendelian randomization study. *Skin Res Technol*. 2023;29(9):e13473. doi:10.1111/srt.13473
31. He X, Zhang Z, Jiang H, et al. Causal association of gut microbes and blood metabolites with acne identified through systematic Mendelian randomization. *Sci Rep*. 2024;14(1):26816. doi:10.1038/s41598-024-78603-z
32. Wang Y, Yao T, Lin Y, et al. Association between gut microbiota and pan-dermatological diseases: a bidirectional Mendelian randomization research. *Front Cell Infect Microbiol*. 2024;14:1327083. doi:10.3389/fcimb.2024.1327083
33. Feng F, Li R, Tian R, Wu X, Zhang N, Nie Z. The causal relationship between gut microbiota and immune skin diseases: a bidirectional Mendelian randomization. *PLoS One*. 2024;19(3):e0298443. doi:10.1371/journal.pone.0298443
34. Gu Y, Zhang W, Zhao W, Zeng X. Investigating causal relationships between the gut microbiota and inflammatory skin diseases: a Mendelian randomization study. *Australas J Dermatol*. 2024;65(4):319–327. doi:10.1111/ajd.14231
35. Wang X, Wu Y, Zhao P, Wang X, Wu W, Yang J. The causal relationship between serum metabolites and acne vulgaris: a Mendelian randomization study. *Sci Rep*. 2024;14(1):11045. doi:10.1038/s41598-024-61850-5
36. Li M, Zhan DD, Fan LL, et al. Unraveling the causal relationship between blood metabolites and acne: a metabolomic Mendelian randomization study. *J Cosmet Dermatol*. 2025;24(1):e16763. doi:10.1111/jocd.16763
37. Ju R, Ying Y, Zhou Q, Cao Y. Exploring genetic drug targets in acne vulgaris: a comprehensive proteome-wide Mendelian randomization study. *J Cosmet Dermatol*. 2024;23(12):4223–4229. doi:10.1111/jocd.16567
38. Deng S, Mao R, He Y. Unveiling new protein biomarkers and therapeutic targets for acne through integrated analysis of human plasma proteomics and genomics. *Front Immunol*. 2024;15:1452801. doi:10.3389/fimmu.2024.1452801
39. Fang M, Lei J, Zhang Y, Zhang B. Repurposing lipid-lowering drugs as potential treatment for acne vulgaris: a Mendelian randomization study. *Front Med*. 2024;11:1385948. doi:10.3389/fmed.2024.1385948
40. Li J, Lu Y, Zhao X. Genetic perspectives on the influence of circulating cytokines on acne: a Mendelian randomization study. *Medicine*. 2023;102 (50):e36639. doi:10.1097/MD.0000000000036639
41. Liu W, Zhang X, Chen X. Unraveling the causal associations between systemic cytokines and six inflammatory skin diseases. *Cytokine*. 2025;185:156810. doi:10.1016/j.cyto.2024.156810
42. Juhl CR, Bergholdt HKM, Miller IM, Jemec GBE, Kanters JK, Ellervik C. Lactase persistence, milk intake, and adult acne: a Mendelian randomization study of 20,416 Danish adults. *Nutrients*. 2018;10(8). doi:10.3390/nu10081041
43. Wu R, Tian H, Zhao T, Tian Y, Jin X, Zhu M. A Mendelian randomization analysis of inflammatory skin disease risk due to mineral deficiencies. *Front Nutr*. 2024;11:1404117. doi:10.3389/fnut.2024.1404117
44. Gallitano SM, Berson DS. How acne bumps cause the blues: the influence of acne vulgaris on self-esteem. *Int J Womens Dermatol*. 2018;4 (1):12–17. doi:10.1016/j.ijwd.2017.10.004
45. Nandy P, Shrivastava T. Exploring the multifaceted impact of acne on quality of life and well-being. *Cureus*. 2024;16(1):e52727. doi:10.7759/cureus.52727
46. Arenas DJ, Thomas A, Wang J, DeLisser HM. A systematic review and meta-analysis of depression, anxiety, and sleep disorders in US adults with food insecurity. *J Gen Intern Med*. 2019;34(12):2874–2882. doi:10.1007/s11606-019-05202-4
47. Naranjo C, Del Reguero L, Moratalla G, Hercberg M, Valenzuela M, Failde I. Anxiety, depression and sleep disorders in patients with diabetic neuropathic pain: a systematic review. *Expert Rev Neurother*. 2019;19(12):1201–1209. doi:10.1080/14737175.2019.1653760
48. Sejbuk M, Mironczuk-Chodakowska I, Witkowska AM. Sleep quality: a narrative review on nutrition, stimulants, and physical activity as important factors. *Nutrients*. 2022;14(9):1912. doi:10.3390/nu14091912

49. Ghodsi SZ, Orawa H, Zouboulis CC. Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *J Invest Dermatol*. 2009;129(9):2136–2141. doi:10.1038/jid.2009.47
50. Alshammrie FF, Alshammari R, Alharbi RM, Khan FH, Alshammari SK. Epidemiology of acne vulgaris and its association with lifestyle among adolescents and young adults in Hail, Kingdom Of Saudi Arabia: a community-based study. *Cureus*. 2020;12(7):e9277. doi:10.7759/cureus.9277
51. Short RW, Agredano YZ, Choi JM, Kimball AB. A single-blinded, randomized pilot study to evaluate the effect of exercise-induced sweat on truncal acne. *Pediatr Dermatol*. 2008;25(1):126–128. doi:10.1111/j.1525-1470.2007.00604.x
52. Feldman S, Careccia RE, Barham KL, Hancox J. Diagnosis and treatment of acne. *Am Fam Physician*. 2004;69(9):2123–2130.