Increased risk for incident thyroid diseases in people with psoriatic disease: A cohort study

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Background: The association between psoriasis and thyroid diseases is unclear.

Objective: To examine the risk for thyroid diseases among psoriasis patients.

Methods: We used Taiwan's National Health Insurance Research Database to conduct a nationwide cohort study. We examined the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for incident thyroid diseases in relation to psoriasis and psoriatic arthritis.

Results: We identified 13,266 patients with psoriatic arthritis (psoriatic arthritis group), 149,576 with psoriasis alone (psoriasis group), and 162,842 nonpsoriasis controls. Compared with the nonpsoriasis controls, the psoriatic arthritis and psoriasis groups had increased risk for incident hyperthyroidism (aHR 1.32, 95% CI 1.07-1.65 [psoriatic arthritis]; aHR 1.22, 95% CI 1.11-1.33 [psoriasis]) and Graves disease (aHR 1.38, 95% CI 1.07-1.79 [psoriatic arthritis]; aHR 1.26, 95% CI 1.13-1.41 [psoriasis]). Both groups also had increased risk for incident hypothyroidism (aHR 1.74, 95% CI 1.34-2.27 [psoriatic arthritis]; aHR 1.38, 95% CI 1.23-1.56 [psoriasis]) and Hashimoto thyroiditis (aHR 2.09, 95% CI 1.34-3.24 [psoriatic arthritis]; aHR 1.47, 95% CI 1.18-1.82 [psoriasis]).

Limitations: Lack of data on psoriasis severity.

Conclusion: People with psoriatic disease are associated with an increased incident thyroid diseases, including hyperthyroidism, hypothyroidism, thyroiditis, Graves disease, and Hashimoto thyroiditis. Endocrinology consultation may be considered when psoriasis patients present with thyroid symptoms. (J Am Acad Dermatol 2019;80:1006-12.)

Key words: cohort study; hyperthyroidism; hypothyroidism; National Health Insurance Research Database; psoriasis; psoriatic arthritis; thyroid diseases.

Psoriasis is a chronic, immune-mediated inflammatory dermatosis.[1,2] Previous epidemiologic studies have reported associated inflammatory comorbidities including psoriatic arthritis, myocardial infarction, stroke, chronic kidney disease, and uveitis.[3-5] On the other hand,

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concurrence of autoimmune diseases in psoriasis is not uncommon. In a previous study, an increase in autoimmune diseases was found among patients with psoriasis.[6]

An autoimmune etiology has been indicated for a few thyroid diseases (eg, Graves disease and Hashimoto thyroiditis).[7] However, to date, there are only a limited number of studies that have examined the link between psoriasis and thyroid disease. In a Taiwanese cross-sectional study, an increased prevalence was reported for both hyperthyroidism (prevalence ratio 1.28, 95% confidence interval [CI] 1.07-1.53) and hypothyroidism (prevalence ratio 1.33, 95% CI 1.05-1.70) in psoriasis patients.[8] In another Taiwanese cross-sectional study, only hypothyroidism was examined, and no association of psoriasis with hypothyroidism (odds ratio 1.23, 95% CI 0.93-1.63) was found.[9] An Israeli case-control study showed no significant differences in thyroid function between psoriasis patients and nonpsoriasis controls.[10] Another European case-control study showed no significant association between psoriasis and autoimmune thyroiditis.[11] However, in a US study, increased levels of thyroid-stimulating hormone was observed in psoriasis patients.[12] In a Danish case-control study, patients with pustulosis palmoplantaris had increased goiter and thyroid autoantibodies.[13] Because a causal relationship cannot be concluded from these case-control studies with inconsistent results, the association of psoriasis with thyroid diseases remains largely unclear.

To examine the causal relationship between psoriasis and thyroid disease, we conducted a retrospective nationwide cohort study to assess the risk for incident thyroid diseases among patients with psoriasis and psoriatic arthritis. In addition to specific autoimmune thyroid diseases including Graves disease and Hashimoto thyroiditis, we also examined the risk for other incident thyroid diseases including nontoxic simple goiter, hyperthyroidism, hypothyroidism, and thyroiditis.

