Causal Relationships Among Air Pollution, Testosterone Levels, and Acne: A Two-Sample Mendelian Randomization Study

Keywords
single nucleotide polymorphism, air pollution, acne, testosterone levels, two□sample Mendelian randomization

Abstract

Introduction

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Material and methods

This two-sample Mendelian randomization (MR) study was performed by applying genome-wide association study (GWAS) summary statistics. Multiple MR methods, including inverse variance weighted (IVW), MR-Egger, weighted median (WM), and weighted mode, were applied to assess causality. Sensitivity analyses, such as MR-Egger regression, WM, and MR-PRESSO, were conducted to evaluate pleiotropy and heterogeneity.

Results

Genetically predicted NDAP and PM2.5 exposure exhibited significant causal effects on both TTL and BTL, which in turn were associated with acne development. However, NOAP, PM2.5-10, and PM10 showed no causal links with acne. Sensitivity analyses confirmed the robustness of the IVW results, with no substantial evidence of pleiotropy or heterogeneity.

Conclusions

This MR study provides evidence supporting a causal role of NDAP and PM2.5 in influencing testosterone levels and acne risk. These findings underscore the importance of environmental factors, particularly air pollution, in modulating hormonal pathways involved in acne. Future research should explore mechanisms underlying these associations,while public health strategies should consider reducing air pollution exposure as part of acne prevention and management approaches.

Causal Relationships Among Air Pollution, Testosterone Levels, and Acne: A Two-Sample Mendelian Randomization Study

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Conclusions: This MR study provides evidence supporting a causal role of NDAP and PM2.5 in influencing testosterone levels and acne risk. These findings underscore the importance of environmental factors, particularly air pollution, in modulating hormonal pathways involved in acne. Future research should explore mechanisms underlying these associations,while public health strategies should consider reducing air pollution exposure as part of acne prevention and management approaches.

Keywords: two-sample Mendelian randomization; air pollution; testosterone levels; acne; single nucleotide polymorphism

Introduction

Acne is one of the most common skin disorders globally, ranked as the eighth most prevalent disease, with a striking 94% prevalence(1-3). It primarily affects areas such as the face, back, chest, neck, and shoulders, typically onset during adolescence - impacting around 85% of this population - and often persists into adulthood(4). Beyond physical symptoms and potential scarring, acne carries significant psychological burdens, including anxiety, low self-esteem, and reduced confidence. Without timely intervention, approximately 20% may develop severe forms, increasing the risk of permanent scars(5). Its development is influenced by genetic and hormonal factors, air pollution, diet, lifestyle, and demographic variables(6, 7).

Air pollution is the leading environmental health risk, linked to a wide range of diseases(8-10). Beyond its well-known effects on respiratory health, growing evidence highlights its harmful impact on the skin - the body's largest organ and first line of defense(11). Key pollutants such as nitrogen oxides, particulate matter (PM10, PM2.5), volatile organic compounds (VOCs), and sulfur dioxide can penetrate the skin barrier, induce oxidative stress, disrupt cellular function, and trigger inflammation, collectively contributing to skin damage(12-15). Testosterone plays a key role in acne development and severity(16). Beyond its association with male traits, it stimulates sebum production, alters skin lipid composition(17), and promotes sebaceous gland activity, follicular hyperkeratinization, and *Cutibacterium acnes* colonization(18). The effects of testosterone on acne are well documented, but emerging evidence also suggests that environmental pollutants such as air pollution can significantly alter testosterone levels(19). These environmental effects on hormone balance further highlight the complex interplay of hormone regulation, genetic predisposition, and external exposures in the pathogenesis of acne. These effects drive inflammatory immune responses, highlighting testosterone's central involvement in acne pathogenesis and the broader interplay of hormonal, genetic, and environmental factors.

Mendelian randomization (MR) is a state-of-the-art method in epidemiology that overcomes the limitations of observational studies by using genetic variation to determine a link between exposures and outcomes(20, 21). For example, studies have shown that exposures including PM2.5, PM10 and nitrogen oxides may reduce bone density(22). Specifically, our survey adopted a two-sample MR methodology, drawing on summary statistics from genome-wide association studies (GWAS), to scrutinize and elucidate the causal connections between air pollution, testosterone levels, and acne. By leveraging genetic information, the study aims to provide deeper insights into the underlying mechanisms of acne development and potentially inform future therapeutic interventions.

