Association between psoriasis and asthma risk: A meta-analysis

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ABSTRACT

Background: Psoriasis has been shown to be related to an increased risk of asthma, although the results remain inconclusive. Therefore, we performed a meta-analysis to determine whether psoriasis increases the risk of asthma.

Methods: A comprehensive search of medical literature data bases was conducted through May 2017. The pooled odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated.

Results: A total of six studies with 66,772 psoriasis cases and 577,415 controls were included. Our meta-analysis showed that psoriasis was significantly associated with the increased risk of asthma (OR 1.32 [95% CI, 1.20–1.46]). The older age patients with psoriasis (≥ 50 years) (OR 1.64 [95% CI, 1.44–1.88]) had a higher risk of asthma susceptibility compared with the younger patients (20–49 years old) (OR 1.25 [95% CI 1.09–1.44]). Subgroup analysis by ethnicity indicated a significant increase in asthma risk in both Asian populations (OR 1.35 [95% CI, 1.18–1.54]) and white populations (OR 1.27 [95% CI, 1.05–1.54]) with psoriasis compared with those without psoriasis.

Conclusion: Results of this meta-analysis indicated that the patients with psoriasis had a higher risk of asthma susceptibility, especially among the older patients with psoriasis.

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Asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness, airway inflammation, reversible airflow obstruction, and airway wall remodeling.¹ It is estimated that >300 million people worldwide have asthma, and this disease has caused a significant economic burden.^{2,3} The worldwide prevalence of asthma has increased in recent years.^{2,4} The complex causes of asthma likely depend on the interaction of environmental, immunologic, and genetic factors.^{5,6} Two studies found that asthma is associated with allergic rhinitis, gastrointestinal symptoms, obesity, and psoriasis.^{7,8}

Psoriasis is a chronic, immune-mediated inflammatory disease of the skin and/or joints,⁹ and its prevalence varies in different populations.¹⁰ The interaction between genetics and immunity has been shown to be involved in the pathogenesis of psoriasis.^{9,11,12} Research into the immunopathogenesis of psoriasis has focused on the central roles of T-helper (Th) type 1 cells and the interleukin (IL) 23/Th17 axis.^{9,12} Recently, psoriasis

has been found to be associated with numerous diseases, including metabolic syndrome, autoimmune disorders, cardiovascular diseases, chronic obstructive pulmonary disease, allergic rhinitis, obesity, and asthma.¹³ However, it is still controversial whether psoriasis can be considered as an independent risk factor for these diseases.^{14,15}

According to the previous studies, asthma and psoriasis may share some common pathomechanisms. It is now thought that asthma may not solely be controlled by the Th2 subset; there are a variety of T cells and cytokines involved in the pathogenesis of asthma, including Th1 cells and the IL-23/Th17 axis.^{16–18} Furthermore, epidemiologic research has shown that there are some associations between psoriasis and asthma,^{8,13,19–22} and Fang *et al.*⁸ indicated that patients with psoriasis have an increased risk of developing asthma. When considering that the conclusion of a single study could be unreliable, we performed this meta-analysis, which included all eligible studies to clarify and quantify the association between psoriasis and asthma risk.

METHODS

Data Sources and Search Strategy

To obtain relevant studies that examined the risk of asthma susceptibility in patients with psoriasis, two independent reviewers (WS, XY) searched PubMed, EMBASE (Elsevier, Amsterdam, Netherlands), Google Scholar (Google Inc., California, USA), China Knowledge Resource Integrated Database (Chinese National

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Knowledge Infrastructure, Beijing, P.R. China), and Wanfang data bases (Wanfang Data, Beijing, P.R. China) by using the search terms asthma and psoriasis. Articles published up to May 2017 were included in this study, and, to minimize any potential bias, there were no limits on language, population, sample size, or date of publication. We also obtained additional studies from the reference lists of relevant reviews and original articles.

Selection Criteria

The selection criteria for inclusive in this meta-analysis were that studies had to meet all the following terms: (1) cohort, case-control, or cross-sectional design; (2) had analyzed the prevalence or incidence of asthma in patients with psoriasis; (3) inclusion of a reference group; and (4) the odds ratios (OR) and their 95% confidence intervals (CI) were provided. The exclusion criteria of studies were the following: (1) basic publications, cell or animal models; (2) insufficient data; (3) duplicated report; (4) reviews, comments, abstracts, case report.

Data Extraction

Two independent reviewers (RK, QW) extracted the following information from eligible studies: first author, study design, ethnicity, diagnostic criteria of asthma and psoriasis, number of psoriasis cases and controls, number of asthma cases, number of patients who received systemic therapy for asthma or psoriasis, gender, and mean age of patients with psoriasis and controls. Disagreement was resolved by discussion.

