Patrick Matthew T (Orcid ID: 0000-0002-6174-9002)

Li Yingjun (Orcid ID: 0000-0001-8899-916X)

# Alcohol consumption and smoking in relation to psoriasis: a Mendelian randomization study

Jiahe Wei,[1] Jiahao Zhu,[1] Huiqing Xu,[1] Dan Zhou,[2,3] James T. Elder,[4,5] Lam C. Tsoi,[4,6] Matthew T. Patrick[4] and Yingjun Li[1]

[1]Department of Epidemiology and Health Statistics, School of Public Health, Hangzhou Medical College, Hangzhou, China; [2]School of Public Health and the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [3]Vanderbit Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA; [4]Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA; [5]Ann Arbor Veterans Affairs Hospital, Ann Arbor, Michigan, USA; [6]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, United States.

**Corresponding author:** Yingjun Li

**Email**: 2016034036@hmc.edu.cn

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**What's already known about this topic?**

- Alcohol consumption and smoking have been reported to be associated with psoriasis risk.
- Whether alcohol consumption and smoking have causal effect on psoriasis risk remains unclear.

**What does this study add?**

- This Mendelian randomization study shows a causal association between smoking, but not alcohol consumption, and the risk of developing psoriasis.
- Restricting smoking could be helpful in reducing the burden of psoriasis.

## Abstract

**Background:** Alcohol consumption and smoking have been reported to be associated with psoriasis risk. However, a conclusion with high-quality evidence of causality couldn't be easily drawn from regular observational studies.

**Objectives:** This study aims to assess the causal associations of alcohol consumption and smoking with psoriasis.

**Methods:** Genome-wide association study (GWAS) summary-level data for alcohol consumption (N = 941,280), smoking initiation (N = 1,232,091), cigarettes per day (N = 337,334), and smoking cessation (N = 547,219) was obtained from GSCAN consortium (Sequencing Consortium of Alcohol and Nicotine use). The GWAS results for lifetime smoking (N = 462,690) were obtained from the UK Biobank samples. Summary statistics for psoriasis were obtained from a recent GWAS meta-analysis of eight cohorts comprising 19,032 cases and 286,769 control and FinnGen consortium comprising 4,510 cases and 212,242 control. Linkage disequilibrium score regression was applied to compute the genetic correlation. Bidirectional Mendelian randomization (MR) analyses were conducted to determine casual direction using independent genetic variants that reached genome-wide significance ($P < 5 \times 10^{-8}$).

**Results:** There were genetic correlations between smoking and psoriasis. MR revealed a causal effect of smoking initiation [odds ratios (OR): 1.46, 95% confidence interval (CI): 1.32-1.60, *P* = 6.24E-14), cigarettes per day (OR: 1.38, 95% CI: 1.13-1.67, *P* = 0.001), and lifetime smoking (OR: 1.96, 95% CI: 1.41-2.73, *P* =7.32E-05) on psoriasis. Additionally, a suggestive causal effect of smoking cessation on psoriasis was observed (OR: 1.39, 95% CI: 1.07-1.79, P =0.012). We found no causal relationship between alcohol consumption and psoriasis (*P* = 0.379). The reverse associations were not statistically significant.

**Conclusions:** Our findings provide causal evidence for the effects of smoking on psoriasis risk.

## Introduction

Psoriasis is a complex chronic immune-mediated inflammatory disease of the skin or joints affecting approximately 2% of the global population and is a leading cause of severe comorbidities.[1] Modifiable lifestyle factors, such as smoking and alcohol consumption, were considered potential risk factors for psoriasis.[2,3] A prospective study showed that alcohol consumption could increase psoriasis risk.[4] However, another two recent cohort studies did not support a clear link between alcohol consumption and psoriasis.[5,6] Current evidence on the relationship between alcohol consumption and psoriasis is controversial. Although a positive association between smoking and psoriasis was well-identified by observational studies,[2,7] these studies are susceptible to uncontrolled confounders.[5] For example, depression is a potential confounder since it increases the risk of both smoking and psoriasis. [8,9]

Considering the weakness of regular observational studies, whether the association between alcohol consumption as well as smoking and psoriasis reflects true causation or is confounded remains unclear. Mendelian Randomization (MR) offers a mean, utilizing genetic variants as instrumental variables (IV), to infer the causal effect between the exposure and the outcome .[10] Because genetic variation (1) is fixed and randomly assigned during meiosis, and (2) is not affected by environmental factors, which minimizes potential confounders and reverse causality. [11] Here, we implemented the bidirectional MR analyses to explore the causal relationship between alcohol consumption as well as smoking and psoriasis.