Material and Methods

Study design

This study utilized a two-sample MR design. Informed consent and ethical approval were secured in the original studies from which data were derived. The MR methodology is predicated on several critical assumptions for the validity of causal estimates. Specifically, for MR-derived causal estimates to be considered valid, three foundational assumptions must be met: (1) instrumental variables (IVs) are required to be strongly correlated with exposure; (2) IVs are required not to be correlated with any possible confounders; and (3) IVs are required to affect the outcome only through its effect on exposure (23).

Data sources

We obtained a summary of GWAS statistics for acne through the FinnGen data store, encompassing 212,438 samples of European origin (Finn-b-L12_ACNE), featuring 16,380,454 single nucleotide polymorphisms (SNPs). Summary statistics for air pollution were acquired from the UK Biobank, covering various pollutants: nitrogen oxides air pollution (NOAP) (UKB-b-12417), nitrogen dioxide air pollution (NDAP) (UKB-b-5620), particulate matter

(PM2.5) absorbance (UKB-b-11312), particulate matter (PM2.5) (UKB-b-12963), and particulate matter (PM10) (UKB-b-589). The UK Biobank is a prospective study containing over 500 000 individuals of mainly European ancestry (24).

GWAS data on testosterone levels were sourced from a previous study investigating testosterone levels and related sex hormone traits among 425,097 participants in the UK Biobank, including total testosterone levels (TTL) and bioavailable testosterone levels (BTL) (25). Details regarding the exposure factors are presented in Table 1.

In addition, the exposure dataset (air pollution and testosterone levels) and the outcome dataset (acne) were obtained from independent biobanks, the UK Biobank and the FinnGen database, respectively. As these datasets were from different populations with no overlapping samples, the key underlying assumption of independence between exposure and outcome data was upheld in this study, thus minimizing the risk of bias due to sample overlap.

Instrumental variables selection

In order to verify the accuracy and reliability of causal conclusions, we undertook a comprehensive set of assurance measures to select the most suitable genetic tools. Initially, we utilized an array of SNPs that surpassed the genome-wide statistical significance threshold as IVs. For air pollution, a P-value threshold of less than $5 * 10^{-7}$ was required, while for particulate matter air pollution (PM2.5), the threshold was less than $5 * 10^{-6}$, and for testosterone levels, less than $5 * 10^{-8}$ was necessary (26). Then, the SNPs that have minor allele frequency (MAF) above 0.01 were saved for further analysis. To address the possible interference of linkage disequilibrium (LD) on our findings, we further refined the SNPs based on the LD critical value (r^2) of less than 0.001 within a genomic window of 10,000kb (27). So that effect alleles were consistent across datasets, we aligned the exposure and outcome data sets by removing uncertain SNPs with inconsistent genotypes and SNPs with centered allele frequencies. The instrumental strength of each IV was quantified using F calculated as R^2 ×

(N-2) / (1-R^2), where R^2 is the amount of observable trait variation caused by heritable variation in the exposure and N represents the population size(28). If the F-statistic exceeds 10, it indicates the presence of stable instrumental variables(29). Assuming that the selected SNPs were not present in the resulting pooled data, alternative SNPs with high linkage ($r^2 > 0.8$) were utilized as substitutes(30).

MR analyses

We conducted two-sample MR analyses employing the R software package TwoSampleMR (version 4.0.5). Afterward, MR evaluations were performed using inverse variance weighting (IVW), MR Egger linear regression, weighted median (WM), and weighted mode. The primary analyses comprised two-sample MR analyses conducted using the IVW method (31). MR-Egger regression provides both an estimation of effect and a test for directional pleiotropy, known as the MR-Egger intercept test. A non-significant MR-Egger intercept ($P > 0.05$) indicates evidence against pleiotropy (32).