Quality Assessment

The quality of eligible studies was assessed by using the Newcastle-Ottawa Scale^{23,24} by two reviewers (XY, QZ) independently. In our meta-analysis, the following items were assessed: selection, comparability, and outcome for both cohort studies and cross-sectional studies. According to the Newcastle-Ottawa Scale, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars can be given for Comparability.²³ Discrepancy was resolved by discussion before reaching a consensus. The number of stars ranged from 0 to 9 (≥ 7 , high quality; 4–6, medium quality; < 4 , low quality). Studies with medium-high quality were included in our analysis.

Statistical Analysis

The data in our study were analyzed by using the Cochrane Collaboration software Review Manager 5.3.5 (The Cochrane Collaboration, 2014; The Nordic Cochrane Centre, Copenhagen, Denmark). The summary ORs and 95% CIs were used to analyze the risk of

asthma susceptibility in patients with psoriasis. A statistical test was performed based on the Cochrane Q-test and the I^2 index to assess the heterogeneity among the eligible studies. A Dersimonian and Laird random-effects model was selected to pool the data if a significant heterogeneity was observed among the studies ($I^2 > 50\%$; or $p < 0.1$). Otherwise, a Mantel-Haenszel fixed-effect model was adopted to pool the data. Subgroup analysis was performed by ethnicity and study design to investigate the effect of possible clinical and methodologic heterogeneity. Sensitivity analysis was performed by sequentially omitting an individual study to evaluate the influence of each study on the global effect. Potential publication bias was assessed through visual inspection of funnel plots.

RESULTS

Literature Search and Study Characteristics

A total of 549 articles were identified after removing duplications. After reading the titles and abstracts, 532 articles were excluded. The remaining 17 articles were retrieved for further evaluation: 5 articles were excluded because they were reviews, comments, or case reports; 2 articles were not relevant to the risk of asthma susceptibility in patients with psoriasis; and 3 articles failed to extract sufficient data; therefore, seven articles (six studies) were included in this meta-analysis.^{8,13,19–22,25} The details of the selected studies are listed in Table 1, with a total 66,772 psoriasis cases and 577,415 controls to investigate the risk of susceptibility asthma in patients with psoriasis. There were three retrospective cohort studies^{8,13,19} and three cross-sectional cohort studies.^{20–22,25}

As for ethnicity, three studies investigated white populations,^{19,20,22,25} three studies investigated Asian populations.^{8,13,21} All the studies included patients of all ages, and two studies provided detailed incidences of asthma at different ages.^{8,20,25} Two studies provided the incidence of asthma in the mild psoriasis group and the moderate-to-severe psoriasis group.^{8,13} The Newcastle-Ottawa Scale scores of all eligible studies are shown in Table 2. Three studies were deemed to be high quality (7–9 stars),^{8,13,21} whereas the other three studies were deemed to be of medium quality (4–6 stars).^{19,20,22,25}

Main Results of the Meta-Analysis

Because of the substantial heterogeneity among all the eligible studies ($I^2 = 52\%$; $p < 0.1$) (Fig 1), a random-effects model was selected to pool the data. The main results of this meta-analysis indicated that the asthma risk was higher in the cohort with psoriasis than in the general population (OR 1.32 [95% CI, 1.20–1.46]; $p < 0.00001$) (Fig. 1). In addition, the older age patients with psoriasis (≥ 50 years) (OR 1.64 [95% CI,