CAPSULE SUMMARY

- There is an increased incidence of hyperthyroidism, Graves disease, hypothyroidism, and Hashimoto thyroiditis among patients with psoriasis. This risk is further increased in those with psoriatic arthritis.
- Our findings can serve as a guide for thyroid disease risk stratification for patients with psoriatic disease.

METHODS

Data source

In Taiwan, >99% of the Taiwanese population is covered by the National Health Insurance, a compulsory single-payer health care system. The National Health Insurance Research Database (NHIRD) provides anonymized linked data for clinical and epidemiologic research that include characteristics and registration data of beneficiaries, claim data from general practices and hospitals, as well as dispensing claims from general practices, hospitals, and community pharmacies. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used to record diagnoses in the NHIRD. Previous studies have validated the wholeness and accuracy of the NHIRD linked data, such as clinical diagnoses.[14-16] The NHIRD has been widely used in thousands of epidemiologic studies.[17]

In this study, we identified psoriasis patients from a specialized data set that contained all psoriasis patients present in the NHIRD during January 1, 2000-December 31, 2011.[4] Nonpsoriasis controls were selected using the 2005 Longitudinal Health Insurance Database (LHID), which provides longitudinally linked anonymized data of 1,000,000 enrollees (~5% of Taiwan's population) randomly sampled from the 2005 registry for beneficiaries of the NHIRD. The LHID also has been validated as a representative sample of the Taiwanese population in terms of age, sex, and average payroll bracket.[18] This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201701058B1). Because use of the NHIRD assures patient confidentiality, this study was conducted in accordance with the Declaration of Helsinki.

Study population

The selection of the study population is presented in Figure 1. Psoriasis patients were identified from the NHIRD by using ICD-9-CM codes 6960, 6961, and 6968. These codes have been utilized in previous epidemiologic studies employing the NHIRD.[4,5,8,9] To avoid overestimation of the risk for incident thyroid diseases, we also excluded patients with psoriasis diagnosed before 2000; if the development of thyroid diseases correlates with the disease duration of psoriasis, inclusion of patients with psoriasis diagnosed before 2000 would have led to an overestimation of risk for incident thyroid diseases. We also excluded those with psoriasis diagnosed after 2011 to ensure at least 1-year's follow-up.

We also excluded patients with a history of thyroid diseases or comorbidities that might have caused thyroid diseases: congenital hypothyroidism

Abbreviations used:

aHR:	adjusted hazard ratio
CI:	confidence interval
HR:	hazard ratio
ICD-9-CM:	International Classification of Diseases, 9th Revision, Clinical Modification
LHID:	Longitudinal Health Insurance Database
NHIRD:	National Health Insurance Research Database

(ICD-9-CM code 243), postsurgical hypothyroidism (ICD-9-CM code 244.0), other postablative hypothyroidism (ICD-9-CM code 244.1), iodine hypothyroidism (ICD-9-CM code 244.2), other iatrogenic hypothyroidism (ICD-9-CM code 244.3), iatrogenic thyroiditis (ICD-9-CM code 245.4), and thyroid dysfunction (ICD-9-CM code 648.1).

For each psoriasis patient, 1 nonpsoriasis control was selected by matching with age (±365.25 days) and sex from the 2005 LHID. The nonpsoriasis control had never received a diagnosis of psoriasis or any thyroid diseases before the index date. The index date for the psoriasis group was the date when psoriasis was diagnosed for the first time, whereas the index date for the nonpsoriasis control was the psoriasis-diagnosed date of the matched psoriasis patient.

Because psoriatic arthritis has been associated with increased inflammation and associated inflammatory comorbidities,[4,5] we divided psoriasis patients into 2 groups: those with and without psoriatic arthritis (Fig 1). The ICD-9-CM code 696.0 was used to identify the presence of comorbid psoriatic arthritis. We confirmed the diagnosis of psoriasis and psoriatic arthritis by requiring records of the diagnosis on at least 2 outpatient visits or 1 hospital admission to enhance the accuracy of diagnosis.