## Method

### Study design

A flow of our study design is shown in Figure 1A. Firstly, we applied linkage disequilibrium score regression (LDSC) to assess the genetic correlations between alcohol consumption as well as smoking and psoriasis. Secondly, we carried out MR to evaluate the causal effect of alcohol consumption as well as smoking on psoriasis as the discovery stage (Psoriasis 2017 Tsoi et al.) and then replicated these relationships in the FinnGen consortium. Finally, we performed reverse MR to assess whether psoriasis was associated with alcohol consumption and smoking.

**Data source**

In this study, we obtained genetic variables for alcohol consumption (N = 941,280), smoking initiation (N = 1,232,091), cigarettes per day (N = 337,334) (by combining smoking status as well as smoking duration, heaviness, and cessation in ever smokers), and smoking cessation (N = 547,219) (contrasting current versus former smokers) from a large genome-wide association study (GWAS) released by the GSCAN consortium (GWAS & Sequencing Consortium of Alcohol and Nicotine use).[12] The lifetime smoking (reflecting a composite measure of smoking initiation, years of smoking, smoking heaviness, and smoking cessation) GWAS results (N = 462,690) [8] was obtained from the UK Biobank as a supplementary. Summary statistics for both smoking and alcohol consumption do not include the subjects from 23andMe.

We obtained genetic instruments for psoriasis from a recent GWAS meta-analysis of eight cohorts with 305,801 samples (where 19,032 of them are cases).[13] The summary statistics for psoriasis lack samples from 23andMe owing to restricted access to genome-wide 23andMe data. Hence, the summary statistics as the outcome data for psoriasis in our summary-level MR analysis only included 34,842 individuals (13,299 psoriasis cases and 21,543 controls) (as the discovery stage). All psoriasis cases were diagnosed by clinicians. Besides, we used the summary statistics for psoriasis from the FinnGen consortium (4,510 psoriasis cases and 212,242 controls) for replication. The detailed information of the data source is presented in Table 1.

**Statistical analysis**

The genetic correlations between alcohol consumption, smoking, and psoriasis were estimated using the LDSC.[14] This method utilizes the genome, multiplies the Z-cores genetically associated with trait 1 by the Z-cores genetically associated with trait 2, and then regresses the product on the LD score to obtain the slope, which represents genetic correlation.

MR analysis should satisfy the three MR assumptions (Figure 1B). Initially, we selected reported SNPs that were independently distributed and reached genome-wide significance ($P < 5 \times 10^{-8}$) as IVs to represent genetic susceptibility to exposure. The SNPs having a direct association with the outcome ($P < 5 \times 10^{-8}$) were excluded from the corresponding MR analysis. Data harmonization was made to ensure the correspondence of the allele between the exposure and the outcome. The random-effects inverse-variance weighted (IVW) was considered as the primary method. Awaring the third assumption of MR, we also applied a series of sensitivity analyses: (1) The weighted median method provides a robust estimate of the effect, when more than half of IVs are valid.[15] (2) The MR Egger regression method gives a consistent causal effect estimate even when all the IVs are invalid based on the InSIDE (INstrument Strength Independent of Direct Effect) assumption. The InSIDE hypothesis is violated when variation is pleiotropically affected by different confounders.[16] The intercept from MR Egger was adopted to assess the directional pleiotropy. $P < 0.05$ suggests the existence of pleiotropy.[17] (3) The MR pleiotropy residual sum and outlier (MR-PRESSO) method provides a corrected estimate by removing potentially pleiotropic SNPs.[18] MR-PRESSO global test was used to evaluate overall horizontal pleiotropy. Derived causal estimates in the discovery stage and the replication stage were combined using fixed-effects meta-analysis. Furthermore, we checked the heterogeneity among SNPs in IVW and MR Egger estimators using the Cochran's Q statistic. We applied leave-one-out method to examine whether each SNP causes drive or bias on the summary estimates by eliminating each SNP and calculating the meta-effect of the remaining SNPs. In addition, we conducted the MR analysis to test potential for reverse causality (that is, assessing the effects of psoriasis on alcohol consumption as well as smoking).

