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ORIGINAL RESEARCH

Disentangling Nicotine vs Non-Nicotine Components of Tobacco Exposure in Psoriasis and Psoriatic Arthritis: A Multivariable and Trans-Ethnic Mendelian Randomization Study

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Objective: To disentangle tobacco constituents in psoriasis, we contrasted nicotine exposure—proxied by the nicotine metabolite ratio (NMR)—with smoking intensity (cigarettes per day, CPD) and evaluated cross-ancestry effects.
Methods: This study applied multivariable Mendelian randomization (MR) jointly modeling genetically proxied NMR (instrumented using variants from a European-ancestry GWAS) and CPD to estimate their independent effects on liability to psoriasis and psoriatic arthritis (PsA). Chronic obstructive pulmonary disease (COPD) served as a positive control. Cross-ancestry generalizability was tested using a trans-ethnic MR (TEMR) framework under conditional likelihood with Nelder–Mead optimization. Sensitivity analyses assessed pleiotropy, heterogeneity, directionality (Steiger), MRLap, RadialMR, and multiple testing (Benjamini–Hochberg).
Results: NMR showed an independent association with higher PsA risk irrespective of CPD (OR = 1.104, 95% CI: 1.039–1.174). CPD retained an independent effect on overall psoriasis after conditioning on NMR (OR = 1.305, 95% CI: 1.082–1.573), while the NMR effect on psoriasis attenuated (P > 0.05). In univariable MR, genetically predicted NMR increased psoriasis risk in Europeans (EUR; OR = 1.032, 95% CI: 1.013–1.051). CPD associated with psoriasis in EUR (OR = 1.130, 95% CI: 1.031–1.239) and strongly in Hispanics (HIS; OR = 1.448, 95% CI: 1.434–1.463), with suggestive evidence in East Asians. Reverse-direction MR indicated psoriasis liability correlated with lower CPD across EUR, EAS, AFR, and HIS ($\beta < 0$, $P_{adj} < 0.05$).
Conclusion: This study supports ancestry-specific differences and suggests distinct roles of nicotine-related versus non-nicotine tobacco smoke constituents in psoriasis and its subtypes, while the underlying biological mechanisms remain to be clarified.
Keywords: tobacco exposure, psoriasis, trans-ethnic, nicotine

Introduction

Psoriasis is a prevalent chronic inflammatory skin disease of immune-mediated origin, characterized by aberrant keratinocyte proliferation that leads to the formation of red plaques topped with silvery-white scales.[1] According to the World Health Organization (WHO), psoriasis affects approximately 2%–3% of the global population, amounting to more than 125 million individuals worldwide.[2] Beyond its cutaneous manifestations, psoriasis is associated with multiple comorbidities—including psoriatic arthritis, cardiovascular diseases, and mental health disorders—that together compound the physical and psychological burden on patients.[1] Furthermore, psoriasis imposes a substantial economic burden at both the individual and societal levels; in the United States alone, total annual costs related to the disease are estimated at around $112 billion, with direct medical expenditures accounting for roughly $51.7–63.2 billion of that sum.[3] Patients

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also face considerable out-of-pocket expenses: on average, U.S. patients spend about $2,528 per year on psoriasis-related care, while German patients lose approximately 4.9 workdays annually due to the disease.[4] Due to the intricate genetic and environmental interplay in psoriasis etiology, the disease remains incurable with limited preventive options. Thus, identifying modifiable risk factors and clarifying pathophysiological mechanisms is essential for better prevention and management.

Smoking, as a modifiable risk factor, is widely recognized as a significant global contributor to preventable diseases and premature mortality.[5] Cigarette smoke comprises thousands of chemical substances, notably including nicotine, tar, and carbon monoxide, which induce oxidative stress and immune dysregulation. These processes lead to excessive inflammatory responses involving keratinocytes and immune cells, significantly elevating the risk of various diseases, including psoriasis.[6] Numerous observational studies have explored the association between smoking and psoriasis.[7,8] Recently, Mendelian randomization (MR) studies leveraging genome-wide association studies (GWAS) data have revisited this association, effectively addressing previous concerns related to confounding factors and reverse causality, thereby providing robust causal evidence.[9–11] The MR approach resembles randomized controlled trials (RCTs) by using genetic variants as instrumental variables (IVs) to simulate random exposure assignment, facilitating causal inference.[12] Given the ethical constraints associated with conducting RCTs in smoking research, MR offers a valuable alternative. Nevertheless, considerable ethnic differences exist in the epidemiological and genetic profiles of psoriasis, and previous MR studies primarily focused on European (EUR) populations, thus limiting their generalizability and reflecting broader methodological limitations of existing MR studies.

Moreover, the specific constituents within tobacco smoke—such as nicotine or carbon monoxide—that negatively influence psoriasis risk remain unclear. Observational studies suggest a positive correlation between e-cigarette use and psoriasis prevalence,[13] particularly in certain psoriasis subtypes such as palmoplantar psoriasis or pustulosis.[14] However, few individuals who have never smoked conventional cigarettes frequently use e-cigarettes,[15,16] complicating efforts to differentiate the effects of nicotine from those of other tobacco constituents. Since smoking and e-cigarette use may share underlying genetic predispositions, isolating the independent causal effect of nicotine versus non-nicotine components presents methodological challenges. Additionally, there currently exist no GWAS focused on nicotine exposure independent of cigarette smoking (eg., e-cigarette usage among non-smokers), limiting our understanding of nicotine's specific effects.

GWAS of smoking behavior have identified several genetic variants associated with smoking intensity and nicotine metabolism.[17,18] Cigarettes per day (CPD) is commonly used to quantify total tobacco exposure, while the nicotine metabolite ratio (NMR) serves as a biomarker for individual nicotine metabolism rates at equivalent exposure levels.[17] Smokers with higher NMR clear nicotine more rapidly, typically resulting in higher CPD.[19] Epidemiological studies have reported that greater smoking intensity and longer duration are associated with an increased risk of developing psoriatic arthritis, supporting the biological plausibility that inter-individual differences in nicotine metabolism—and hence cumulative tobacco exposure—may modulate PsA susceptibility.[20,21] Consequently, under a univariable analytical framework, the effects of NMR on health outcomes include both direct and indirect pathways, yielding ambiguous results. Similar multivariable MR frameworks combining CPD and NMR have already been applied in other disease settings, providing a methodological precedent for the present study.[22] To address two critical limitations in current research—namely, the predominant focus on EUR populations and the challenge in distinguishing the causal effects of nicotine from other tobacco constituents—this study builds on and extends existing MR work by integrating two complementary methodological approaches. We employ trans-ethnic Mendelian randomization (TEMR), leveraging cross-ancestry genetic correlation under a conditional likelihood-based inference framework to integrate causal effects across different ancestries (including EAS [East Asian], AFR [African], and HIS [Hispanic]), thus enhancing the generalizability and statistical power for non-EUR populations.[23] In addition, a multivariable Mendelian randomization (MVMR) approach is adopted,[24] simultaneously incorporating CPD and NMR to dissect the independent causal effects of nicotine and non-nicotine components on psoriasis risk, providing clearer genetic evidence to elucidate the pathophysiology of tobacco-induced diseases.

