

These articles have been accepted for publication in the *British Journal of Dermatology* and are currently being edited and typeset. Readers should note that articles published below have been fully refereed, but have not been through the copy-editing and proof correction process. Wiley-Blackwell and the British Association of Dermatologists cannot be held responsible for errors or consequences arising from the use of information contained in these articles; nor do the views and opinions expressed necessarily reflect those of Wiley-Blackwell or the British Association of Dermatologists

This article is protected by copyright. All rights reserved.

Received Date: 17-Jul-2014

Revised Date: 23-Sep-2014

Accepted Date: 24-Oct-2014

Article type: Epidemiology and health services research

Association Between Psoriasis and Asthma: A Population-Based Retrospective Cohort Analysis

Running title: Psoriasis Increases Risk of Asthma

H.-Y. Fang^{a,1}, W.-C. Liao^{b,c,1}, C.-L. Lin^{d,e}, C.-H. Chen^{b,c,*}, C.-H. Kao^{c,f,*}

^aDepartment of Dermatology, China Medical University Hospital, Taichung, Taiwan

^bDivision of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

^cGraduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

This article is protected by copyright. All rights reserved.

^dManagement Office for Health Data, China Medical University Hospital, Taichung, Taiwan

^eCollege of Medicine, China Medical University, Taichung, Taiwan

^fDepartment of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

¹Contributed equally to this article.

***Corresponding authors:**

Chia-Hung Kao, MD, Professor, Graduate Institute of Clinical Medical Science and School of

Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447,

Taiwan. Tel.: +886 4 22052121x7412; fax: +886 4 22336174

E-mail address: d10040@mail.cmuh.org.tw

Chia-Hung Chen, MD, Division of Pulmonary and Critical Care Medicine, Department of Internal

Medicine, China Medical University Hospital, Taichung, Taiwan. Tel.: +886 4 22052121x3485; fax:

+886 4 22038883

E-mail address: hsnu758@gmail.com

This article is protected by copyright. All rights reserved.

Author Contributions:

Conception/Design: Hsin-Yu Fang, Wei-Chih Liao, Chia-Hung Chen, Chia-Hung Kao

Provision of study materials: Chia-Hung Kao

Collection and/or assembly of data: Cheng-Li Lin

Data analysis and interpretation: Hsin-Yu Fang, Wei-Chih Liao, Chia-Hung Chen, Chia-Hung Kao

Manuscript writing: All authors

Final approval of manuscript: All authors

Acknowledgments:

The study was supported in part by the study projects (DMR-103-018 and DMR-103-020) in China Medical University Hospital and Taiwan, Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW103-TDU-B-212-113002), Health and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW103-TD-B-111-03, Taiwan). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

This article is protected by copyright. All rights reserved.

Conflicts of interest:

The authors have no actual or potential conflicts of interest.

Abstract

Background: Both of psoriasis and asthma are chronic immune-mediated inflammatory diseases. We evaluate the risk of asthma development in patients with psoriasis compared with controls.

Methods: This cohort study was conducted using data from the Taiwan National Health Insurance Research Database (NHIRD). Patients with psoriasis (n = 10 288) and matched comparison patients without psoriasis (n = 41 152) were evaluated. A Cox proportional hazard regression analysis was used to determine the risk of asthma in patients with and without psoriasis.

Results: The risk of asthma was 1.38-fold higher (95% confidence interval (CI) = 1.23–1.54) in the psoriasis cohort than in the reference cohort, after adjusting for age, sex, and comorbidities. The incidence of asthma in male and female patients with psoriasis exhibited nonsignificant differences.

This article is protected by copyright. All rights reserved.

Among all patients aged > 50 years, psoriasis was associated with higher risk of asthma compared without psoriasis (adjusted hazard ratio (HR), 1.49 (95% CI = 1.18–1.88) in patients aged 50–64 years; adjusted HR, 1.63 (95% CI = 1.34–1.99) in patients aged > 65 years).

Conclusion: Our study results indicate that patients with psoriasis are associated with increased risk of asthma development.

Keywords: psoriasis, asthma, National Health Insurance Research Database (NHIRD), cohort study.

What's already known about this topic?

1. Both of psoriasis and asthma are chronic immune-mediated inflammatory diseases.
2. Studies have shown that psoriasis is associated with systemic comorbidities.
3. Recent studies have defined psoriasis as a systemic chronic inflammatory disease.