All statistical tests were two-sided and performed using the "TwoSampleMR" package (version 0.5.6) and "MR-PRESSO" package (version 1.0) in R software 4.1.0 and software package LDSC (version 1.0.1). To account for multiple testing, we used Bonferroni-corrected thresholds of 0.003 ($\alpha = 0.05/15$) in our LDSC analyses and 0.005 ($\alpha = 0.05/10$) in our bidirectional MR analyses. We considered *P* below the threshold as significant evidence of associations.

## Result

### Genetic Correlations

Smoking initiation ($r_g = 0.152$, $P = 5.9E\text{-}08$), cigarettes per day ($r_g = 0.139$, $P = 4.3E\text{-}05$), lifetime smoking ($r_g = 0.171$, $P = 8.27E\text{-}08$), and smoking cessation ($r_g = 0.217$, P = 2E-04) showed a positive genetic correlation with psoriasis. However, the significance of the genetic correlation between alcohol consumption and psoriasis did not survive after Bonferroni-correction ($r_g = 0.067$, $P = 0.028$). There are positive genetic correlations between different smoking phenotypes and between smoking and alcohol consumption (Figure 2, Table S7).

### Mendelian randomization

The SNPs used in this study were presented in Tables S1-S6. There are 99, 378, 55, 126, 24, and 58 SNPs as instrumental variables for alcohol consumption, smoking initiation, cigarettes per day, lifetime smoking, smoking cessation, and psoriasis, respectively.

As shown in Figure 3 and Table S8-S9, higher smoking initiation, cigarettes per day, and lifetime smoking led to a higher risk of psoriasis in the discovery stage

(Psoriasis 2017 Tsoi et al.). The positive association of smoking initiation and lifetime smoking was replicated in the dataset from the FinnGen consortium. The combined odds ratios (ORs) for the effect of smoking initiation and lifetime smoking on psoriasis were 1.46 (95% confidence interval [CI]: 1.32-1.60, $P$ = 6.24E-14) and 1.96 (95% CI: 1.41-2.73, $P$ =7.32E-05), respectively. The association between cigarettes per day and psoriasis was statistically nonsignificant in the FinnGen consortium, but was consistent in direction with the discovery stage results. The combined OR of effect of cigarettes per day on psoriasis was 1.38 (95% CI: 1.13-1.67, $P$ =0.001). In the FinnGen consortium, we additionally observed a suggestive association between smoking cessation and psoriasis. The combined OR in meta-analysis was 1.39 (95% CI: 1.07-1.79, $P$ =0.012). However, we found no significant evidence to support an increased risk of psoriasis on alcohol consumption neither in the discovery nor in the replication stage.

Sensitivity analysis results are generally consistent with the main results (Figure 3, Table S8-S9). Heterogeneity was found in most analyses. Although the MR-Egger intercept test did not provide a significant result, the MR-PRESSO global indicated the presence of pleiotropic effects of smoking, specifically in the discovery stage (using psoriasis data from Tsoi et al.) (Table S8). The leave-one-out analysis suggested the risk estimates of alcohol consumption and all smoking phenotype on psoriasis generally remained consistent after eliminating each single SNP at a time (Figures S1-S60). In addition, scatter, forest, and funnel plots were provided in Figures S1-S60.

Reverse MR suggested that the effect of psoriasis unlikely to increase alcohol consumption and smoking behavior (Table S10).

## Discussion

This is the first MR investigation to assess the associations of alcohol consumption as well as smoking with psoriasis from the genetic perspective. The genetic correlation test showed that smoking, rather than alcohol consumption, was genetically correlated with psoriasis. The MR analyses revealed a causal link between smoking, but not alcohol, and psoriasis risk. Besides, reverse MR showed that psoriasis is not associated with neither smoking nor alcohol consumption.