Sensitivity analyses and horizontal pleiotropy tests

We conducted various statistical methods for sensitivity analyses and horizontal pleiotropy tests, including MR Egger, and MR-PRESSO. MR-PRESSO was also utilized for pleiotropy assessment, as it identifies and corrects for horizontal pleiotropy via distortion tests and outlier correction methods (33). Moreover, within the IVW framework, we conducted Cochran's Q Test to assess heterogeneity, measuring the variance among SNP-specific estimates(34). Additionally, a leave-one-SNP-out analysis was performed to evaluate the impact of individual variants on the observed associations (35).

Results

Selection of instrumental variables

We incorporated 25, 25, 12, 24, 83, 181, and 124 independent SNPs for NOAP, NDAP, PM2.5, PM2.5-10, PM10, total testosterone levels and bioavailable testosterone levels, respectively. However, we could not find 1 NOAP-associated SNP, 1 PM2.5-10-associated SNP, 1 PM10-associated SNP, 14 TTL-associated SNPs and 11 BTL-associated SNPs in the summary statistic of acne. Detailed information of IVs was listed in Supplementary Table 1.

Causal effects of air pollution, testosterone levels, and acne

Table 1 lists the MR calculations for the different methods. NDAP (IVW OR = 2.66, 95% CI: 2.07 - 3.41, P < 0.001), PM2.5 (IVW OR = 2.66, 95% CI: 1.93 - 3.67, P < 0.001), TTL (IVW OR = 2.49, 95% CI: 2.14 - 2.88, P < 0.001), and BTL (IVW OR = 2.47, 95% CI: 2.15 - 2.83, P < 0.001) were positively associated with acne. The estimates of the IVW test indicated no causal association between NOAP (IVW OR = 0.93, 95% CI: 0.26 - 3.31, P = 0.9118), PM2.5-10 (IVW OR = 1.42, 95% CI: 0.46 - 4.37, P = 0.5365), and PM10 (OR = 1.59, 95% CI: 0.79 - 3.21, P = 0.1979) and acne.

In addition, the MR-Egger, the Weighted Median, and the Weighted Mode methods showed consistent results. The scatter diagrams were shown in Figure S1. According to the heterogeneity test, there is no heterogeneity among individual SNPs. Based on the results from the Cochran's Q test, MR-Egger, and MR-PRESSO tests, horizontal pleiotropy is unlikely to bias the causal inference. Notably, the analyses of heterogeneity and pleiotropy revealed all p-values exceeding 0.05 (Tables 2 and 3), as well as MR-PRESSO (Table 4), indicating the reliability of our results. Leave-one-out analysis indicated that the causal estimates were not driven by any single SNP. The leave-one-out analysis plots, funnel plots, and forest plots were shown in Figures S2-4.

Discussion

This groundbreaking study represents the inaugural exploration into the causal dynamics linking air pollution, testosterone levels, and acne, employing a comprehensive suite of MR methodologies. While our two-sample MR analysis revealed significant associations between exposure to NDAP, PM2.5, TTL, and BTL, and the occurrence of acne, the absence of causal links with NOAP, PM2.5-10, and PM10 prompts further investigation into the intricate genetic predispositions and environmental factors influencing acne development.

Our investigation into the causal relationships between NDAP, PM2.5, and acne corroborates a growing body of evidence identifying air pollution as a potential risk factor for dermatological conditions, notably acne. This alignment is underscored by a time-series study conducted in China, which found a significant correlation between high levels of ambient PM2.5, PM10, and NO_2 and an increase in outpatient visits for acne vulgaris (36). Additionally, clinical comparisons between individuals residing in areas of high pollution versus those in lower pollution zones in Shanghai and Mexico have documented a decline in skin quality associated with chronic exposure to ambient air pollution, further supporting our findings (37, 38). These studies point to polluted environmental conditions as catalysts for alterations in sebum composition and an increase in sebum excretion rates, alongside damage to the stratum corneum (SC). Such disturbances in the SC and heightened sebum production are acknowledged contributors to acne's pathology(37). The mechanisms underlying these observations are multifaceted, with ambient air pollution known to alter skin's lipids, DNA, and proteins through oxidative stress induction. This process can lead to an increase in oxidized squalene and a decrease in linoleic acid levels in the lipids overlying the stratum corneum(39, 40). Additionally, the production of reactive oxygen species (ROS) initiates a lipid peroxidation cascade, prompting a proinflammatory response that is detrimental to skin health (15). Furthermore, exposure to polycyclic aromatic hydrocarbons (PAHs) has been linked to the

activation of the aryl hydrocarbon receptor (AhR), which may also trigger inflammatory pathways relevant to acne development(41, 42).