Outcomes

The outcomes of this study were incident thyroid diseases, including simple nontoxic goiter (ICD-9-CM codes 240 and 241), hyperthyroidism (ICD-9-CM code 242), Graves disease (ICD-9-CM code 242.0), toxic nodular goiter (also called Plummer syndrome) (ICD-9-CM codes 242.1, 242.2, and 242.3), hyperthyroidism (ICD-9-CM code 244), thyroiditis (ICD-9-CM code 245), and Hashimoto thyroiditis (ICD-9-CM code 246). We confirmed the outcomes by requiring records of the diagnosis on at least 2 outpatient visits or 1 hospital admission to enhance the accuracy of outcomes. We also used prescription records to confirm outcomes. For confirmation of simple nontoxic goiter, the patient was required to have a diagnosis corresponding with the appropriate ICD-9-CM code and never have been prescribed antithyroid drugs (eg, propylthiouracil and methimazole). For hyperthyroidism, Graves disease, and toxic nodular goiter, patients had to have a diagnosis corresponding with the appropriate ICD-9-CM code and been prescribed antithyroid drugs. Regarding acquired hypothyroidism, patients had to have been prescribed thyroxine and received a diagnosis corresponding with the appropriate ICD-9-CM code.

For patients who developed an incident thyroid disease, the length of follow-up was the period from the index date to the date of first diagnosis of thyroid disease according to inpatient or outpatient records. The censored time for patients who did not have an incident thyroid disease was the period from the index date to either December 31, 2012, or the date of withdrawal from the National Health Insurance.

Statistical analysis

SAS software, version 9.4 (SAS Institute, Cary, North Carolina) was used for carrying out all statistical analyses. A descriptive analysis of baseline characteristics, including age, sex, as well as comorbidities of the psoriasis, psoriatic arthritis, and nonpsoriasis control groups was conducted. We compared the categorical and continuous variables by using the chi-squared test and analysis of variance test, respectively. The incidence (per 1000 person-years) was calculated by dividing the number of patients with the incident thyroid disease by the total person-years of each group. The Poisson distribution was used to obtain the confidence interval and compare the incidence among different groups.[19] The univariate and multivariate Cox proportional hazard models were used to calculate the respective hazard ratios (HRs) and 95% confidence intervals (CIs) for incident thyroid diseases in the psoriasis and psoriatic arthritis groups compared with the nonpsoriasis control group. In the multivariate analysis, potential confounders, including age, sex, type 2 diabetes mellitus, hypertension, and hyperlipidemia were used to adjust values. We deemed a P value of $<.05$ and a CI not containing 1 significant.

RESULTS

Table I shows the baseline characteristics of the study population. We identified 162,842 patients with psoriasis (149,576 with psoriasis alone and 13,266 with comorbid psoriatic arthritis) and 162,842 matched nonpsoriasis controls from data collected during January 1, 2000-December 31, 2012. The mean age in the psoriasis, psoriatic arthritis, and control groups were 45.11 ± 20.09 years, 43.17 ± 17.72 years,