In contrast to our findings, Poikolainen et al. [3] found that alcohol was related to psoriasis risk among young and middle-aged men. Similar conclusions were drawn by Jankovic et al.[19]. Besides, some studies have reported that alcohol abuse is more common in patients with psoriasis, and patients with psoriasis may continue to drink.[3,6] Nevertheless, most current evidence have been obtained from cross-sectional or case-control studies, which are more susceptible to recall bias and confounders. MR offers the possibility to overcome confounders and reverse causation by utilizing genetic variants as IVs. The current study suggested that there was a null causal link between alcohol consumption and psoriasis risk. This is in line with the results of a cohort study of a Taiwanese population of 60,136 people, which found no significant link between alcohol consumption and the development of psoriasis. Besides, recent studies suggest that depression increases the risk of alcohol dependence,[20] while also increasing the risk of psoriasis through the brain-skin axis.[9] Whether psoriasis leads to increased alcohol consumption or whether other confounding factors (for example, depression) lead to increased alcohol consumption needs further investigation in future studies.

MR results showed that smoking was linked to a higher risk of psoriasis, consistent with previous observational studies. A meta-analysis of 28 studies suggested that smoking may be a risk factor for psoriasis.[7] A Korea nationwide cohort study also suggested that the risk for psoriasis increase with the amount and duration of smoking.[2] This conclusion was confirmed in another cohort study in Taiwan.[5] Our

MR study provide suggestive evidence that current smokers have higher risk of developing psoriasis compared to former smokers, which supports a previous cohort study observing a graded reduction of psoriasis risk with an increase in time since smoking cessation.[21] Such findings highlight smoking cessation programs may be helpful for reducing the adverse impact of smoking on psoriasis.

Substantial evidence shown that cigarette smoke causes systemic oxidative damage, charactered by the excessive formation of reactive oxygen species (ROS). In the pathogenesis of psoriasis, ROS may serve as second messengers triggering a variety of cellular effects parallel the findings of their role in endothelial dysfunction and atherosclerosis.[22] ROS-related cellular pathways active in psoriasis comprise mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB) and Janus kinase/signal transducers and activators of transcription (JAK-STAT).[23] These pathways are likely to converge on nitric oxide, as its expression levels were elevated in dendritic cells (DCs) in psoriatic plaques.[24] Smoking also activates innate immune cells involved in the psoriasis pathogenesis including DCs, macrophages, and keratinocytes. These cells produce a cascade of cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-23, which stimulates T lymphocytes and in turn innate cells, perpetuating a cycle of chronic inflammation.[25] In addition, an important genetic component has long been involved in the pathogenesis of psoriasis, and studies have shown that smoking alters several psoriasis-related genes expression.[26] The association was suggested by our LDSC findings, which found that there was genetic correlation between smoking and psoriasis.

Our study has several strengths. First, the use of genetic variants in the MR setting could minimize potential confounding and reverse causation. Second, the identified potential causal associations were consistent across sensitivity analyses, and were replicated in FinnGen except for the cigarettes per day. Third, we applied multiple smoking phenotypes, which capture smoking status at various stages and comprehensively reflect smoking duration and smoking heaviness. The consistency of associations between these phenotypes and psoriasis suggests the robustness of our results. In addition, we combined two psoriasis datasets with approximately 23,542 cases using a meta-analysis to strengthen the power. However, our study also has some limitations. First, there is only one alcohol consumption phenotype at our disposal, which does not adequately reflect the various stages of drinking, such as duration of drinking, amount of drinking, etc. The association between alcohol intake and psoriasis requires further investigation in future studies. Second, since our study population is all European, the generalization of this conclusion to other races requires further research. One major vulnerability of MR study is pleiotropy-induced bias, the presence of pleiotropy affects true causal estimates. In order to enhance the results of robustness, we applied a series of sensitivity analyses. And our results suggested that the estimated effects were approximately unbiased on the basis of sensitivity analyses. Considering the issue of low statistical power, we did not investigate the different types of psoriasis. Further MR studies looking into the type-specific associations would be of interest when GWAS data with larger sample sizes is available.

In summary, our study provides genetic evidence supporting the causal effects of smoking on psoriasis risk, suggesting that restricting smoking could be helpful in reducing the burden of psoriasis.

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**Figure legends**

Figure 1. Flow chart of study design. (A) The process of research analysis. (B) Graphical relationship diagrams of Mendelian randomization (MR). MR relies on 3 assumptions; the genetic variants selected as instruments must (1) associate robustly with the exposure, (2) be independent of confounders, and (3) not directly affect the outcome, except through their effect on the exposure.