The association between acne and elevated levels of TTL and BTL observed in our research is supported by scientific literature. Hormonal imbalances, especially those involving androgens such as testosterone, play a pivotal role in acne development and its severity. Acne pathogenesis involves processes such as follicular hyperkeratinization, colonization by Propionibacterium acnes, and increased sebum production, all influenced significantly by androgens. The relevance of androgens in acne pathogenesis is further evidenced by the timing of acne onset, often coinciding with puberty—a period marked by rising androgen levels. Moreover, conditions characterized by androgen excess, such as polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia (CAH), are associated with higher rates of acne(43, 44), whereas those with androgen deficiency or insufficiency are less likely to develop acne(45).

Androgen-mediated sebum production is acknowledged as a necessary, though not solely sufficient, condition for acne formation. The transition of the androgen testosterone to the stronger androgen, 5α-dihydrotestosterone (5α-DHT), through 5α reductase type 1 is a key step in this process. 5α-DHT influences the lipid-secreting glands through the nuclear androgen receptor (AR)(46-48). However, some studies challenge the direct correlation between acne severity and serum androgen excess, suggesting that acne can be prevalent even in women with normal serum androgen profiles. In a notable study involving 835 postadolescent females with acne, nearly 43.47% exhibited normal androgen levels(49). While androgens are undeniably important in acne development, the diversity in acne presentation and severity, even among individuals with normal androgen profiles, calls for further research to unravel the additional underlying mechanisms and factors influencing acne pathogenesis.

On the clinical side, this study emphasizes the importance of air pollution as a potentially modifiable risk factor for acne development. These findings not only support the need for environmental regulations to reduce air pollution, especially for those pollutants that have a direct impact on skin health, but also suggest that improving air quality may be one of the effective strategies for acne prevention. From a clinical practice perspective, recognizing the interactions between environmental factors such as air pollution and hormone levels (e.g., testosterone) is critical to developing more individualized and comprehensive treatment plans. Incorporating environmental exposure assessment into the acne management process can help physicians more accurately identify high-risk patients and take preventive measures to reduce the burden of disease, thereby improving patients' overall health and quality of life. In addition, this association calls for public health policymakers to emphasize air quality control as a long-term investment in promoting public health, especially adolescent and young adult skin health. Conversely, our analysis did not identify a causal relationship between NOAP and acne. This divergence from the expected may suggest that not all air pollutants uniformly influence acne development, possibly due to differences in their inflammatory potential, or other yet unidentified factors. The lack of association could also reflect methodological differences or limitations in the available data, emphasizing the need for further research to dissect the specific contributions of various pollutants to acne and other skin conditions.

However, our investigation is not without its limitations. One notable concern is the generalizability of our findings, primarily derived from a dataset reflecting a specific population, which may not fully represent the global diversity of acne sufferers. More studies with ethnically diverse populations are needed in the future to validate our findings. And, due to the use of pooled-level data in a two-sample MR framework, we were unable to incorporate longitudinal information or adjust for potential confounders such as lifestyle, dietary habits, or environmental exposures. These factors may influence testosterone levels and acne

development, and the absence of these factors limits the precision of our causal estimates. Future studies could provide repeated measures of air pollution exposure, hormonal profiles, and dermatologic outcomes, as well as comprehensive lifestyle and microbiome data. Additionally, while our MR approach reduces potential biases, the reliance on summary statistics and genetic instruments assumes no pleiotropy or unmeasured confounding, assumptions that may not hold universally. Despite these challenges, the strength of our analytical methods, including the use of instrumental variables with a strong association with the exposure variables, aims to mitigate these concerns, providing a solid foundation for future research into the causal factors contributing to acne. Despite these potential limitations, utilizing summary statistics from a dataset of 212,438 individuals helps significantly reduce confounding and reverse causation—frequent issues in observational studies. This robust method provides a more reliable basis for examining the intricate interactions between environmental factors, hormonal imbalances, and their impact on acne development.