What does this study add?

1. The risk of asthma was 1.38-fold higher in the psoriasis cohort than in the reference cohort, after adjusting for age, sex, and comorbidities.
2. The incidence of asthma in male and female patients with psoriasis exhibited nonsignificant differences.
3. Among all patients aged > 50 years, patients with psoriasis were more likely to have higher risk of asthma compared without psoriasis.

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease characterized by keratinocyte abnormalities and immune dysfunction. Psoriasis typically presents as erythematous scaly papules and plaques. The prevalence of psoriasis varies in different populations and is higher in men than in women.^{1,2} Studies have shown that psoriasis is associated with systemic comorbidities,^{3,4} including cardiovascular events, chronic kidney disease (CKD), ischemic stroke, and metabolic syndrome.⁵⁻⁸ Recent studies have defined psoriasis as a systemic chronic inflammatory disease, characterized by dysregulation of the T-cell response and proinflammatory cytokines.

This article is protected by copyright. All rights reserved.

Asthma is a chronic inflammatory disease of the airways. The most common characteristics of asthma are airway hyperresponsiveness, and variable airflow obstruction and reversibility, associated with intense persistent airway inflammation and structural remodeling.⁹ The incidence rate of asthma ranges from 1 to 5 cases per 1000 person-years, with a higher incidence range in women than in men.¹⁰ Numerous asthma patients also suffer from chronic conditions such as hypertension, ischemic heart disease, diabetes, gastroesophageal reflux disease (GERD), and osteoarthritis.¹¹ The causes of asthma are multifactorial and include environmental, immunological, and host genetic factors. Several types of inflammation can occur in the lungs and many of the cytokines and chemokines produced are related to asthma.¹²

According to Chiang and Lin (2012), psoriasis is significantly associated with chronic obstructive pulmonary disease (COPD).¹³ Therefore, we hypothesized that psoriasis might increase the risk of asthma development. In this study, we investigated the risk of asthma development in psoriasis patients by using claims data from the National Health Insurance Research Database (NHIRD) of Taiwan. We also evaluated the effects of age, sex, coexisting cardiovascular risk factors, rhinitis, and sinusitis on asthma development in psoriasis patients.

This article is protected by copyright. All rights reserved.

Methods

Data source

Taiwan's National Health Insurance (NHI) program was established in 1995. It has enrolled up to 99% of the Taiwan population and contracted with 97% of the medical providers since 1998.¹⁴ The National Health Insurance Research Database (NHIRD) stores the NHI program reimbursement claims data, includes data on outpatient visits, hospital admissions, prescriptions, disease status for all insurants, and is maintained and updated by the National Health Research Institute. All personal information in the NHIRD is anonymized before release for administrative use and research, in the interest of patient privacy. This study was conducted using the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD. The LHID contains annual historical claims data on 1 000 000 randomly sampled beneficiaries enrolled in the NHI program in 2010, including all records on these beneficiaries from 1996 to 2010. There were no significant differences in the distribution of gender, age, or health costs between the LHID and all insurance enrollees. In this study, disease diagnoses were defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes in outpatient and inpatient data.

This article is protected by copyright. All rights reserved.

Ethical Considerations

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claim information, including patients' sex, dates of birth, medical services utilized, and prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012). Our IRB specifically waived the consent requirement.

Study sample

Patients aged ≥ 20 years with newly diagnosed psoriasis (ICD-9-CM Codes 696, 696.0, 696.1, and 696.8) were included in the psoriasis cohort, and the date of diagnosis of psoriasis was defined as the index date. For each psoriasis patient, 4 reference patients without a diagnosis of psoriasis were selected as the nonpsoriasis comparison cohort, frequency matched according to sex, age (within 5 years), and index year. In both cohorts, patients with asthma (ICD-9-CM Code 493) who were diagnosed prior to the index date were excluded. The baseline comorbidity history was determined for each patient, including coronary artery disease (CAD) (ICD-9-CM Codes 410–414), hypertension

This article is protected by copyright. All rights reserved.

