Association between psoriasis and chronic obstructive pulmonary disease: A systematic review and meta-analysis

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Abstract
Psoriasis has been linked to an increased risk of several co-morbidities. However, its association with chronic obstructive pulmonary disease (COPD) remains unclear. To further characterize this relationship, we conducted a systematic review and meta-analysis of case-control and cross-sectional studies that compared the risk of COPD in patients with psoriasis versus non-psoriasis participants. Generic inverse variance method of DerSimonian and Laird was used to combine all the point estimates. Out of 502 potentially relevant articles, seven studies met our inclusion criteria and were included in the data analysis. The pooled odds ratio of COPD in patients with psoriasis versus control was 1.45 (95% CI, 1.21–1.73). The statistical heterogeneity was high with an I² of 91%. Therefore, our study provided evidence to support the increased risk of COPD among patients with psoriasis.

Introduction
Psoriasis is a chronic immune-mediated skin disorder characterized by well-demarcated erythematous plaques with thick, silvery scales. It is a common disease with an estimated prevalence in Europe and North America of 2% (1,2). The etiology and pathogenesis of psoriasis are not well-understood despite the extensive research effort. The most widely accepted hypothesis is related to the interplay between genetic predisposition and acquired factors such as smoking, obesity, human immunodeficiency virus infection and alcohol consumption (3,4).

Several studies have demonstrated an increased risk of developing other comorbidities among patients with psoriasis, especially metabolic syndrome and cardiovascular diseases (2,5–7). Chronic inflammation from psoriasis is believed to be the cornerstone of this association as both in vivo and in vitro studies have illustrated the deleterious effect of oxidative stress and inflammatory cytokines on endothelial function, resulting in premature atherosclerosis (8–11).

Patients with psoriasis might also have a higher risk of chronic obstructive pulmonary disease (COPD) as smoking is a strong risk factor for both diseases. Chronic inflammatory state associated with psoriasis might also have detrimental effect on the lungs, possibly resulting in alveolar epithelial cell injury and COPD (12). Nonetheless, the relationship between psoriasis and COPD is not well-studied. Therefore, to further characterize this possible association, we conducted a systematic review and meta-analysis of case-control and cross-sectional studies that compared the risk of COPD in patients with psoriasis versus non-psoriasis participants.

Method
Search strategy
Two investigators (P.U. and N.S.) independently searched published studies indexed in MEDLINE and EMBASE from inception to May 2015 using the terms for psoriasis combined with the terms for COPD. Details of our search strategy are described in supplementary data. A manual search of references of selected retrieved articles was also performed.

Inclusion criteria
The inclusion criteria were as follows: (1) case–control or cross-sectional study published as original study to evaluate the association between psoriasis and COPD; (2) odds ratios (OR) with 95% confidence intervals (CIs) or sufficient raw data to calculate the ratios were provided; (3) participants without psoriasis were used as control group.

Study eligibility was independently determined by the two investigators. Newcastle–Ottawa quality assessment scale was used to appraise the quality of the included studies (13). This scale assessed each study in three areas including: (1) the selection of the participants for each group; (2) the comparability between the study groups; and (3) the ascertainment of the exposure in each group. The two aforementioned investigators independently performed this quality appraisal and agreement between the two investigators, which was determined by kappa statistics. The senior investigator (C.T.) oversaw this literature review process and resolved any different decisions in the determination of study eligibility.

Data extraction
A standardized data collection form was used to extract the following information: first author name, study name, year of publication, year when the study was conducted, country of study,
Psoriasis and COPD: A meta-analysis

DOI: 10.3109/09546634.2015.1107180

study size, study population, method used to diagnose psoriasis and COPD, baseline demographics for each group, confounders that were adjusted and adjusted effect estimates with 95% CI. This data extraction process was independently performed by all investigators. Any data discrepancy was resolved by referring back to the original studies.

**Statistical analysis**

Review Manager 5.3 software from the Cochrane Collaboration was used for the data analysis. ORs and their corresponding 95% CIs were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird (14). In light of the high likelihood between study variance due to the different study designs and populations, random-effect model rather than a fixed-effect model was used. Statistical heterogeneity was assessed using the Cochran’s Q test and the I² statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I² of 0–25% represents insignificant heterogeneity, 25–50% low heterogeneity, 50–75% moderate heterogeneity and 75–100% high heterogeneity (15). Publication bias was assessed by using Funnel plot and Egger’s regression test.