Methods

Study Design

The research design is illustrated in Figure 1 and comprises six key components: 1) conducting univariable MR analyses to investigate the causal relationship between CPD and psoriasis risk across multiple ancestries; 2) calculating genetic correlations using linkage disequilibrium score regression (LDSC) to construct a genetic correlation matrix; 3) applying TEMR to examine the bidirectional causal relationship between CPD and psoriasis across ancestries; 4) assessing the association of NMR with psoriasis risk and related subtypes; 5) evaluating independent causal effects within a MVMR framework; and 6) performing mediation MR analysis to identify potential mediating factors. This study adheres to the guidelines outlined in the STROBE-MR reporting standards.[25] This study was a secondary analysis of lawfully obtained, publicly available and anonymized data; therefore, no ethical approval or clinical trial registration was required. Under Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, effective February 18, 2023), research using such public and anonymized data is exempt from ethical review, and our study meets these conditions.

Data Sources

GWAS data from EUR, EAS, AFR, and HIS populations were used in this study (Figure 1A). Details including sample sizes, sources, and GWAS Catalog identification numbers are summarized in Table S1. Published GWAS effect sizes were standardized, reflecting the influence of a one standard deviation (SD) increase in NMR or CPD on outcome variables. When psoriasis was utilized as an exposure in reverse analyses, effect sizes were expressed as log odds ratios (OR). Given that publicly available GWAS summary statistics were used for secondary analyses, ethical approval, clinical registration, and patient consent were not required. Sample overlap between certain exposures and outcomes was accounted for and detailed in the section "Correction for Sample Overlap."

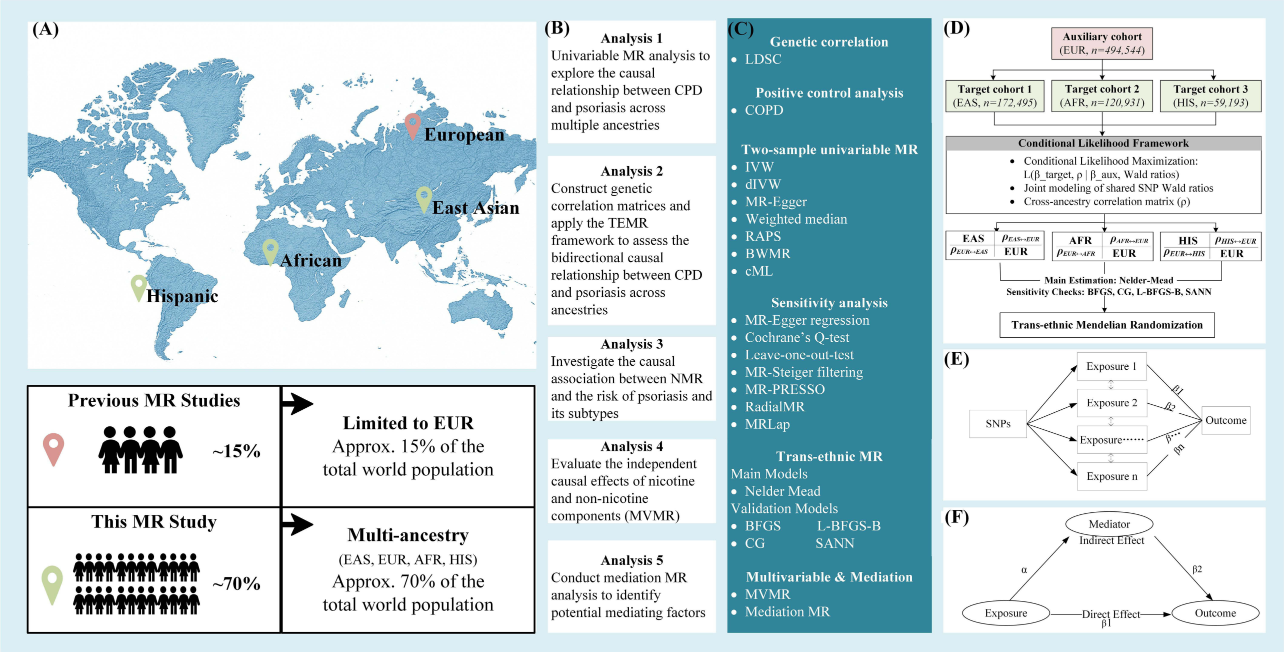

Figure 1 Study design. (**A**) Highlights the contrast between previous Mendelian randomization (MR) studies and the present study. Red markers indicate prior MR analyses were largely restricted to EUR populations, which only represent approximately 15% of the global population. Green markers denote the inclusion of EAS, AFR, and HIS populations in the present study, collectively capturing ~70% of the global population when combined with EUR. (**B**) Outlines the main analytical components of the study. LDSC and trans-ethnic Mendelian randomization (TEMR) are grouped under Analysis 2. (**C**) Summarizes the key methods used across the study. (**D**) Illustrates the analytical workflow of TEMR, which utilizes large-scale EUR GWAS data as an auxiliary cohort to infer causal effects in target populations (EAS, AFR, HIS). (**E**) Depicts the framework of multivariable Mendelian randomization (MVMR), wherein instruments (SNPs) relevant to each exposure are combined to create a unified instrument set, allowing for the adjustment of potential confounding by covariates through joint modeling. (**F**) Shows the conceptual model of the two-step mediation MR approach, which estimates the total, direct, and indirect (mediated) effects of NMR on disease risk through the mediator CPD, and quantifies the proportion of mediation.

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GWAS Data on Smoking Behavior

Consistent with previous studies,[22,26] CPD was utilized as a measure of smoking heaviness (expressed as the SD change in CPD categories, equivalent to an increase of 2–3 cigarettes per day). The most recent and comprehensive GWAS data on CPD from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) were used, covering EUR (*n=618,489*), EAS (*n=108,275*), AFR (*n=20,157*), and HIS (*n=35,129*) ancestries.[18] This consortium combined data from 60 cohorts and conducted analyses specifically among ever-smokers (current and former smokers), with adjustments for age, sex, genetic principal components, and smoking status (current vs. former smokers). Further cohort details are provided in Table S2. GSCAN employed a partial correlation method involving conditional analyses to progressively incorporate previously identified top single nucleotide polymorphisms (SNPs) as covariates, identifying additional SNPs that explained further phenotypic variance. Using this method, GSCAN identified a total of 153 EUR, 16 EAS, 2 AFR, and 2 HIS genome-wide significant and conditionally independent SNPs for CPD (Table S3).