(ICD-9-CM Code 401–405), rhinitis (ICD-9-CM Codes 477 and 472.0), chronic sinusitis (ICD-9-CM Code 473), GERD (ICD-9-CM Codes 530.11 and 530.81), psychological disorder, including depression and anxiety (ICD-9-CM Codes 300.0 and 311), atopic dermatitis (ICD-9-CM Codes 691) and chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 496). Severe psoriasis was defined by the presence of a prescription code for treatments consistent with severe psoriasis on or after the diagnosis of psoriasis (such as phototherapy including ultraviolet B or psoralen and ultraviolet A (PUVA); immunomodulator, including methotrexate, azathioprine, cyclosporine, oral retinoids, hydroxyurea, mycophenolate mofetil, tacrolimus, etanercept, adalimumab, and ustekinumab). Patients without treatment codes for systemic or biologic treatment or phototherapy for psoriasis were classified as having mild disease.⁶

Main outcomes

The psoriasis patients (n = 10 288) and control patients without psoriasis (n = 41 152) were followed up until a diagnosis of asthma, loss to follow-up, withdrawal from the NHI, or the end of 2010.

Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables. Chi-square and *t* tests were used to compare the baseline characteristics of the 2 cohorts. The asthma-free Kaplan-Meier curves of the 2 cohorts were compared using the log-rank test. Follow-up time (in person-years) was used to estimate incidence density rates and psoriasis cohort to non-psoriasis cohort hazard ratio (HR) with 95% confidence interval (CI), by gender, age and comorbidities. The HR was determined using univariable and multivariable Cox proportional hazard regression model. The Cox proportion hazard regression analyses were also used to evaluate the effects of risk factors on risk of asthma, simultaneously adjusted for age, sex, and the comorbidities associated with significant differences in univariable Cox proportion hazard regression analyses. Further analysis was performed to verify the impact of psoriasis severity on asthma. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). Two-tailed *p* < 0.05 was considered statistically significant.

Results

Table 1 presents the demographic characteristics and comorbidities of the 2 cohorts. Men accounted for 52.7% of the study sample. The mean age of the nonpsoriasis cohort was 43.2 ± 17.1 years and that of the psoriasis cohort was 43.5 ± 17.0 years, with 68.3% of all patients aged < 50 years. The psoriasis cohort was more likely to have CAD (10.3% vs. 8.14%, $p < 0.0001$), hypertension (21.3% vs. 17.8%, $p < 0.0001$), rhinitis (16.6% vs. 13.0%, $p < 0.0001$), GERD (1.33% vs. 0.98%, $p = 0.002$), psychological disorder (7.86% vs. 6.10%, $p < 0.0001$), atopic dermatitis (4.50% vs. 1.46%, $p < 0.0001$) and COPD (1.64% vs. 1.22%, $p < 0.0001$) compared with the nonpsoriasis cohort. The mean follow-up was 6.37 ± 3.75 years in the psoriasis cohort and 6.39 ± 3.77 years in the nonpsoriasis cohort (data not shown). The incidence of asthma was 6.41 per 1000 person-years in the psoriasis cohort, which was 1.38-fold higher than that in the nonpsoriasis cohort (4.38 per 1000 person-years), with an adjusted HR of 1.38 (95% CI = 1.23–1.54) (Table 2). The incidence of asthma was higher in men than in women and increased with age in both cohorts. We analyzed the sex-specific risk of asthma in patients with psoriasis and observed significantly higher risk of asthma for both women (adjusted HR = 1.29, 95% CI = 1.09–1.53) and men (adjusted HR = 1.46, 95% CI = 1.25–1.70). The age-specific risk of psoriasis was highest in the patients age ≥ 65 years (adjusted HR = 1.63; 95% CI = 1.34–1.99). We analyzed the association between psoriasis and the risk of asthma stratifying by

This article is protected by copyright. All rights reserved.

comorbidity and found the similarly about 1.42-fold of asthma risk were significantly observed in patients without comorbidity (adjusted HR=1.42, 95% CI = 1.24-1.62) or with comorbidity (adjusted HR=1.43, 95% CI=1.16-1.76). The results of univariable and multivariable Cox proportional hazard analyses for association between asthma and psoriasis are shown in table 3. The risk of developing asthma was 1.11 time (95% CI = 1.00-1.23) for women patients and 1.02 times (95% CI = 1.02-1.03) increased with age (every one year). The risk of developing asthma was greater for patients with comorbidity of hypertension (adjusted HR=1.29, 95% CI = 1.13-1.48), rhinitis (adjusted HR=1.57, 95% CI = 1.37-1.80), atopic dermatitis (adjusted HR=1.54, 95% CI = 1.17-2.03), and COPD (adjusted HR=2.87, 95% CI=2.31-3.56).