Figure 2. Heat map of genetic correlation (LD score regression). Blue boxes indicate negative correlation; orange boxes positive genetic correlation. Distance on cluster dendrogramm measures the similarity between traits. Correlation values including *P* between alcohol consumption as well as smoking and psoriasis are presented in Supplementary Table S7.

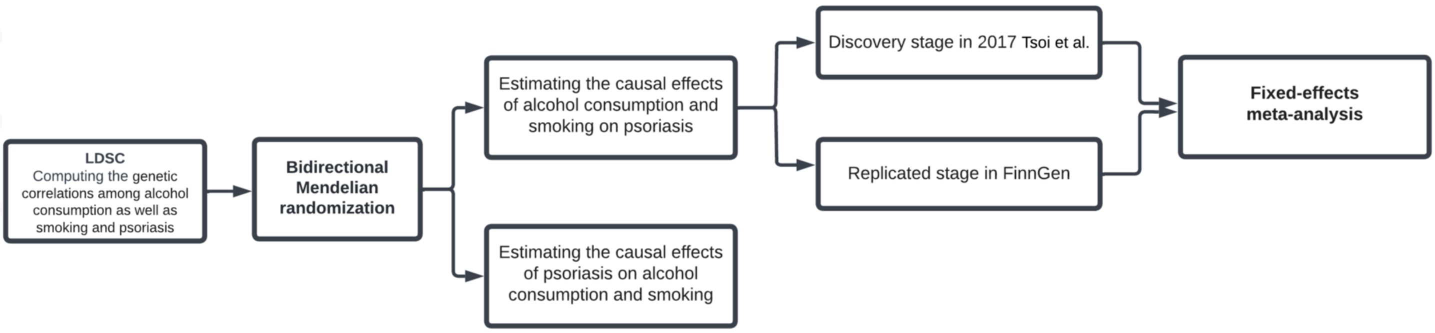
Figure 3. Forest plot of the association of alcohol consumption and smoking with psoriasis. Subtotal estimates in the discovery stage and the replication stage were combined using fixed-effects meta-analysis. CI, confidence interval; OR, odds ratio. IVW, inverse variance weighted; WM, weighted median; MR PRESSO, MR pleiotropy residual sum and outlier. To account for multiple testing, we used Bonferroni-corrected thresholds of 0.005 ($\alpha = 0.05/10$) in our MR analyses. We considered *P* below the threshold as significant evidence of associations.

Table 1 Characteristics of data in this study

| Trait | Sample size (cases) | Population | Data source (PubMed ID (PMID)) | Unit |
|---|---|---|---|---|
| Psoriasis | 305,801 (19,032) | European | PMID: 28537254 | LogOR |
| Psoriasis | 216,752 (4,510) | European | FinnGen | LogOR |
| Alcohol consumption | 941,280 | European | GSCAN | 1-SD increase in log-transformed alcoholic drinks/week |
| Smoking initiation | 1,232,091 | European | GSCAN | Ever smoked regularly compared with never smoked |
| Cigarettes per day | 337,334 | European | GSCAN | 1-SD increase in the number of cigarettes smoked per day |
| Smoking cessation | 547,219 | European | GSCAN | Contrasting current versus former smokers |
| Lifetime smoking | 462,690 | European | UK Biobank | 1-SD increase in the lifetime smoking score is equivalent to an individual smoking 20 cigarettes a day for 15 years and stopping 17 years ago or an individual smoking 60 cigarettes a day for 13 years and stopping 22 years ago. |

GSCAN, Sequencing Consortium of Alcohol and Nicotine use; logOR, log odds ratio; SD, standard deviation.