The GWAS data for NMR used in this study were derived from a large-scale meta-analysis conducted by Buchwald et al, involving 5,185 current smokers of EUR ancestry.[17] All participants had serum cotinine levels ≥10 ng/mL to ensure recent smoking status. The analysis adjusted for population substructure, age, sex, body mass index, alcohol use, and birth year. Using a genome-wide complex trait analysis (GCTA) stepwise conditional regression method, seven genome-wide significant and conditionally independent SNPs were identified, explaining approximately 38% of the variance in NMR. Notably, genetic variants included SNPs such as rs56113850 within the CYP2A6 gene, encoding the key enzyme involved in nicotine metabolism, closely linked to individual smoking behavior (eg., higher NMR correlated with increased daily cigarette consumption). Genetic variant details are presented in Table S3.

GWAS Summary Data Sources for Psoriasis

The GWAS data for psoriasis in individuals of EUR ancestry were obtained from the largest available GWAS meta-analysis, which included data from 18 studies, comprising 36,466 cases and 458,078 controls.[27] The analysis identified 148 independent genetic signals outside the MHC region, collectively explaining approximately 46.5% of the variance in psoriasis susceptibility. Detailed cohort information is provided in Table S4. Diagnoses were primarily confirmed by dermatologists using clinical features, ICD codes, or by rheumatologists applying the CASPAR criteria. Controls were rigorously screened to exclude individuals with psoriasis or related ICD diagnoses. Each participating study underwent uniform quality control measures, including adjustment for population stratification through principal component analysis, and controls for age and sex within respective research centers.

For individuals of AFR and HIS ancestry, psoriasis GWAS summary data were derived from the Million Veteran Program (MVP), an observational cohort and extensive biobank that collects data via questionnaires, VA electronic health records (EHR), and blood samples.[28] Psoriasis cases were defined using ICD-10 code L40.0 and identified through PheCode 696.4, resulting in data from 1,711 cases and 119,220 controls of AFR ancestry, and 1,845 cases and 57,348 controls of HIS ancestry.

Genetic data for psoriasis in EAS populations were sourced from a trans-ancestry GWAS meta-analysis conducted by Sakaue et al, integrating data from the UK Biobank (UKB), FinnGen Consortium, and BioBank Japan (BBJ), totaling approximately 628,000 participants.[29] To ensure genetic background consistency, only data specific to the EAS population were utilized, comprising 206 psoriasis cases and 172,289 controls. Quality control procedures included sample and SNP filtering, genotype data standardization, principal component analysis for population stratification correction, and genotype imputation. It is noteworthy that the phenotype definition used by Sakaue et al was labeled “psoriasis vulgaris”; however, cases were identified using ICD-10 code L40, phecode 696.4, and FinnGen code “L12_PSORIASIS,” all of which specifically refer to psoriasis, ensuring the specificity and consistency of the phenotype for subsequent analyses.[30]

Genetic Instrument Selection and Study Assumptions

Genetic variants selected as IVs must satisfy three assumptions: 1) association with exposure, 2) independence from confounders, and 3) an effect on outcomes exclusively through the exposure[31] (Figure 1B). For genetic variant selection, we used SNPs reported in the original GWAS studies that achieved genome-wide significance ($P<5\times10^{-8}$) and demonstrated conditional independence. Additionally, sensitivity analyses were performed by applying stringent linkage disequilibrium (LD) clumping ($r^2<0.001$ within 10MB window) based on Phase 3 of the 1,000 Genomes Project for different ancestries, acknowledging that stringent clumping may inadvertently remove true association signals. SNPs were subsequently matched with outcome datasets, with proxy SNPs identified automatically using the TwoSampleMR package when exact matches were unavailable. Alleles were harmonized, and palindromic or ambiguous SNPs (eg., T/G vs. T/C) were removed. SNP strength was assessed using F-statistics, with weak genetic instruments (F<10) excluded.[32,33] Additionally, SNPs significantly associated with the outcome ($P<5\times10^{-8}$) were manually identified and removed. A Steiger test was performed to filter out SNPs more strongly associated with outcomes than exposures, aligning with assumption 3. Finally, two methods were employed to rigorously exclude outliers and mitigate horizontal pleiotropy bias (Figure 1B).

Statistical Analysis

All statistical analyses were performed using R software (version 4.2.3), utilizing the following R packages: TwoSampleMR, MendelianRandomization, MRPRESSO, BWMR, mr.raps, RadialMR, TEMR, MRlap, and genomicSEM.

Positive Control Analysis

Previous studies have established smoking as a major causal risk factor for chronic obstructive pulmonary disease (COPD), with clearly defined biological mechanisms. To validate the genetic instruments used in this study, COPD was selected as a positive control outcome.[34] Analyses included discovery and replication datasets, meta-analyses, and corrections for sample overlap. Detailed results are presented in Table S5.

Correction for Sample Overlap

Although pooling multiple cohorts in large-scale GWAS meta-analyses enhances the identification of genetic loci, this approach can lead to overlapping cohorts between exposure and outcome datasets, resulting in "winner's curse" bias. To address this, we employed two complementary strategies for correcting sample overlap: 1) selecting exposure datasets without overlapping samples, specifically conducting sensitivity analyses excluding UKB (*n=143,301*) and 23andMe (*n=291,992*) cohorts from CPD data, and 2) applying MRLap for statistical adjustment.[35]

Genetic Correlation Analysis

LDSC was employed to estimate genetic correlations (*rg*) between traits.[36] LDSC assesses linkage disequilibrium by evaluating the correlation between each SNP and nearby variants, thus distinguishing true polygenic signals from confounding biases. LDSC was primarily used to support the trans-ethnic analyses conducted within the TEMR framework.

Causal Inference Under the Univariable MR Framework

In univariable MR analyses (Figure 1C), the Wald ratio method was applied when a single SNP served as the genetic instrument. For analyses involving two or more SNPs, the primary method was inverse-variance weighted (IVW),[37] supplemented by alternative approaches including MR-Egger, weighted median, robust adjusted profile score (RAPS),[38] debiased IVW (dIVW),[39] constrained maximum likelihood (cML), and Bayesian Weighted MR (BWMR).[40] Sensitivity analyses included MR-Egger regression[41] and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) for detecting and removing horizontal pleiotropy and outliers,[42] Cochran's Q test for heterogeneity,[43] and RadialMR to assist MR-PRESSO in thoroughly excluding outliers.[44] Leave-one-out analyses evaluated result robustness. Finally, statistical power was calculated using the online platform mRnd, with Benjamini–Hochberg corrections applied for multiple testing. Associations were considered significant if the false discovery rate (FDR) adjusted P_{FDR} was <0.05 and suggestive if P_{FDR} >0.05 but raw *P-value* <0.05.