Furthermore, we divided the psoriasis cohort into 2 subgroups according to received treatment with immunomodulator or phototherapy to examine the combined effects of psoriasis and treatment. We observed that patients with psoriasis who received immunomodulator or phototherapy (severe psoriasis) had a significantly lower risk of asthma than mild psoriasis, as shown in Table 4. Patients with psoriasis who had received treatment of phototherapy had a significantly higher risk of asthma than did those without psoriasis. The Kaplan-Meier plot revealed that the probability of remaining

asthma-free was lower in the psoriasis cohort than in the nonpsoriasis cohort (log-rank $p < 0.001$)

(Fig. 1).

Discussion

Our retrospective population-based cohort study, conducted using data from the NHIRD of Taiwan, suggests that patients with a clinical diagnosis of psoriasis are associated with increased risk of asthma development compared with nonpsoriasis patients, after adjusting for age, sex, and medical comorbidities. The incidence rate of asthma was higher in men than in women, and increased with age in both cohorts. In the psoriasis patients, increased incidence rate of asthma was associated with medical comorbidities (such as CAD, hypertension, rhinitis, chronic sinusitis, GERD, and psychological disorder). In all patients aged > 50 years, patients with psoriasis are associated with higher risk of asthma compared without psoriasis; adjusted HR, 1.49 (95% CI = 1.18–1.88) in patients aged 50–64 years; adjusted HR, 1.63 (95% CI = 1.34–1.99) in patients aged > 65 years).

Psoriasis is a type of chronic inflammatory dermatosis that can restrict patients' work, social, family, leisure, and sexual activities.^{15,16} Psoriasis is associated with multiple comorbidities and has

This article is protected by copyright. All rights reserved.

been described as a systemic chronic inflammatory disorder.⁴ Tumor necrosis factor alpha, dendritic cells, cytokines, and T cells all contribute substantially to psoriasis pathogenesis, and increase the risk of systemic diseases.¹⁷ The associations between psoriasis and comorbidities have been well described; however, an emerging concern is the association between psoriasis and cardiovascular disease.¹⁸ Few studies have evaluated the relationship between pulmonary disorder and psoriasis. Chiang and Lin (2012) reported that psoriasis patients are associated with increased risk of developing the chronic inflammatory airway disease COPD.¹³

Patients with asthma are associated with increased risk of coronary heart disease, diabetes mellitus, hypertension, and CKD.¹⁹⁻²² Various factors have been suggested as contributors to asthma, including immune regulation, genetic susceptibility, infection, and environmental factors. Studies have described the immune reaction in asthma as allergic, eosinophilic, IgE-dependent, and Th2-driven.²³ The crucial role of another subset of CD4+ T cells, the Th17 cells, in inflammatory and autoimmune diseases has also been reported.^{24,25} Th1 and Th17 phenotypes reportedly correlate with airway neutrophilic inflammation frequently found in the lungs of patients with severe or corticosteroid-resistant asthma.²⁶ Studies have also identified increased concentration of interleukin-17, which is predominantly produced by Th17 cells, in the sputum of asthma patients.²⁷

This article is protected by copyright. All rights reserved.

The leucocyte infiltrate in psoriasis predominantly consists of CD4-positive and CD8-positive T cells, and might precede epidermal hyperplasia.^{17,28} The imbalance between Th1 and Th2 cells is critical in inflammatory and immune disorders. Psoriasis is classified as a Th1 disease, which is consistent with the relative underrepresentation of Th2 diseases, such as atopic dermatitis, in patients with psoriasis.²⁹ A study reported that mesenchymal stem cells isolated from psoriasis showed an imbalance between the Th1-Th17 and Th2 pathways, which reflects the well-known abnormal balance observed in differentiated skin cells.³⁰ Systemic inflammation is involved in both psoriasis and asthma. Dendritic cells are also associated with both conditions,^{31,32} and might partially explain their immunological similarities. Although asthma is a representative atopic disorder, its underlying pathophysiological mechanisms are complex. Multiple factors can contribute to asthma development, including genetic and environmental factors, infection, occupational exposure, air pollution, and diet. Race and ethnicity, lifestyle, and socioeconomic status have also been associated with asthma development. Further investigation of the pathophysiology of psoriasis and asthma is warranted.