A

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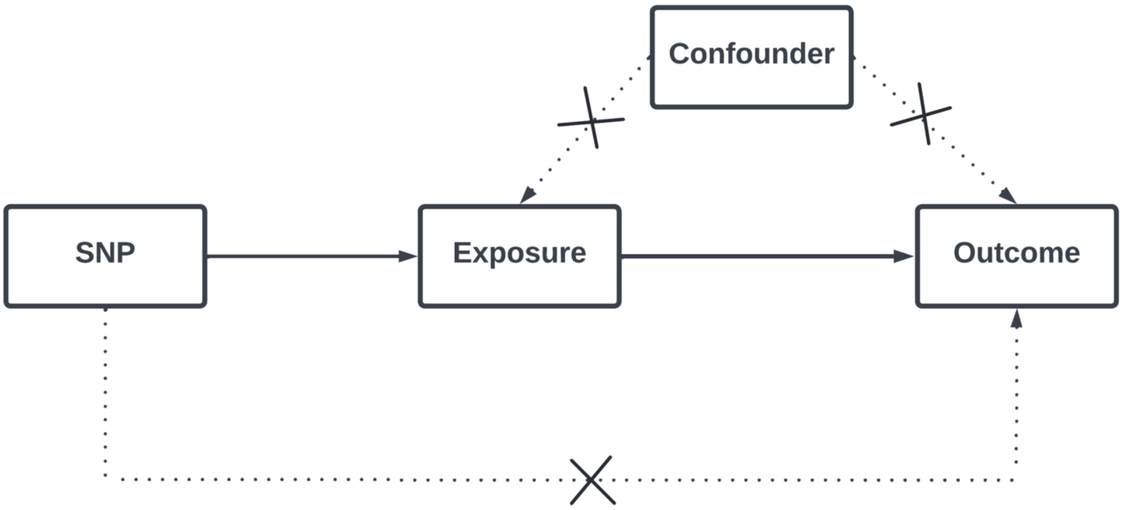


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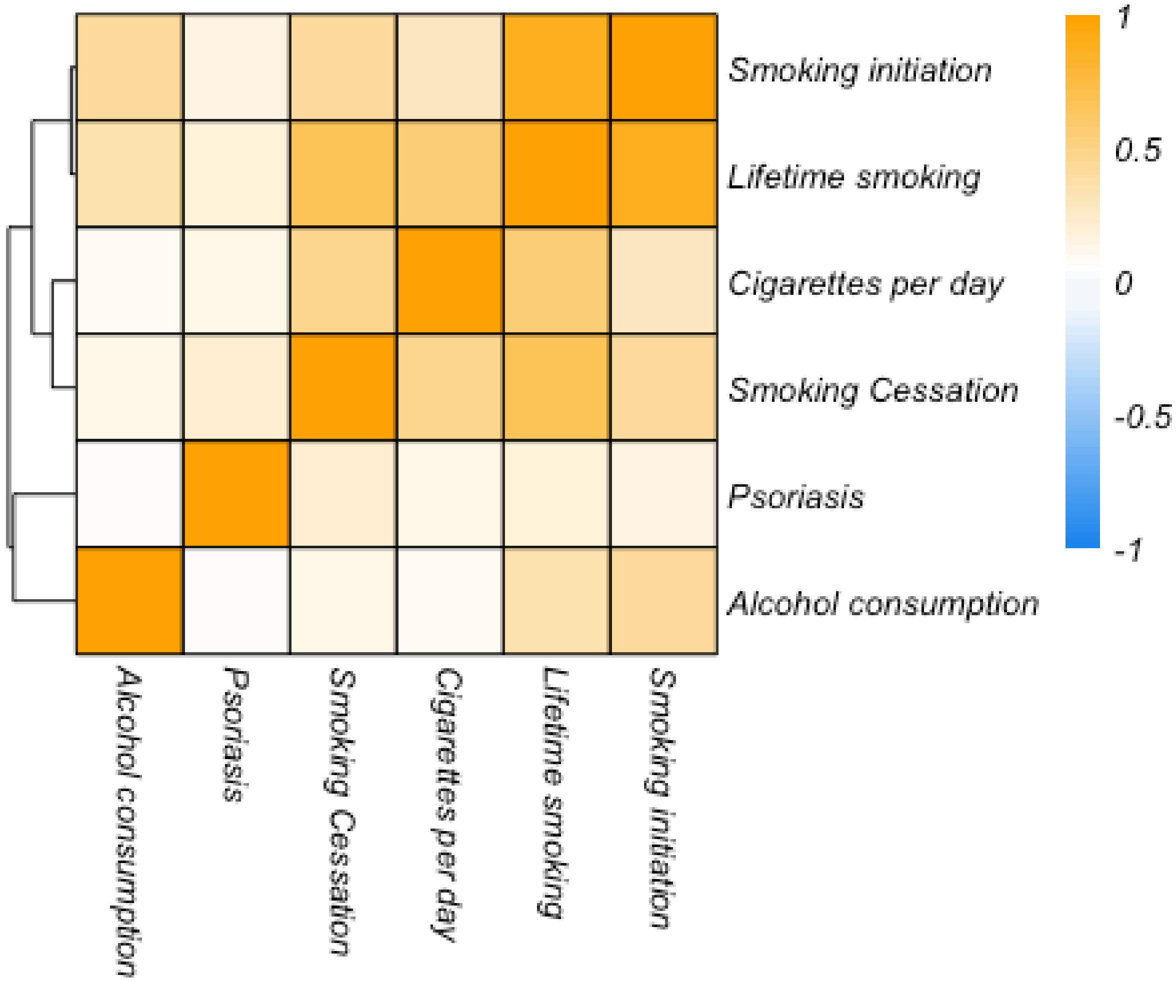