Trans-Ethnic Mendelian Randomization

For trans-ethnic causal inference, we applied the TEMR method proposed by Hou et al, using large-scale GWAS data from EUR ancestry as an auxiliary cohort to estimate the bidirectional causal effects between smoking and psoriasis for

EAS, AFR, and HIS populations[23] (Figure 1D). TEMR employs a conditional likelihood framework that jointly models the Wald ratios (β_{YG}/β_{XG}) derived from SNPs shared across populations, utilizing a Bayesian shrinkage approach guided by the cross-ancestry genetic correlation matrix (ρ). This approach effectively enhances causal effect estimation in the target populations while accounting for population-specific genetic variations. Intuitively, this conditional-likelihood TEMR framework lets smaller ancestry cohorts borrow strength from larger ones via the cross-ancestry genetic correlation matrix, stabilizing ancestry-specific estimates while still allowing genuine differences when supported by the data.

Initially, cross-ancestry *rg* between EUR-EAS, EUR-AFR, and EUR-HIS exposure SNP effects were calculated using LDSC. These rg values were arranged in a correlation matrix ρ, ordered as “EAS, AFR, HIS, EUR,” and fixed within the TEMR model. In cases where rg could not be stably estimated due to negative heritability from insufficient sample sizes, the respective cells were set to NA, and rho was set to NULL in TEMR, allowing missing ρ values to be inferred concurrently with β estimation under the maximum likelihood framework (Figure 1D). TEMR imposes stringent input requirements for the matrix ρ, necessitating either fully numerical values or entirely NULL values. Mixing numerical values and NA entries can result in Hessian singularity and convergence failure. To avoid arbitrarily imputing values (eg., 0.10) and contaminating the matrix, while also leveraging available EUR-target rg data, we partitioned the analysis into three independent 2×2 models: EAS-EUR, AFR-EUR, and HIS-EUR. EUR was consistently employed as the auxiliary column in each model, and missing rg values were handled by setting rho = NULL. The primary analysis utilized the Nelder-Mead Simplex Method (Nelder Mead) for TEMR likelihood estimation. To confirm robustness and consistency of the results, additional algorithms including Broyden–Fletcher–Goldfarb–Shanno (BFGS), Conjugate Gradient (CG), Limited-memory BFGS Bound Constrained (L-BFGS-B), and Simulated Annealing (SANN) were also employed (Figure 1D). The consistency of β estimates, standard errors, and p-values across methods was compared to validate model reliability. Descriptions of the advantages and underlying principles of each method are detailed in Table S6.

Multivariable and Mediation Causal Analysis Framework

MVMR extends traditional univariable MR methods by selecting instrumental variables that reflect a combination of genetic variants associated with all relevant exposures.[24] Operationally, significant SNPs from GWAS for each exposure were combined to create a unified list of unique SNPs. Joint modeling controlled for potential confounding influences from covariates, enabling more precise identification of independent causal pathways for each exposure. This study applied MVMR analyses to all identified significant results, estimating the independent causal contributions of nicotine and non-nicotine components to psoriasis risk (Figure 1E). Given the strong genetic correlation between higher NMR levels and increased CPD, the total effect of NMR on psoriasis observed in univariable MR analyses may encompass both direct and indirect effects mediated by CPD. In the MVMR framework, indirect effects are adjusted out, thus prompting further use of two-step mediation MR analysis to explore potential mediation mechanisms explicitly (Figure 1F).

Results

Validation of Genetic Instrument Strength and Efficacy

This study employed COPD as a positive control outcome to validate genetic instruments. Results demonstrated significant and unbiased causal associations between CPD and COPD across EUR, EAS, AFR, and HIS populations, confirming the validity of genetic instruments (Table S5). The number of SNPs included in the final analyses ranged from 2 to 139, all passing Steiger filtering criteria. Outliers were systematically excluded using MR-PRESSO and RadialMR, with detailed RadialMR results presented in Figure S1A–E. Each SNP had an F-statistic exceeding 10, with average F-statistics across analyses ranging from 36 to 509, indicating strong genetic instruments not subject to weak SNP bias. Detailed SNP selection and filtering procedures are provided in Table S7, while Table S8 lists specific SNP information utilized in the analyses.

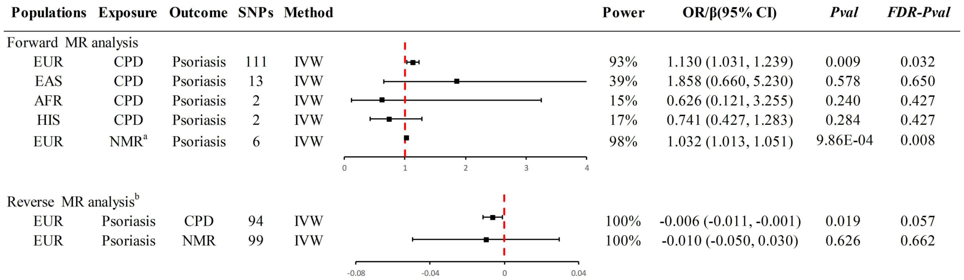
Univariable Mendelian Randomization Analyses

The summary of all univariable MR analysis results is provided in Table S9, with statistical power calculations presented in Table S10. Univariable analyses assessing the causal effect of genetically predicted CPD on psoriasis risk provided strong evidence of a significant association within the EUR population (OR = 1.130, 95% CI: 1.031~1.239, P = 0.008, P_{FDR} = 0.032) (Figure 2). Complementary analyses, including RAPS, cML, dIVW, and BWMR, consistently supported this association, achieving 93% statistical power at an OR of 1.130. Additionally, reverse analyses indicated a suggestive causal association between psoriasis and lower CPD frequency among EUR populations (β = −0.006, 95% CI: −0.011 ~ −0.001, P = 0.019, P_{FDR} = 0.057), with consistent evidence across all complementary analyses and 100% statistical power. No statistically significant causal associations were observed for EAS, AFR, and HIS ancestries, and statistical power ranged from limited to moderate (17%–39%). Reanalysis using stricter LD criteria yielded similar results (Table S11). For EUR ancestry, genetically predicted higher NMR levels demonstrated a robust causal association with increased psoriasis risk (OR = 1.032, 95% CI: 1.013~1.051, $P = 9.86\times10^{-4}$, P_{FDR} = 0.008), consistent across all complementary analyses except MR-Egger, with 98% statistical power.