The strengths of our study include its use of population-based data, which are highly representative of the general population. However, it also has limitations. First, the NHIRD does not contain detailed information on smoking habits, body mass index (BMI), dietary preference, occupational exposure,

This article is protected by copyright. All rights reserved.

reproductive history, drug history, family history of systemic diseases, and socio-economic status, all of which can be risk factors for asthma. Even BMI is an important in psoriasis and asthma and socio-economic status is associated to asthma. Second, evidence deriving from a retrospective cohort study is generally of lower statistical quality than that from randomized trials because of potential biases related to adjustment for confounding variables. Although our study design was meticulous, including control for confounding factors, bias resulting from unknown confounders could have affected our results. Third, all data in the NHIRD are anonymous. Therefore, relevant clinical variables, such as serum laboratory data, pulmonary function tests, and imaging and pathology results were unavailable. So, we have difficult to differentiate between allergic and non-allergic asthma. However, all insurance claims in the NHI are scrutinized by medical reimbursement specialists and subject to peer review. Data on the diagnoses of psoriasis and asthma can thus be considered reliable.

Conclusion

In conclusion, the results from our nationwide retrospective cohort study indicate that psoriasis is associated with increased risk of asthma development after adjusting for CAD, hypertension, rhinitis, GERD, and psychological disorder (anxiety and depression). We observed higher incidence of asthma in the psoriasis patients aged ≥ 50 years. However, additional prospective studies are required to

This article is protected by copyright. All rights reserved.

elucidate the detailed underlying pathophysiology of asthma and psoriasis. We suggest that dermatologists should remain aware of increased risk of asthma in psoriasis patients, and refer to a specialist at an early stage if a patient exhibits chronic respiratory symptoms.

References

1. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch. Dermatol.* 2005;141(12):1537-1541.
2. Chang YT, Chen TJ, Liu PC, et al. Epidemiological study of psoriasis in the national health insurance database in Taiwan. *Acta Derm. Venereol.* 2009;89(3):262-266.
3. Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. *Br. J. Dermatol.* 2009;161(1):1-7.
4. Tsai TF, Wang TS, Hung ST, et al. Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *J. Dermatol. Sci.* 2011;63(1):40-46.

5. Coumbe AG, Pritzker MR, Duprez DA. Cardiovascular risk and psoriasis: beyond the traditional risk factors. *Am. J. Med.* 2014;127(1):12-18.
6. Wan J, Wang S, Haynes K, Denburg MR, Shin DB, Gelfand JM. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ.* 2013;347:f5961.
7. Chiang CH, Huang CC, Chan WL, et al. Psoriasis and increased risk of ischemic stroke in Taiwan: a nationwide study. *J. Dermatol.* 2012;39(3):279-281.
8. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br. J. Dermatol.* 2007;157(1):68-73.
9. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *The European respiratory journal.* 2008;31(1):143-178.
10. Toren K, Gislason T, Omenaas E, et al. A prospective study of asthma incidence and its predictors: the RHINE study. *The European respiratory journal.* 2004;24(6):942-946.
11. Sumino K, O'Brian K, Bartle B, Au DH, Castro M, Lee TA. Coexisting chronic conditions associated with mortality and morbidity in adult patients with asthma. *J. Asthma.* 2014.

This article is protected by copyright. All rights reserved.

12. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat. Rev. Immunol.* 2008;8(3):183-192.
13. Chiang YY, Lin HW. Association between psoriasis and chronic obstructive pulmonary disease: a population-based study in Taiwan. *J. Eur. Acad. Dermatol. Venereol.* 2012;26(1):59-65.
14. Cheng TM. Taiwan's National Health Insurance system: high value for the dollar. In Okma, K.G.H. and Crivelli, L. ed. Six Countries, Six Reform Models: The Health Reform Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. *New Jersey: World Scientific.* 2009:pp.71-204.
15. Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br. J. Dermatol.* 1995;132(2):236-244.
16. Chen YJ, Chen CC, Lin MW, et al. Increased risk of sexual dysfunction in male patients with psoriasis: a nationwide population-based follow-up study. *J. Sex. Med.* 2013;10(5):1212-1218.
17. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet.* 2007;370(9583):263-271.

18. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741.
19. Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts. *Am. J. Epidemiol.* 2012;176(11):1014-1024.
20. Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care*. 2010;33(1):55-60.
21. Johnson M, Nriagu J, Hammad A, Savoie K, Jamil H. Asthma, environmental risk factors, and hypertension among Arab Americans in metro Detroit. *Journal of immigrant and minority health / Center for Minority Public Health*. 2010;12(5):640-651.
22. Huang HL, Ho SY, Li CH, et al. Bronchial asthma is associated with increased risk of chronic kidney disease. *BMC Pulm. Med.* 2014;14(1):80.
23. Sittka A, Vera J, Lai X, Schmeck BT. Asthma phenotyping, therapy, and prevention: what can we learn from systems biology? *Pediatr. Res.* 2013;73(4 Pt 2):543-552.

24. Stockinger B, Veldhoen M. Differentiation and function of Th17 T cells. *Curr. Opin. Immunol.* 2007;19(3):281-286.
25. Li Y, Hua S. Mechanisms of pathogenesis in allergic asthma: Role of interleukin-23. *Respirology.* 2014;19(5):663-669.
26. Simpson JL, Grissell TV, Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in neutrophilic asthma and bronchiectasis. *Thorax.* 2007;62(3):211-218.
27. Bullens DM, Truyen E, Coteur L, et al. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? *Respir. Res.* 2006;7:135.
28. Valdimarsson H, Baker BS, Jonsdottir I, Powles A, Fry L. Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? *Immunol. Today.* 1995;16(3):145-149.
29. Landgren E, Braback L, Hedlin G, Hjern A, Rasmussen F. Psoriasis in Swedish conscripts: time trend and association with T-helper 2-mediated disorders. *Br. J. Dermatol.* 2006;154(2):332-336.

30. Campanati A, Orciani M, Consales V, et al. Characterization and profiling of immunomodulatory genes in resident mesenchymal stem cells reflect the Th1-Th17/Th2 imbalance of psoriasis. *Arch. Dermatol. Res.* 2014.
31. Kim TG, Kim DS, Kim HP, Lee MG. The pathophysiological role of dendritic cell subsets in psoriasis. *BMB reports.* 2014;47(2):60-68.
32. Yahia SA, Azzaoui I, Everaere L, et al. CCL17 production by dendritic cells is required for NOD1-mediated exacerbation of allergic asthma. *American journal of respiratory and critical care medicine.* 2014;189(8):899-908.

Figure Legend:

Figure 1. Probability free of Asthma for patients with (dashed line) or without (solid line) Psoriasis

Table 1. Comparisons in demographic characteristics and comorbidities in patient with and without Psoriasis

	Psoriasis		<i>p</i> -value
	No (N =41152)	Yes (N =10288)	
Gender			0.99
Women	19456(47.3)	4864(47.3)	
Men	21696(52.7)	5424(52.7)	
Age stratified			0.99
≤ 34	15824(38.5)	3956(38.5)	
35-49	12256(29.8)	3064(29.8)	
50-64	7332(17.8)	1833(17.8)	
65+	5740(14.0)	1435(14.0)	
Age, mean±SD ^a	43.2(17.1)	43.5(17.0)	0.13
Comorbidity			
Coronary artery disease	3351(8.14)	1062(10.3)	<0.0001
Hypertension	7321(17.8)	2191(21.3)	<0.0001
Rhinitis	5354(13.0)	1709(16.6)	<0.0001
Chronic sinusitis	639(1.55)	186(1.81)	0.07
GERD	404(0.98)	137(1.33)	0.002
Psychological disorder	2509(6.10)	809(7.86)	<0.0001
Atopic dermatitis	602(1.46)	463(4.50)	<0.0001
COPD	501(1.22)	169(1.64)	<0.0001

Chi-Square Test, ^a t-test

Table 2. Comparison of incidence densities of Asthma and hazard ratio between with and without psoriasis by demographic characteristics and comorbidity