Conclusion

In conclusion, our MR analysis establishes a causal link between exposure to NDAP, PM2.5, TTL, and BTL, and acne occurrence. However, no causal associations were found for NOAP, PM2.5-10, and PM10 with acne. These findings underscore the need for further research to elucidate the complex interplay between air pollution, testosterone levels, and acne pathogenesis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Disclosure statement

The authors declare that they have no competing interests.

Data Availability Statement

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

Funding details

None.

Authors' contributions

Xiaoli Kou and Junjie Wang carried out the studies, participated in collecting data, and drafted the manuscript. Shimeng Ma performed the statistical analysis and participated in its design. Xiaoli Kou and Junjie Wang participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Table 1. Exposure factors

Exposure	GWAS ID	N	SNPs
Nitrogen oxides air pollution	ukb-b-12417	456,380	9,851,867
Nitrogen dioxide air pollution	ukb-b-5620		
Particulate matter air pollution (pm2.5) absorbance	ukb-b-11312		
Particulate matter air pollution (pm2.5)	ukb-b-12963	423,796	9,851,867
Particulate matter air pollution (pm10)	ukb-b-589		
Total testosterone levels	GCST90012114	NA	16,132,861
Bioavailable testosterone levels	GCST90012104	NA	16,137,327

Table 2. MR estimates for the causal effect

Exposure	Outcome	N.SNPs	Methods	OR (95% CI)	P
NOAP	Acne	24	IVW	0.93 (0.26 - 3.31)	0.9118
			MR-Egger	2.5 (0.25 - 25.33)	0.4469
			Weighted Median	1.52 (0.22 - 10.42)	0.6725
			Weighted Mode	1.34 (0.17 - 10.44)	0.7806
NDAP		25	IVW	2.66 (2.07 - 3.41)	0
			MR-Egger	2.78 (1.62 - 4.77)	0.0011
			Weighted Median	2.72 (1.78 - 4.16)	0
			Weighted Mode	2.73 (1.89 - 3.93)	0
PM2.5		12	IVW	2.66 (1.93 - 3.67)	0
			MR-Egger	4.15 (1.08 - 15.89)	0.0648
			Weighted Median	2.72 (1.68 - 4.41)	0
			Weighted Mode	2.8 (1.82 - 4.31)	0.0007
PM2.5-10		23	IVW	1.42 (0.46 - 4.37)	0.5365
			MR-Egger	1.21 (0.24 - 6.01)	0.8202
			Weighted Median	1.59 (0.35 - 7.26)	0.5483
			Weighted Mode	1.63 (0.38 - 6.98)	0.5154
PM10		82	IVW	1.59 (0.79 - 3.21)	0.1979
			MR-Egger	2.87 (0.88 - 9.36)	0.0849
			Weighted Median	3.36 (0.94 - 12.01)	0.0618
			Weighted Mode	3.75 (1.16 - 12.09)	0.03
TTL		167	IVW	2.49 (2.14 - 2.88)	0
			MR-Egger	1.97 (0.83 - 4.65)	0.1252
			Weighted Median	2.72 (2.12 - 3.49)	0

		Weighted Mode	2.77 (2.22 - 3.46)	0
BTL	113	IVW	2.47 (2.15 - 2.83)	0
		MR-Egger	2.11 (1.34 - 3.32)	0.0017
		Weighted Median	2.72 (2.13 - 3.46)	0
		Weighted Mode	2.63 (2.17 - 3.19)	0