Sensitivity analyses considered potential “winner’s curse” bias within EUR ancestry; results remained robust after correcting using non-overlapping samples (Table S12) and the MRLap method (Table S13). Apart from minor heterogeneity detected in the CPD-to-psoriasis analysis for AFR ancestry (P=0.049), which led to adopting a random-effects model, no heterogeneity was observed using Cochran’s Q tests for other analyses, thus fixed-effects models were selected. Neither MR-Egger regression nor MR-PRESSO identified horizontal pleiotropy, and leave-one-out analyses indicated positive results were not driven by any single SNP (Figure S2–S6). Detailed sensitivity analysis results are summarized in Table S14.

Trans-Ethnic Mendelian Randomization

Cross-population genetic correlation (ρ) results are summarized in Table S15. In the forward analysis (Table 1), the primary model employing the Nelder–Mead demonstrated a significant positive causal association between genetically predicted CPD and psoriasis risk in the HIS population (OR = 1.448, 95% CI: 1.434~1.463, $P = 1.10\times10^{-17}$, $P_{FDR} = 3.30\times10^{-17}$), a suggestive association in the EAS population (P=0.046), and no significant association in the AFR population (P=0.752). Recalculations using BFGS, CG, L-BFGS-B, and SANN produced consistent results in terms of effect sizes and significance, indicating no methodological bias. It should be noted that the confidence interval for the EAS population was notably wide (OR = 2.97×10^{4}, 95% CI: 1.91×10^{2}~4.63×10^{6}); the β estimate was influenced substantially by a single high-noise SNP and cross-ancestry shrinkage toward EUR values, highlighting the sensitivity of the EAS results to the cross-population correlation coefficient (ρ). To assess robustness, TEMR was repeated by setting ρ to fixed values (0.1, 0.3, 0.5, 0.7, 0.9) and allowing model estimation (ρ = NULL). Sensitivity analyses indicated that at low correlation values or model-estimated correlation, the shrinkage effect between EAS and EUR diminished, and the β estimate became insignificant, demonstrating a lack of reliable evidence for a causal effect of CPD on psoriasis risk in EAS populations due to limited sample sizes and low cross-ancestry correlation (Table S16 and Figure S7).



Populations	Exposure	Outcome	SNPs	Method	Power	OR/β(95% CI)	*Pval*	*FDR-Pval*
Forward MR analysis								
EUR	CPD	Psoriasis	111	IVW	93%	1.130 (1.031, 1.239)	0.009	0.032
EAS	CPD	Psoriasis	13	IVW	39%	1.858 (0.660, 5.230)	0.578	0.650
AFR	CPD	Psoriasis	2	IVW	15%	0.626 (0.121, 3.255)	0.240	0.427
HIS	CPD	Psoriasis	2	IVW	17%	0.741 (0.427, 1.283)	0.284	0.427
EUR	NMR[a]	Psoriasis	6	IVW	98%	1.032 (1.013, 1.051)	9.86E-04	0.008
Reverse MR analysis[b]								
EUR	Psoriasis	CPD	94	IVW	100%	-0.006 (-0.011, -0.001)	0.019	0.057
EUR	Psoriasis	NMR	99	IVW	100%	-0.010 (-0.050, 0.030)	0.626	0.662

Figure 2 Summary of results from univariable Mendelian randomization analyses. (**a**) Indicates that NMR data were only available for EUR ancestry. (**b**) Indicates that in the reverse MR analysis, genome-wide significant and independent SNPs for psoriasis were identified exclusively in the EUR population. The red dotted vertical line indicates the null effect reference line (OR = 1 for binary outcomes and β = 0 for continuous outcomes).

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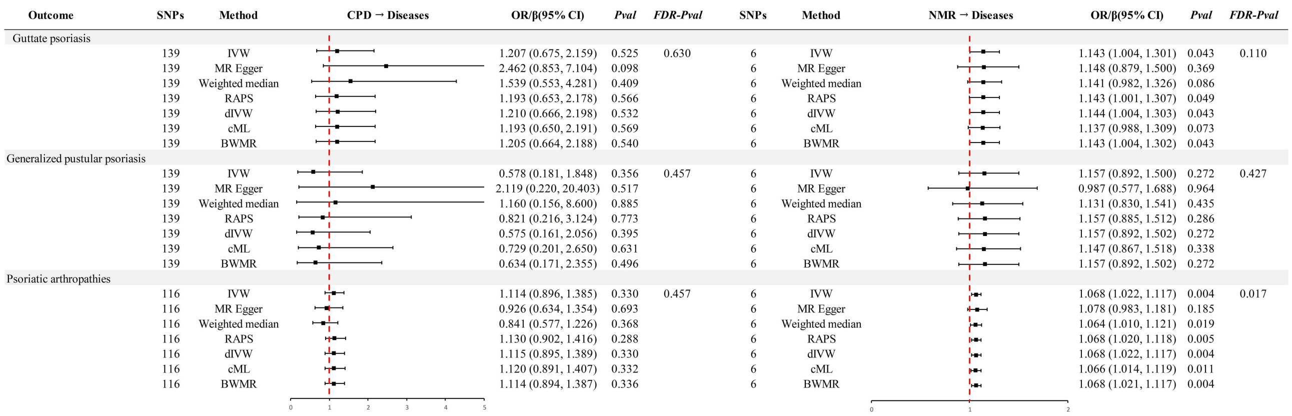
Table 1 TEMR-Based to Explore the Causal Association of Multi-Ancestry CPD-Psoriasis