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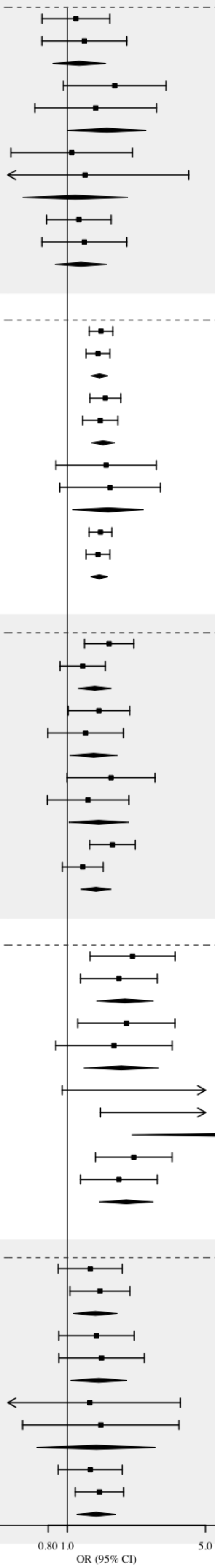
| Lifestyle factor and data source | Methods | OR (95% CI) | P-value |
|---|---|---|---|
| **Alcohol consumption** | | | |
| Psoriasis 2017 Tsoi et al. | IVW | 1.11 (0.74, 1.64) | 0.620 |
| Psoriasis FinnGen | | 1.22 (0.74, 2.00) | 0.431 |
| **Subtotal** | | **1.15 (0.84, 1.56)** | **0.379** |
| Psoriasis 2017 Tsoi et al. | WM | 1.74 (0.96, 3.16) | 0.070 |
| Psoriasis FinnGen | | 1.39 (0.69, 2.83) | 0.361 |
| **Subtotal** | | **1.60 (1.01, 2.54)** | **0.048** |
| Psoriasis 2017 Tsoi et al. | MR Egger | 1.05 (0.52, 2.14) | 0.888 |
| Psoriasis FinnGen | | 1.23 (0.37, 4.11) | 0.738 |
| **Subtotal** | | **1.12 (0.60, 2.07)** | **0.771** |
| Psoriasis 2017 Tsoi et al. | MR PRESSO | 1.14 (0.79, 1.67) | 0.485 |
| Psoriasis FinnGen | | 1.22 (0.74, 2.00) | 0.433 |
| **Subtotal** | | **1.20 (0.89, 1.62)** | **0.301** |
| **Smoking initiation** | | | |
| Psoriasis 2017 Tsoi et al. | IVW | 1.48 (1.29, 1.70) | 2.50E-08 |
| Psoriasis FinnGen | | 1.43 (1.24, 1.64) | 4.77E-07 |
| **Subtotal** | | **1.46 (1.32, 1.60)** | **6.24E-14** |
| Psoriasis 2017 Tsoi et al. | WM | 1.56 (1.30, 1.86) | 1.57E-06 |
| Psoriasis FinnGen | | 1.47 (1.19, 1.80) | 2.56E-04 |
| **Subtotal** | | **1.52 (1.32, 1.74)** | **1.73E-09** |
| Psoriasis 2017 Tsoi et al. | MR Egger | 1.57 (0.88, 2.82) | 0.131 |
| Psoriasis FinnGen | | 1.65 (0.92, 2.96) | 0.097 |
| **Subtotal** | | **1.61 (1.06, 2.43)** | **0.025** |
| Psoriasis 2017 Tsoi et al. | MR PRESSO | 1.47 (1.29, 1.68) | 2.74E-08 |
| Psoriasis FinnGen | | 1.43 (1.24, 1.64) | 7.64E-07 |
| **Subtotal** | | **1.45 (1.32, 1.60)** | **3.31E-14** |
| **Cigarettes per day** | | | |
| Psoriasis 2017 Tsoi et al. | IVW | 1.63 (1.22, 2.17) | 8.73E-04 |
| Psoriasis FinnGen | | 1.20 (0.92, 1.56) | 0.184 |
| **Subtotal** | | **1.38 (1.13, 1.67)** | **1.00E-03** |
| Psoriasis 2017 Tsoi et al. | WM | 1.44 (1.01, 2.07) | 0.044 |