Table 1 Characteristics of included studies

Study, y	Study Design	Ethnicity	Diagnostic Criteria, Psoriasis/Asthma	Cases, No. with Asthma/Total No.	Controls, No. with Asthma/Total No.	Males, Case/Control, %	Included age range, Patient Ages, mean $\pm$ SD, y	Included age range, Age of Controls, mean $\pm$ SD, y	Patients Who Received Systemic Therapy, Psoriasis/Asthma
Augustin <i>et al.</i> , ¹⁹ 2015	Retrospective cohort study	White	ICD-10 code L40/ICD-10 (detailed code has not been provided)	160/1313	27,319/291,868	NR	<18, NR	<18, NR	NR
Fang <i>et al.</i> , ⁸ 2015	Retrospective cohort study	Asian	ICD-9-CM codes 696.0, 696.1, 696.8/ICD-9-CM code 493	420/10288	1153/41,152	52.7/52.7	≥ 20 , 43.5 $\pm$ 17.0	≥ 20 , 43.2 $\pm$ 17.1	Patients with moderate-to-severe psoriasis received systemic therapy (<i>e.g.</i> , phototherapy, or immunomodulator drugs); mild psoriasis without treatment codes for systemic or biological treatment, or phototherapy/NR
Hajdarbegovic <i>et al.</i> , ²² 2013	Cross-sectional cohort study	White	Diagnosed by a certified rheumatologist or dermatologists/self report	19/301	14/147	(60/53)*/44	All ages, 49 $\pm$ 15.5/52 $\pm$ 12.0*	All ages, 54 $\pm$ 15.6	NR
Lonnberg <i>et al.</i> , ²⁵ 2013; Lonnberg <i>et al.</i> , ²⁰ 2015	Cross-sectional cohort study	White	Self report/self report	151/1385	2714/31,993	NR	≥ 20 , matched with the patient group in terms of age (20–49 y, 50–71 y)	≥ 20 , matched with the patient group in terms of age (20–49, 50–71 y)	NR
Tsai <i>et al.</i> , ¹³ 2011	Retrospective cohort study	Asian	ICD-9-CM codes 696.0, 696.1/ICD-9-CM codes 493.0, 493.1, 493.9	861/51,800	2793/207,200	60/60 in mild sample, 69.1/69.1 in moderate-to-severe sample	All ages, 46.2 $\pm$ 19.1 in mild sample, 47.5 $\pm$ 16.4 in moderate-to-severe sample	All ages, 46.1 $\pm$ 19.1 in mild sample, 47.5 $\pm$ 16.7 in moderate-to-severe sample	Patients with moderate-to-severe psoriasis had received any systemic therapy or phototherapy; mild psoriasis had not/NR
Yang <i>et al.</i> , ²¹ 2011	Cross-sectional cohort study	Asian	ICD-9-CM code 696.1 or 696.0/ICD-9-CM (detailed code has not been provided)	102/1685	227/5055	67.4/67.4	≥ 18 , matched with the patient group in terms of age (<30, 30–39, 40–49, 50–59, >59 y)	≥ 18 , matched with the patient group in terms of age (<30, 30–39, 40–49, 50–59, >59 y)	NR

SD = Standard deviation; ICD-10 = The International Classification of Diseases, Tenth Revision; NR = not reported; ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification.

*Psoriasis vulgaris/psoriatic arthritis.

Table 2 Newcastle-Ottawa Scale Quality Assessment

Study, y	Selection	Comparability	Outcome	Overall Star Rating
Augustin <i>et al.</i> , ¹⁹ 2015	+++		++	5
Fang <i>et al.</i> , ⁸ 2015	++++	++	+++	9
Hajdarbegovic <i>et al.</i> , ²² 2013	+++	++	+	6
Lonnberg <i>et al.</i> , ²⁰ 2015	+++		+	4
Tsai <i>et al.</i> , ¹³ 2011	++++	++	+++	9
Yang <i>et al.</i> , ²¹ 2011	+++	++	++	7

+ = One star.

Figure 1. A meta-analysis of the prevalence of asthma in patients with psoriasis compared with controls. “Events” means the number of asthma patients. The odds ratios (OR) for asthma in subjects with psoriasis compared with subjects without psoriasis. Horizontal lines indicate 95% confidence intervals (CI). The pooled OR was analyzed by using a random-effects model.

1.44–1.88]; $p < 0.00001$) had a higher asthma risk compared with the younger age patients (20–49 years) (OR 1.25 [95% CI, 1.09–1.44]; $p = 0.002$) (the p value for subgroups²⁶ < 0.05) (Fig. 2). Subgroup analysis by ethnicity showed a significant increase in asthma risk in both Asian populations (OR 1.35 [95% CI, 1.18–1.54]) and white populations (OR 1.27 [95% CI, 1.05–1.54]) with psoriasis compared with those without psoriasis (Supplemental Fig. S1). The association between psoriasis and asthma risk was strong in patients with either moderate-severe psoriasis (OR 1.36 [95% CI, 1.03–1.80]) or mild psoriasis (OR 1.34 [95% CI, 1.14–1.57]) compared with those without psoriasis (Supplemental Fig. S2).

Test of Heterogeneity, Sensitivity Analysis, Publication Bias

There was a substantial heterogeneity among selected studies ($I^2 = 52\%$; $p < 0.1$) (Fig 1). Subgroup

analysis based on the design of selected studies failed to reveal the possible methodologic heterogeneity (retrospective cohort study: $I^2 = 69\%$, $p < 0.1$; cross-sectional cohort study: $I^2 = 49\%$, $p > 0.1$) (Fig. 1). Ethnicity subgroup analysis also failed to find the potential clinical heterogeneity (Asian: $I^2 = 69\%$, $p < 0.1$; white: $I^2 = 49\%$, $p > 0.1$) (Supplemental Fig. S1). We then performed a sensitivity analysis as described, and no significant alterations were found, which indicated that our results were statistically stable (data not shown). A funnel plot was used to evaluate publication bias, and no significant asymmetry was detected (Fig. 3).

DISCUSSION

Our results indicated that there was a significant association between psoriasis and asthma, patients with psoriasis had an increased risk for asthma sus-

Figure 2. A meta-analysis of the prevalence of asthma in younger and older patients with psoriasis compared with controls. “Events” means the number of asthma patients. The odds ratios (OR) for asthma in subjects with psoriasis compared with subjects without psoriasis. Horizontal lines indicate 95% confidence intervals (CI). The pooled OR was analyzed by using a random-effects model.