Exposure	Outcome	Models	Ancestry	stat	SE	OR	Low 95% CI	Up 95% CI	*Pval*	*FDR-Pval*
CPD	Psoriasis	Nelder-Mead	EAS	−3.999	2.576	2.97E+04	1.91E+02	4.63E+06	0.046	6.84E-02
			AFR	−0.1	2.133	0.809	0.012	53.1	0.752	0.752
			HIS	−73.331	0.005	1.448	1.434	1.463	1.10E-17	3.30E-17
		CG	EAS	−3.997	2.528	2.45E+04	1.72E+02	3.47E+06	0.046	6.84E-02
			AFR	−0.1	2.09	0.812	0.014	48.8	0.752	0.752
			HIS	−73.332	0.005	1.449	1.435	1.463	1.10E-17	3.30E-17
		SANN	EAS	−3.999	2.587	3.10E+04	1.89E+02	5.04E+06	0.046	6.84E-02
			AFR	−0.1	2.09	0.812	0.014	48.8	0.752	0.752
			HIS	−73.332	0.005	1.449	1.435	1.463	1.10E-17	3.30E-17
		BFGS	EAS	−3.999	2.587	3.10E+04	1.89E+02	5.04E+06	0.046	6.84E-02
			AFR	−0.1	2.09	0.812	0.014	48.8	0.752	0.752
			HIS	−73.332	0.005	1.449	1.435	1.463	1.10E-17	3.30E-17
		L-BFGS-B	EAS	−3.999	2.587	3.10E+04	1.89E+02	5.04E+06	0.046	6.84E-02
			AFR	−0.1	2.09	0.812	0.014	48.8	0.752	0.752
			HIS	−73.332	0.005	1.449	1.435	1.463	1.10E-17	3.30E-17
Exposure	**Outcome**	**Models**	**Ancestry**	**stat**	**SE**	**beta**	**Low 95% CI**	**Up 95% CI**	***Pval***	***FDR-Pval***
Psoriasis	CPD	Nelder-Mead	EAS	−460.842	4.69E-06	−0.002	–0.00217	–0.00215	3.15E-102	4.73E-102
			AFR	−7.241	0.002	−0.011	–0.014	–0.008	0.007	7.00E-03
			HIS	−1346.677	1.08E-04	−0.145	–0.1451	–0.1447	8.13E-295	2.44E-294
		CG	EAS	−460.842	4.69E-06	−0.002	–0.00217	–0.00215	3.15E-102	4.73E-102
			AFR	−7.241	0.002	−0.011	–0.014	–0.008	0.007	7.00E-03
			HIS	−1346.677	1.08E-04	−0.145	–0.1450	–0.1447	8.12E-295	2.44E-294
		SANN	EAS	−460.842	4.70E-06	−0.002	–0.00217	–0.00215	3.15E-102	4.73E-102
			AFR	−7.241	0.002	−0.011	–0.014	–0.008	0.007	7.00E-03
			HIS	−1346.677	1.08E-04	−0.145	–0.1450	–0.1447	8.12E-295	2.44E-294
		BFGS	EAS	−460.842	4.69E-06	−0.002	–0.00217	–0.00215	3.15E-102	4.73E-102
			AFR	−7.241	0.002	−0.011	–0.014	–0.008	0.007	7.00E-03
			HIS	−1346.677	1.08E-04	−0.145	–0.1450	–0.1447	8.12E-295	2.44E-294
		L-BFGS-B	EAS	−460.842	4.69E-06	−0.002	–0.00217	–0.00215	3.15E-102	4.73E-102
			AFR	−7.241	0.002	−0.011	–0.014	–0.008	0.007	7.00E-03
			HIS	−1346.677	1.08E-04	−0.145	–0.1450	–0.1447	8.12E-295	2.44E-294

In the reverse TEMR analysis (Table 1), psoriasis was treated as the exposure and CPD as the outcome. The primary model (Nelder–Mead) revealed a significant negative causal association between genetically predicted psoriasis and CPD in all three target populations (EAS [$\beta = -0.002$, 95% CI: $-0.00217 \sim -0.00215$], AFR [$\beta = -0.011$, 95% CI: $-0.0144 \sim -0.00828$], HIS [$\beta = -0.145$, 95% CI: $-0.1451 \sim -0.1447$]). Subsequent analyses using BFGS, CG, L-BFGS-B, and SANN confirmed these results, showing consistent β estimates, standard errors, and *P-values*, validating the robustness of reverse causal findings. Notably, in EAS populations, some TEMR odds ratios were very large with wide confidence intervals, consistent with limited precision due to small sample sizes and modest cross-ancestry genetic correlations; these EAS estimates should therefore be interpreted cautiously as exploratory rather than definitive evidence of ancestry-specific effects.

Further Analyses: Psoriasis Subtypes

Additional analyses incorporated psoriasis subtypes (Guttate psoriasis, generalized pustular psoriasis, and psoriatic arthropathies) from the EUR population obtained from the FinnGen consortium to examine causal associations with CPD and NMR (Figure 3). Results showed a significant causal association between genetically predicted NMR and increased risk of psoriatic arthropathies (OR = 1.068, 95% CI: 1.022~1.117, $P = 0.004$, $P_{FDR} = 0.17$), with a suggestive causal relationship observed for generalized pustular psoriasis (OR = 1.143, 95% CI: 1.004~1.301, $P = 0.043$, $P_{FDR} = 0.110$). No other causal associations were identified. Sensitivity analyses did not detect significant heterogeneity or



Outcome	SNPs	Method	OR/β(95% CI)	*Pval*	*FDR-Pval*	SNPs	Method	OR/β(95% CI)	*Pval*	*FDR-Pval*
Guttate psoriasis										
	139	IVW	1.207 (0.675, 2.159)	0.525	0.630	6	IVW	1.143 (1.004, 1.301)	0.043	0.110
	139	MR Egger	2.462 (0.853, 7.104)	0.098		6	MR Egger	1.148 (0.879, 1.500)	0.369	
	139	Weighted median	1.539 (0.553, 4.281)	0.409		6	Weighted median	1.141 (0.982, 1.326)	0.086	
	139	RAPS	1.193 (0.653, 2.178)	0.566		6	RAPS	1.143 (1.001, 1.307)	0.049	
	139	dIVW	1.210 (0.666, 2.198)	0.532		6	dIVW	1.144 (1.004, 1.303)	0.043	
	139	cML	1.193 (0.650, 2.191)	0.569		6	cML	1.137 (0.988, 1.309)	0.073	
	139	BWMR	1.205 (0.664, 2.188)	0.540		6	BWMR	1.143 (1.004, 1.302)	0.043	
Generalized pustular psoriasis										
	139	IVW	0.578 (0.181, 1.848)	0.356	0.457	6	IVW	1.157 (0.892, 1.500)	0.272	0.427
	139	MR Egger	2.119 (0.220, 20.403)	0.517		6	MR Egger	0.987 (0.577, 1.688)	0.964	
	139	Weighted median	1.160 (0.156, 8.600)	0.885		6	Weighted median	1.131 (0.830, 1.541)	0.435	
	139	RAPS	0.821 (0.216, 3.124)	0.773		6	RAPS	1.157 (0.885, 1.512)	0.286	
	139	dIVW	0.575 (0.161, 2.056)	0.395		6	dIVW	1.157 (0.892, 1.502)	0.272	
	139	cML	0.729 (0.201, 2.650)	0.631		6	cML	1.147 (0.867, 1.518)	0.338	
	139	BWMR	0.634 (0.171, 2.355)	0.496		6	BWMR	1.157 (0.892, 1.502)	0.272	
Psoriatic arthropathies										
	116	IVW	1.114 (0.896, 1.385)	0.330	0.457	6	IVW	1.068 (1.022, 1.117)	0.004	0.017
	116	MR Egger	0.926 (0.634, 1.354)	0.693		6	MR Egger	1.078 (0.983, 1.181)	0.185	
	116	Weighted median	0.841 (0.577, 1.226)	0.368		6	Weighted median	1.064 (1.010, 1.121)	0.019	
	116	RAPS	1.130 (0.902, 1.416)	0.288		6	RAPS	1.068 (1.020, 1.118)	0.005	
	116	dIVW	1.115 (0.895, 1.389)	0.330		6	dIVW	1.068 (1.022, 1.117)	0.004	
	116	cML	1.120 (0.891, 1.407)	0.332		6	cML	1.066 (1.014, 1.119)	0.011	
	116	BWMR	1.114 (0.894, 1.387)	0.336		6	BWMR	1.068 (1.021, 1.117)	0.004	

Figure 3 Summary of additional analyses assessing the effects of CPD and NMR on the risk of psoriasis subtypes.