**Results**

Our search strategy yielded 502 potentially relevant articles (433 articles from EMBASE and 69 articles from MEDLINE). After the exclusion of 61 duplicated articles, 441 articles underwent title and abstract review. Four hundred and eleven articles were excluded as they were clearly not observational studies or were not conducted in patients with psoriasis, leaving 30 articles for full-length article review. Twenty two articles were excluded after the full-length review as they reported prevalence of COPD in patients with psoriasis, but did not have a control group for comparison. Eight studies met all three inclusion criteria (16–23). However, two studies from Taiwan utilized the same database (21,23). To avoid potential patients’ duplication, we excluded the study by Yang et al. (23) as the study by Tsai et al. (21) was more comprehensive and included more patients. Therefore, seven studies with 331 347 patients with psoriasis were included to the data analysis. Figure 1 outlines our search methodology and

![Figure 1. Outline of our search methodology.](image-url)
| Country                  | Year of publication | Study design | Cases                                                                 | Controls | Ascertainment of COPD | Confounders adjusted for | Newcastle-Ottawa scale |
|-------------------------|---------------------|--------------|-----------------------------------------------------------------------|----------|-----------------------|-------------------------|------------------------|
| United States (North Carolina) | 2005                | Cross-sectional | All patients who were diagnosed with psoriasis from 1997 to 2003 from a single institute. Cases were identified from the diagnostic codes of the institute's database and were verified by medical record review. | Age and sex-specific prevalence rates of COPD from the NHIS of 1999 were applied to the age and sex distribution of the study cohort to estimate the expected number of patients with COPD | Diagnostic code of the database | None | Selection 4 stars |
| Israel                  | 2008                | Case–control  | All patients who were diagnosed with psoriasis in the Clalit Health Service system. Cases were identified from the diagnostic codes of the database. | Sex and age matched non-psoriasis subjects who were randomly selected from the same database | Self-report during the survey | None | Comparability 1 star |
| United States           | 2008                | Case–control  | Cases were identified from 40 730 subjects who participated in the Internet National Health and Wellness Survey during May and June 2004. | Sex, age, region and race matched non-psoriasis subjects who were randomly selected from the same database | Diagnostic code of the database plus medical record review | None | Exposure 2 stars |
| Kuwait                  | 2010                | Case–control  | All patients who were diagnosed with psoriasis in the study centers (Al-Fawaniya hospital and Al-Ahmadi hospital) from 2003 to 2007. Cases were identified from the diagnostic codes of the database and were verified by medical record review. | Sex, age and region matched non-psoriasis subjects who were randomly selected from the same database | Diagnostic code of the database | Multiple co-morbidities such as obesity, heart disease and skin infection | Selection 4 stars |
| Italy                   | 2010                | Case-control  | All patients who were newly diagnosed with psoriasis from 2001 to 2004. Cases were identified from the diagnostic codes of the Taiwan National Health Insurance database which comprised data from computer-based records from over 900 primary care physicians throughout Taiwan. | Sex, age and practice matched non-psoriasis subjects who were randomly selected from the same database | Diagnostic code of the database | Age, sex, residential area and co-morbidities | Selection 3 stars |
| Taiwan                  | 2011                | Case-control  | All patients who were diagnosed with psoriasis in 2006. Cases were identified from the diagnostic codes of The Health Improvement Network which comprised data from computer-based records from over 415 primary care physicians throughout the United Kingdom. | Sex, age and region matched non-psoriasis subjects who were randomly selected from the same database | Diagnostic code of the database | Age, sex and years of follow-up | Selection 4 stars |
| United Kingdom          | 2013                | Cross-sectional | All patients who were diagnosed with psoriasis in The Health Improvement Network which comprised data from computer-based records from over 415 primary care physicians throughout the United Kingdom. | Sex, age and practice matched non-psoriasis subjects who were randomly selected from the same database | Diagnostic code of the database | | Selection 4 stars |

COPD indicates chronic obstructive pulmonary disease; N.A.: not available.
literature review process. The detailed characteristics and Newcastle–Ottawa scale of the included studies are described in Table 1. The quality of the included studies was high as reflected by the high Newcastle–Ottawa scores except for the study by Wu et al. (18) that used self-reported diagnosis from internet survey which raised concerns over representativeness and diagnostic validity. It should be noted that the inter-rater agreement for the quality appraisal was high with the kappa statistics of 0.57.

Increased risk of COPD was consistently seen in all studies even though the ORs varied considerably from 1.08 to 2.99. The pooled odds ratio of COPD in patients with psoriasis versus control was 1.45 (95% CI, 1.21–1.73). The statistical heterogeneity was high with an $I^2$ of 91%. Forest plot of this meta-analysis is demonstrated in Figure 2.