Figure 3. A funnel plot for publication bias on selected studies.

ceptibility, and the risk was higher in older patients with psoriasis than in younger patients. Psoriasis is a chronic, genetic, immune-mediated inflammatory disease of the skin and/or joints.^{11,27} Recent studies indicate that tumor necrosis factor (TNF) α , Th1 cells, and the IL-23/Th17 axis play dominant roles in the initiation and maintenance of psoriasis.^{9,12,27}

There is evidence that psoriasis may be associated with asthma risk.^{8,21,28} A longitudinal study by Fang *et al.*⁸ indicated that a psoriasis population has an increased risk of developing asthma. Asthma is a

chronic inflammatory disorder of the airway that is caused by multiple factors that involve environmental, genetic, and immunologic factors.^{5,6} It is now thought that asthma may not solely be controlled by the Th2 subset but that a variety of T cells and cytokines are involved in the pathogenesis of asthma.^{16,17} Th2 cells have been shown to play a critical role in the pathogenesis of eosinophilic asthma by producing IL-4, IL-5, and IL-13 cytokines; whereas Th1 cells, especially Th17 cells, are mainly involved in the pathogenesis of neutrophilic asthma,

and the differentiation and activation of Th17 cells require the presence of cytokines, including IL-1 β , IL-6, transforming growth factor β and IL-23.²⁹

In addition, Nakajima and Hirose³⁰ also reported that the IL-23/Th17 axis and TNF- α are involved in both antigen-induced neutrophil recruitment into the airways and the enhancement of Th2 cell-mediated eosinophil recruitment into the airways. Th17 cells have also been demonstrated to mediate steroid resistant in asthma,³¹ and biologic immunotherapy that limits the progression of the Th1 and Th17 inflammatory immune responses by targeting IL-12 and IL-23 has been reported to be effective in both psoriasis and asthma.³² Further studies indicate that genetic risk loci might be partially overlapped between asthma and psoriasis.^{11,28,33} Interestingly, studies also found that psoriasis is associated with an increased risk of migraine and chronic obstructive pulmonary disease.^{34,35} TNF- α has been shown to promote the pathogenesis of migraine by sensitization of meningeal nociceptors and peripheral nerve endings through activation of the p38 mitogen-activated protein kinases pathway,³⁶ and elevation of TNF- α , interferon γ , and IL-23 in patients with psoriasis could lead to an increased risk of chronic obstructive pulmonary disease by causing pulmonary inflammatory responses.^{37,38}

In our study, we confirmed the association between asthma and psoriasis through meta-analysis, and provided a stable conclusion that patients with psoriasis had an increased risk of asthma susceptibility in both Asian and white populations. Our results further indicated that older patients with psoriasis had a higher increased risk of asthma susceptibility than the younger patients. Notably, Lonnberg *et al.*²⁰ showed that there was no difference between twins with psoriasis and those without psoriasis on the asthma susceptibility due to familial risk factors, which indicated that family history risks are more important in the development of asthma; this may hide or dilute the genetic risk factors.²⁰

There are several weaknesses in this meta-analysis. First, there was heterogeneity among the studies, which may have affected the interpretation of the results. After subgroup analysis based on the design of selected studies or ethnicity, we were still unable to find the possible sources of clinical heterogeneity and methodologic heterogeneity. Interestingly, the sensitivity analysis indicated that the study by Fang *et al.*⁸ study and the study by Hajdarbegovic *et al.*²² might be the main source of heterogeneity (data not shown). Second, only two studies investigated the risk of asthma susceptibility in patients with psoriasis at different ages^{8,20} and stages,^{8,13} and two studies were not powerful enough to perform further analysis.

Third, only published data were retrieved, publication bias may still exist in this meta-analysis, although

no significant asymmetry was identified in the funnel plots. Fourth, Lonnberg *et al.*²⁰ reported that adjusting for atopic dermatitis significantly changed the OR between psoriasis and asthma. However, we could not provide a further analysis due to insufficient information of the enrolled studies; more studies are needed to confirm this result.²⁰ Fifth, both asthma and psoriasis are complex diseases that may be misdiagnosed, and the diagnostic criteria of asthma or psoriasis is not exactly coherent in selected studies. When considering these limitations, the results of this meta-analysis should be interpreted carefully.

CONCLUSION

The current meta-analysis indicated that patients with psoriasis had an increased risk of asthma susceptibility, the risk was higher in older patients with psoriasis than in younger patients. When considering that the specific mechanisms of the association between asthma and psoriasis were not entirely clear, and, based on our results, we suggest that all the patients with psoriasis should be screened for asthma if they experiencing any respiratory symptoms.

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