Notes: GWAS data for psoriasis subtypes were only available for individuals of EUR ancestry. The red dotted vertical line indicates the null effect reference line (OR = 1 for binary outcomes and β = 0 for continuous outcomes).

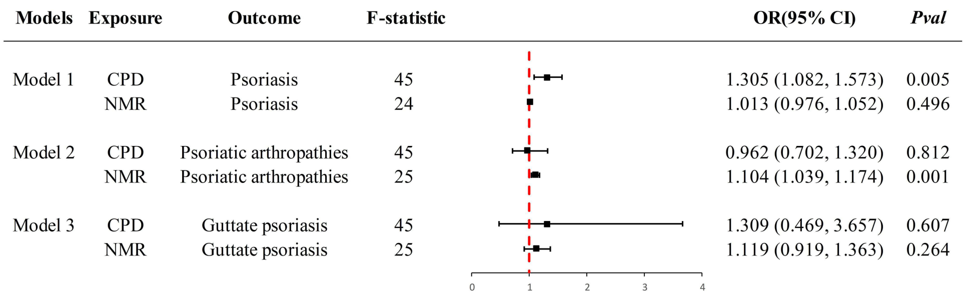
pleiotropy (Table S14), although leave-one-out analysis identified the SNP rs56113850 in the CYP2A6 gene as a critical driver of the NMR-Psoriatic arthropathies causal relationship (Figure S8).

Multivariable Mendelian Randomization Analysis

Due to limited availability of public NMR GWAS data, MVMR analysis was conducted only within the EUR population to distinguish the independent effects of nicotine and non-nicotine components on psoriasis risk (Figure 4). A random-effects IVW method was employed as the primary estimation approach, using stringent LD-clumping ($r^2<0.001$) to mitigate multicollinearity. Based on positive univariable MR findings, three distinct MVMR models were established (Figure 4): Model 1 indicated that CPD remained significantly associated with psoriasis risk after adjusting for NMR (OR = 1.305, 95% CI: 1.082~1.573), whereas NMR effects became insignificant after adjusting for CPD (P>0.05), suggesting an independent contribution from non-nicotine components. Model 2 demonstrated a significant positive association between NMR and Psoriatic arthropathies risk after controlling for CPD (OR = 1.104, 95% CI: 1.039~1.174). Model 3 showed that NMR lost statistical significance in relation to Guttate psoriasis risk after CPD adjustment (P>0.05) (Figure 4).

Mediation Mendelian Randomization Analysis

The mediation MR (Table 2) identified CPD as a significant mediator of NMR's causal pathway to psoriasis, accounting for 73.24% of the total effect (P=0.01). CPD also exhibited mediating effects in Psoriatic arthropathies and Guttate psoriasis subtypes (mediation proportion ranging from 19.41% to 23.81%), although these effects were not statistically significant (P > 0.05).



Models	Exposure	Outcome	F-statistic	OR(95% CI)	*Pval*
Model 1	CPD	Psoriasis	45	1.305 (1.082, 1.573)	0.005
	NMR	Psoriasis	24	1.013 (0.976, 1.052)	0.496
Model 2	CPD	Psoriatic arthropathies	45	0.962 (0.702, 1.320)	0.812
	NMR	Psoriatic arthropathies	25	1.104 (1.039, 1.174)	0.001
Model 3	CPD	Guttate psoriasis	45	1.309 (0.469, 3.657)	0.607
	NMR	Guttate psoriasis	25	1.119 (0.919, 1.363)	0.264

Figure 4 Summary of multivariable Mendelian randomization analysis results. Three models were constructed based on the positive findings obtained from univariable MR analyses. The effect estimates represent the independent causal effects of CPD and NMR on psoriasis risk after mutual adjustment. The red dotted vertical line indicates the null effect reference line (OR = 1 for binary outcomes and β = 0 for continuous outcomes).

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Table 2 Summary of Results From Two-Step Mediation MR Analyses

Exposure	Mediation	Outcome	Confidence Interval of Total Effect (95% CI)	Confidence Interval of Direct Effect (95% CI)	Confidence Interval of Mediation Effect (95% CI)	Proportion of Mediation Effect	*Pval*
NMR	CPD	Psoriasis	0.031 (0.013, 0.050)	0.008 (−0.018, 0.034)	0.023 (0.005, 0.041)	73.24%	*0.011*
NMR	CPD	Psoriatic arthropathies	0.066 (0.021, 0.110)	0.050 (−0.001, 0.102)	0.016 (−0.010, 0.042)	23.81%	0.227
NMR	CPD	Guttate psoriasis	0.134 (0.004, 0.263)	0.108 (−0.044, 0.260)	0.026 (−0.054, 0.106)	19.41%	0.510

Discussion

This study conducted a trans-ethnic causal analysis, revealing robust causal evidence that genetically predicted CPD are associated with increased psoriasis risk in EUR and HIS populations, while evidence in EAS populations was limited. Reverse analysis indicated genetically predicted psoriasis was associated with lower CPD across EUR, EAS, AFR, and HIS populations. Subtype analyses revealed a causal association between NMR and increased risk of guttate psoriasis and psoriatic arthropathies. MVMR analysis further indicated that non-nicotine tobacco components (CPD adjusted for NMR independently contributed to overall psoriasis risk, whereas the NMR specifically influenced psoriatic arthropathies risk. Mediation analyses identified CPD as a prominent mediator in the causal pathway from NMR to psoriasis risk.

Incidence rates of psoriasis vary significantly across populations. Globally, EUR populations typically exhibit higher prevalence rates compared to other ancestries, averaging approximately 2–3% in Western populations,[45] and as high as 8–11% in certain Northern EUR countries.[46] In contrast, psoriasis prevalence in EAS is approximately 0.14%,[47] while data from the United States indicate prevalence rates of 0.7–1.3% among AFR-Americans and approximately 3.0% among HIS populations.[48] Our findings align with prior epidemiological research, providing strong evidence supporting causal roles of NMR in EUR populations and CPD in EUR and HIS populations. The limited evidence for CPD in the EAS population should be interpreted cautiously due to its high sensitivity to cross-ancestry correlation coefficients (ρ), warranting validation in larger cohorts. The absence of causal evidence in AFR populations likely reflects genetic differences rather than insufficient statistical power, given their inherently low psoriasis prevalence. Therefore, behavioral interventions such as smoking cessation to mitigate psoriasis risk may need to consider ancestry-specific genetic backgrounds.