**Sensitivity analysis**

To confirm the robustness of our results, we conducted several sensitivity analyses. First, we excluded the study by Wu et al. (18) as this study was performed using internet-based survey which raised a significant concern over the validity of the diagnosis for both psoriasis and COPD. In fact, the concern of this study’s quality was reflected in its low Newcastle–Ottawa score. This sensitivity analysis only slightly decreased the pooled OR to 1.43 (95% CI, 1.19–1.72).

Second, we replaced Tsai’s study (21) with the study that was originally excluded due to the concern over patients’ duplication (23). The new pooled OR was slightly lower but remained statistically significantly elevated (OR 1.39; 95% CI, 1.17–1.65).

Third, we did another sensitivity analysis to include only studies with case–control design (17–22). Again, this sensitivity analysis did not significantly altered the result (OR 1.37; 95% CI, 1.26–1.49) but dramatically decreased $I^2$ to 27%. Figure 3 demonstrates the forest plot of this sensitivity analysis.

**Publication bias**

Funnel plot to evaluate publication bias is demonstrated in Figure 4. The graph is fairly asymmetric and, therefore, provides a suggestive evidence for publication bias in favor of positive studies. Furthermore, there was an evidence of publication bias detected by Egger’s regression test ($p=0.038$).

**Discussion**

Psoriasis has long been linked to multiple co-morbidities. Our meta-analysis has demonstrated a significant association between psoriasis and COPD, an under-recognized co-morbidity, with an overall 1.45-folds (95% CI, 1.21–1.73) increased risk.

Why patients with psoriasis have a higher risk of COPD are unclear. There are few possible explanations.

First, this association might be non-causal and merely the result of the shared risk factors, especially smoking. The role of smoking as a risk factor for psoriasis is well-documented (3). Moreover, a recent study has suggested that the severity of psoriasis is also associated with the cumulative amount and duration of cigarette use (24).

Second, it has been well-documented that not all smokers develop COPD (25,26) and inflammation in the airway of patients with COPD persists long after they stop smoking (27). This observation suggests a self-perpetuating pathogenic process similar to autoimmune disorders (26) and might imply that COPD is maybe an autoimmune phenomenon induced by cigarette smoking.

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![Figure 2. Forest plot of the included studies.](image_url)

![Figure 3. Forest plot of subgroup analysis of case–control studies.](image_url)
How smoking could trigger an autoimmune response is not well-characterized. One hypothesis is related to the capability of smoking to generate new epitopes by either directly oxidizing existing proteins or indirectly interrupting the clearance process of apoptotic cells and, thus, exposing the sequestered intracellular auto-antigen to the immune system (26,28,29). Moreover, it has also been demonstrated that smoking could up-regulate the population of antigen presenting cells in the lungs and, therefore, amplifying the capability to process new antigens (28,29).

In light of this possible autoimmune-related pathogenesis, it could be hypothesized that psoriasis-related immune dysfunction could also predispose to abnormal inflammatory responses in the respiratory system, leading to a higher likelihood of COPD.

Third, it is well-known that chronic inflammation has several detrimental effects on vascular endothelial cells (30–34). Therefore, it is possible that chronic inflammation from psoriasis might have a similar deleterious effect on alveolar epithelial cell, leading to alveolar wall destruction and may contribute to COPD.

The major strength of this study is the study design of systemic review and meta-analysis that are able to combine all existing data. Our results were also robust as tested by sensitivity analyses.

Nevertheless, we acknowledge that there are some limitations and, thus, the results should be interpreted with caution.

First, most of the included studies were conducted using medical registry-based database. This raises a concern of coding misclassification for both psoriasis and COPD. Second, the statistical heterogeneity was high in the complete analysis. We suspect that difference in study design was, in part, responsible for this high I² as subgroup analysis of case–control studies had a considerably lower heterogeneity. Furthermore, the result of this subgroup analysis was not significantly different from the complete analysis, suggesting that the results of this meta-analysis were robust. Third, publication bias in favor of positive results might be present in this meta-analysis. Moreover, we could not exclude the possibility of detection bias as these patients, because of their psoriasis, might have been exposed to medical examinations and laboratory investigations more often than general population, leading to a higher likelihood of COPD detection.

In conclusion, our meta-analysis demonstrated a significant association between psoriasis and COPD. Whether a routine screening for COPD should be a part of standard care for patients with psoriasis is yet unclear. Further studies are required to clarify how this COPD risk should be addressed.

Declaration of interest
The authors report no conflict of interest.

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Psoriasis and COPD: A meta-analysis

DOI: 10.3109/09546634.2015.1107180

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Supplementary material available online
Supplementary data