Table 3. Heterogeneity and pleiotropy

Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	*P* value	MR-Egger Intercept	*P* value
NOAP	ACNE	13.062	0.951	-0.021	0.329
NDAP		19.118	0.746	-0.001	0.85
PM2.5		7.572	0.751	-0.017	0.521
PM2.5-10		18.138	0.698	0.006	0.781
PM10		73.735	0.676	-0.015	0.227
TTL		132.942	0.948	0.004	0.589
BTL		106.605	0.411	0.003	0.478

Table 4. MR-PRESSO

Exposure	Outcome	Raw		Outlier corrected		Global P	Number of outliers	Distortion P
		OR (CI%)	*P*	OR (CI%)	*P*			
NOAP	ACNE	0.93 (0.36 - 2.42)	0.88	NA	NA	0.949	NA	NA
NDAP		2.66 (2.13 - 3.32)	0	NA	NA	0.865	NA	NA
PM2.5		2.66 (2.04 - 3.47)	0	NA	NA	0.533	NA	NA
PM2.5-10		1.42 (0.51 - 3.94)	0.5	NA	NA	0.74	NA	NA
PM10		1.61 (0.82 - 3.14)	0.17	NA	NA	0.688	NA	NA
TTL		2.46 (2.16 - 2.82)	0	NA	NA	0.963	NA	NA
BTL		2.45 (2.14 -	0	NA	NA	0.509	NA	NA

2.81)

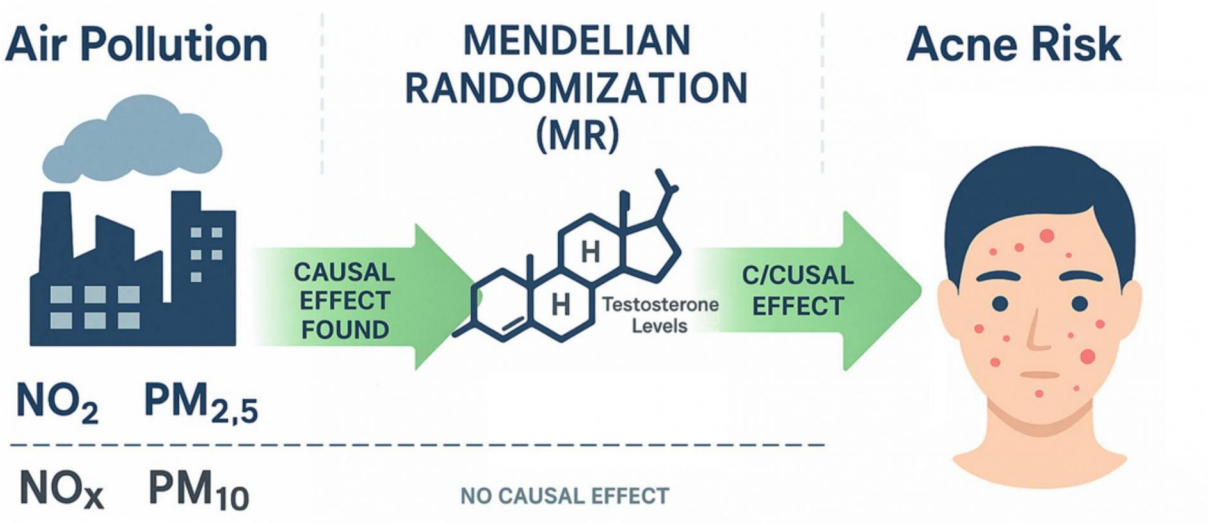
Figure Legends

Figure S1. Scatter plot of the causal relationship between genetically predicted NDAP and acne.

Figure S2. Leave-one-out sensitivity analysis for the causal effect of NDAP on acne.

Figure S3. Funnel plot for assessing heterogeneity and directional pleiotropy in the causal analysis of NDAP on acne.

Figure S4. Forest plot of the causal effects of individual SNPs for NDAP on acne.


Air Pollution
MENDELIAN RANDOMIZATION (MR)
Acne Risk
CAUSAL EFFECT FOUND
H
H
Testosterone Levels
C/CUSAL EFFECT
NO_2 $PM_{2,5}$
NO_X PM_{10}
NO CAUSAL EFFECT