Reverse causal analyses suggested genetically predicted psoriasis susceptibility was associated with lower CPD across EUR, EAS, AFR, and HIS populations. This pattern is plausibly explained by lifestyle changes following diagnosis rather than a distinct biological pathway. Supporting this notion, a large-scale Korean cohort study found significantly reduced psoriasis risk among smokers who quit compared to persistent smokers (adjusted hazard ratio [HR] approximately 0.91), with further reduced risk in long-term quitters (HR approximately 0.77).[49] Taken together, these findings indicate that individuals with psoriasis or at elevated risk may proactively reduce or cease smoking to manage their condition, and we therefore interpret the reverse-direction MR results primarily as reflecting behavioral modification rather than a separate causal mechanism.

Subtype analyses indicated causal associations between NMR—but not CPD—and increased risk of guttate psoriasis and psoriatic arthropathies. Although the NMR analysis utilized only six SNPs, it exhibits high heritability (approximately 80% according to twin studies), primarily driven by functional polymorphisms in the CYP2A6 gene.[50] NMR, characterized by high specificity and biological stability, is less influenced by behavioral factors and captures a substantial variance through fewer SNPs compared to CPD.[17] Conversely, CPD, represented by numerous SNPs, encapsulates a complex behavioral trait highly susceptible to social, psychological, and subjective reporting biases, thereby introducing horizontal pleiotropy and undermining causal inference accuracy.[51] Furthermore, NMR reflects individual nicotine metabolism rates; rapid metabolizers typically increase smoking frequency or inhalation depth to maintain nicotine levels, consequently accumulating greater toxic loads and inflammatory stress. This prolonged metabolic pressure may precisely target immunological pathways specific to psoriasis subtypes, such as guttate psoriasis and psoriatic arthropathies.[19] In contrast, CPD quantifies total cigarette consumption but inadequately captures individual variations in nicotine exposure. Non-nicotine components measured by CPD may contribute to systemic inflammation, potentially influencing common plaque psoriasis rather than specific subtypes. Consequently, NMR, as a metabolically stable and mechanistically clearer exposure marker, demonstrated stronger statistical signals in causal inference analyses of psoriasis subtypes.

In the MVMR analysis, we identified independent pathogenic roles of nicotine and non-nicotine components of tobacco in psoriasis and its subtypes. Firstly, after adjusting for NMR, CPD remained significantly associated with the overall risk of psoriasis, whereas NMR lost its significance when adjusted for CPD. This suggests that non-nicotine components such as polycyclic aromatic hydrocarbons (PAHs), tar, and pro-inflammatory heavy metals independently contribute to psoriasis pathogenesis, potentially through inducing oxidative stress and activating inflammatory pathways including MAPK and NF-κB.[52] The loss of significance of NMR after CPD adjustment further supports the notion that nicotine itself is not the primary driver of overall psoriasis risk. Secondly, after controlling for CPD, NMR retained a significant causal effect on the risk of psoriatic arthropathies, indicating that variations in nicotine metabolism may independently modulate immune responses by enhancing the release of pro-inflammatory cytokines such as TNF and IL-12, specifically influencing the pathogenesis of psoriatic arthropathies.[6] This finding addresses inconsistencies observed in previous epidemiological studies regarding the relationship between smoking and psoriatic arthropathies, highlighting the importance of metabolic phenotypes in immune-inflammatory processes.[53] Finally, in Model 3, NMR was no longer significantly associated with guttate psoriasis after adjusting for CPD, likely due to the limited statistical power arising from the small sample size for guttate psoriasis. Adjusting for CPD introduced substantial confounding, obscuring the impact of nicotine metabolism on disease outcomes, which aligns with mediation analyses that also failed to identify CPD as a mediator in this particular pathway.

This study incorporated genetic data from EAS, AFR, and HIS populations, applying the TEMR approach to address limitations prevalent in previous MR studies, specifically enhancing the generalizability of findings across diverse ancestries. However, because cross-ancestry genetic correlations were relatively unstable and sample sizes were modest in several non-European cohorts, particularly EAS and AFR, these ancestry-specific TEMR estimates should be viewed as hypothesis-generating rather than definitive. We implemented multiple rigorous quality controls, including positive control analyses and corrections for winner's curse bias, to mitigate various sources of bias and ensure the robustness of our results. Additionally, by integrating nicotine and non-nicotine components into an MVMR framework, our analysis identified non-nicotine constituents as independent risk factors for psoriasis overall, and nicotine as an independent risk factor specifically for psoriatic arthropathies, thus overcoming limitations inherent to observational studies. However, it should be noted that subtype, MVMR, and mediation analyses were restricted to EUR populations due to limited data availability. Furthermore, the suggestive evidence regarding the effect of CPD on psoriasis risk in EAS populations observed in TEMR analyses warrants further validation, and future studies should aim to include underrepresented populations such as South Asian (SAS) and Great Middle Eastern (GME) cohorts.

Conclusion

To encapsulate, this study systematically evaluated the relationships between genetically proxied smoking behaviours and liability to psoriasis across multiple ancestries within a conditional likelihood framework. In European populations, our analyses are consistent with a risk-increasing role of higher NMR for psoriasis. We also observed positive associations between genetically proxied CPD and psoriasis in European and Hispanic populations. Reverse-direction analyses suggested that higher genetic liability to psoriasis is associated with lower CPD across EUR, EAS, AFR, and HIS populations, a pattern that is most plausibly explained by smoking reduction or cessation following (or in anticipation of) disease onset. Subtype analyses indicated that NMR may be more strongly related to psoriatic arthropathies and guttate psoriasis than to other forms of psoriasis. Multivariable MR models further suggested that nicotine-related and non-nicotine tobacco components make partly independent contributions to psoriasis risk at the exposure level, without implying fully distinct underlying biological pathways. Overall, our findings support the importance of considering both smoking intensity and inter-individual differences in nicotine metabolism when assessing psoriasis risk, and they may help refine the identification of higher-risk groups and the design of targeted preventive strategies. These potential clinical and public health implications should be regarded as hypothesis-generating rather than prescriptive, given the genetic nature of MR inference.

Data Sharing Statement

The data used in this study are from publicly available downloadable GWAS data, available from Table S1.

Ethics Approval and Consent to Participate

The study was a secondary analysis of publicly available data and therefore did not require ethical approval and clinical registration. According to Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (effective February 18, 2023, China), research projects that meet either of the following conditions may be exempt from ethical review: (1) the research uses legally obtained public data or data generated through observation without interfering with public behavior; or (2) the research uses anonymized information or data. As this study complies with both conditions, ethical review was not required.

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Disclosure

The authors report no competing interests in this study.

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