	Psoriasis						Crude HR [§] (95% CI)	Adjusted HR [†] (95% CI)
	No			Yes				
	Event	PY	Rate [#]	Event	PY	Rate [#]		
All	1153	263158	4.38	420	65496	6.41	1.46(1.31, 1.63)***	1.38(1.23, 1.54)***
Gender								
Women	545	126184	4.32	186	31642	5.88	1.36(1.15, 1.61)***	1.29(1.09, 1.53)**
Men	608	136974	4.44	234	33853	6.91	1.55(1.34, 1.81)***	1.46(1.25, 1.70)***
Stratify age								
≤ 49	542	186664	2.90	176	47222	3.73	1.29(1.08, 1.52)**	1.18(0.99, 1.40)
50-64	263	44955	5.85	102	10739	9.50	1.61(1.28, 2.02)***	1.49(1.18, 1.88)***
65+	348	31539	11.0	142	7534	18.9	1.69(1.39, 2.05)***	1.63(1.34, 1.99)***
Comorbidity [‡]								
No	875	238795	3.66	289	57360	5.04	1.38(1.21, 1.57)***	1.42(1.24, 1.62)***
Yes	278	24363	11.4	131	8136	16.1	1.41(1.14, 1.73)**	1.43(1.16, 1.76)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR[§], relative hazard ratio. Adjusted HR[†]: multivariable analysis including age, gender, and co-morbidities of coronary artery disease, hypertension, rhinitis, chronic sinusitis, psychological disorder, atopic dermatitis and COPD.

Comorbidity[‡]: Patients with any one of the comorbidities coronary artery disease, hypertension, rhinitis, chronic sinusitis, GERD, psychological disorder, atopic dermatitis, and COPD were classified as the comorbidity group.

*p<0.05, **p<0.01, ***p<0.001

Table 3. Cox model with hazard ratios and 95% confidence intervals of asthma associated with psoriasis and covariates

	Crude		Adjusted [†]	
Variable	HR (95% CI)		HR (95% CI)	
Gender				
Women	0.94	(0.85, 1.04)	1.11	(1.00, 1.23)*
Men	1	(Reference)	1	(Reference)
Age, years	1.03	(1.03, 1.04)***	1.02	(1.02, 1.03)***
Baseline comorbidities (yes vs no)				
Psoriasis	1.46	(1.31, 1.63)***	1.38	(1.23, 1.54)**
Coronary artery disease	2.88	(2.54, 3.26)***	1.19	(1.03, 1.39)*
Hypertension	2.77	(2.50, 3.07)***	1.29	(1.13, 1.48)***
Rhinitis	1.67	(1.46, 1.91)***	1.57	(1.37, 1.80)***
Chronic sinusitis	1.76	(1.27, 2.46)***	1.17	(0.83, 1.64)
GERD	1.04	(0.52, 2.08)	-	-
Psychological disorder	1.74	(1.46, 2.08)***	1.04	(0.87, 1.25)
Atopic dermatitis	2.15	(1.64, 2.82)***	1.54	(1.17, 2.03)**
COPD	7.25	(5.93, 8.86)***	2.87	(2.31, 3.56)***

Crude HR*, relative hazard ratio; Adjusted HR[†] : multivariable analysis including age group, gender, and comorbidities of coronary artery disease, hypertension, rhinitis, chronic sinusitis, psychological disorder, atopic dermatitis , and COPD;

*p<0.05, **p<0.01, ***p<0.001

Table 4. Comparison of incidence densities of Asthma and hazard ratio between with and without psoriasis by treatment

Variables	N	Event	PY	Rate [#]	Crude HR [§] (95% CI)	Adjusted HR [†] (95% CI)
Without psoriasis	41152	1153	263158	4.38	1(Reference)	1(Reference)
Mild psoriasis	9301	376	58285	6.45	1.47(1.30, 1.65)***	1.39(1.24, 1.56)***
Severe psoriasis	987	44	7211	6.10	1.43(1.06, 1.93)*	1.29(0.95, 1.74)

Rate[#], incidence rate, per 1,000 person-years; Crude HR[§], relative hazard ratio. Adjusted HR[†] : multivariable analysis including age, gender, and co-morbidities of coronary artery disease, hypertension, rhinitis, chronic sinusitis, psychological disorder atopic dermatitis and COPD.

*p<0.05, **p<0.01, ***p<0.001