| Psoriasis FinnGen | | 1.24 (0.80, 1.92) | 0.344 |
| **Subtotal** | | **1.36 (1.03, 1.79)** | **0.031** |
| Psoriasis 2017 Tsoi et al. | MR Egger | 1.66 (1.00, 2.78) | 0.057 |
| Psoriasis FinnGen | | 1.27 (0.79, 2.05) | 0.323 |
| **Subtotal** | | **1.44 (1.02, 2.04)** | **0.040** |
| Psoriasis 2017 Tsoi et al. | MR PRESSO | 1.69 (1.30, 2.21) | 3.26E-04 |
| Psoriasis FinnGen | | 1.20 (0.94, 1.52) | 0.147 |
| **Subtotal** | | **1.40 (1.17, 1.67)** | **2.38E-04** |
| **Lifetime smoking** | | | |
| Psoriasis 2017 Tsoi et al. | IVW | 2.14 (1.30, 3.51) | 3.00E-03 |
| Psoriasis FinnGen | | 1.82 (1.17, 2.85) | 9.00E-03 |
| **Subtotal** | | **1.96 (1.41, 2.73)** | **7.32E-05** |
| Psoriasis 2017 Tsoi et al. | WM | 1.99 (1.13, 3.51) | 0.017 |
| Psoriasis FinnGen | | 1.72 (0.87, 3.39) | 0.116 |
| **Subtotal** | | **1.87 (1.40, 2.73)** | **5.00E-03** |
| Psoriasis 2017 Tsoi et al. | MR Egger | 7.34 (0.94, 57.17) | 0.059 |
| Psoriasis FinnGen | | 9.48 (1.47, 61.13) | 0.020 |
| **Subtotal** | | **8.44 (2.12, 33.56)** | **2.00E-03** |
| Psoriasis 2017 Tsoi et al. | MR PRESSO | 2.17 (1.39, 3.39) | 9.18E-04 |
| Psoriasis FinnGen | | 1.82 (1.17, 2.85) | 0.010 |
| **Subtotal** | | **1.99 (1.45, 2.73)** | **2.01E-05** |
| **Smoking Cessation** | | | |
| Psoriasis 2017 Tsoi et al. | IVW | 1.31 (0.90, 1.90) | 0.160 |
| Psoriasis FinnGen | | 1.46 (1.03, 2.07) | 0.033 |
| **Subtotal** | | **1.39 (1.07, 1.79)** | **0.012** |
| Psoriasis 2017 Tsoi et al. | WM | 1.41 (0.91, 2.18) | 0.129 |
| Psoriasis FinnGen | | 1.49 (0.91, 2.45) | 0.116 |
| **Subtotal** | | **1.44 (1.04, 2.00)** | **0.030** |
| Psoriasis 2017 Tsoi et al. | MR Egger | 1.30 (0.45, 3.73) | 0.632 |
| Psoriasis FinnGen | | 1.48 (0.59, 3.67) | 0.412 |
| **Subtotal** | | **1.40 (0.70, 2.79)** | **0.341** |
| Psoriasis 2017 Tsoi et al. | MR PRESSO | 1.31 (0.90, 1.90) | 0.174 |
| Psoriasis FinnGen | | 1.45 (1.10, 1.93) | 0.017 |
| **Subtotal** | | **1.40 (1.12, 1.75)** | **3.50E-03** |




BJD_21718_Figure 3.tiff