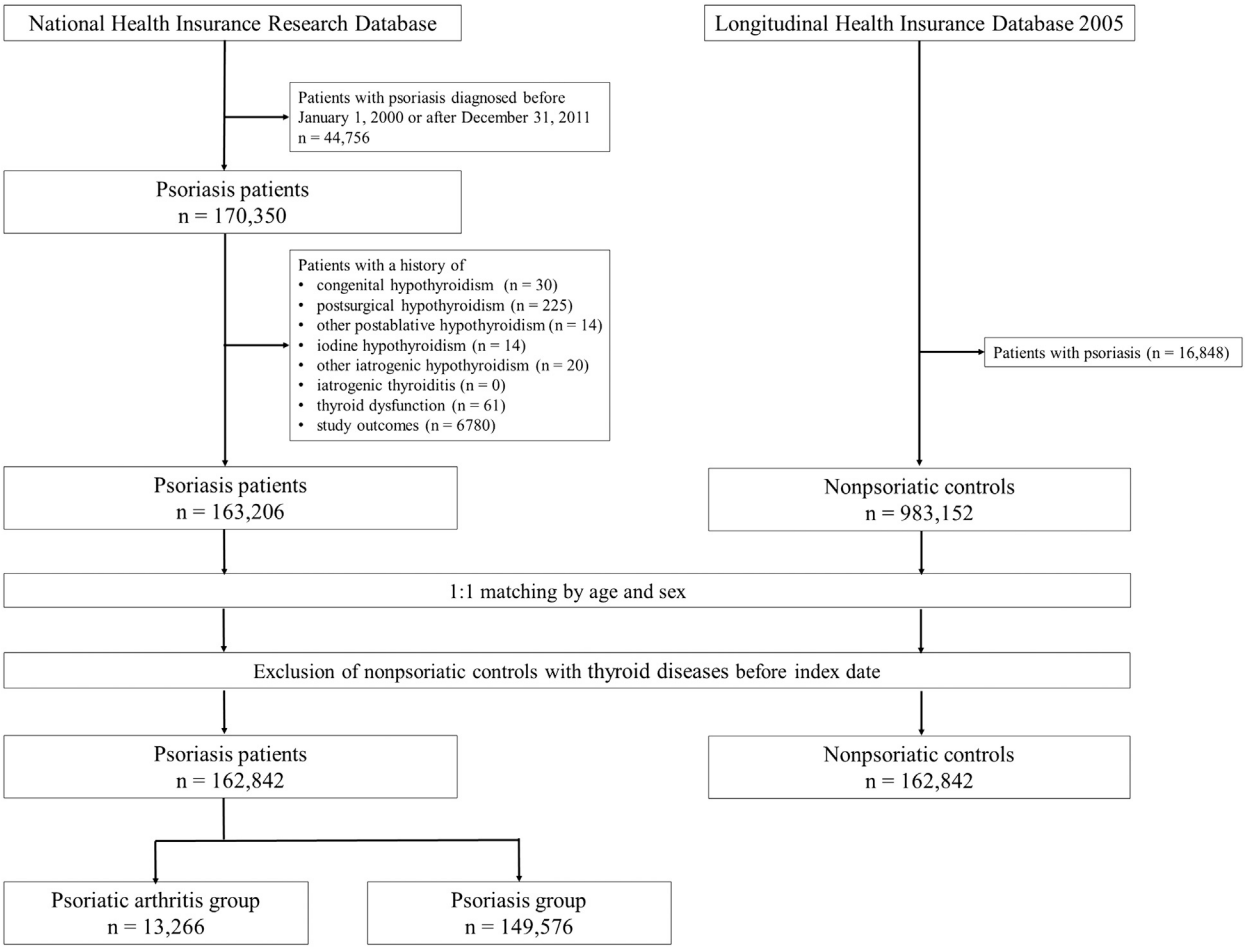

Fig 1. Selection of the study population. This study included 162,842 persons with psoriasis, 149,576 with psoriasis alone and 13,266 with comorbid psoriatic arthritis, and 162,842 matched nonpsoriasis controls.

Table I. Baseline characteristics of the study population

Characteristic	Psoriasis group, n = 149,576	Psoriatic arthritis group, n = 13,266	Nonpsoriasis control group, n = 162,842	*P* value
Age, y	45.11 ± 20.09	43.17 ± 17.72	44.95 ± 19.91	<.0001*
Female sex	61,173 (46.21%)	5018 (37.83%)	66,191 (40.65%)	<.0001†
Mean length ± SD of follow-up, y	7.07 ± 3.45	7.09 ± 3.61	7.10 ± 3.46	.07*
Type 2 diabetes mellitus	20,658 (13.81%)	1613 (12.16%)	16,684 (10.25%)	<.0001†
Hypertension	40,301 (26.94%)	3156 (23.79%)	36,120 (22.18%)	<.0001†
Hyperlipidemia	27,369 (18.30%)	2386 (17.99%)	22,723 (13.95%)	<.0001†

SD, Standard deviation.
*Analysis of variance test.
†Chi-squared test.

and 44.95 ± 19.91 years, respectively ($P < .0001$). Female patients accounted for 46.21%, 37.83%, and 40.65% of the psoriasis, psoriatic arthritis, and control groups, respectively ($P < .0001$). A higher proportion of the psoriasis and psoriatic arthritis groups had type 2 diabetes mellitus, hypertension, and hyperlipidemia compared with the nonpsoriasis control group ($P < .0001$).

The psoriasis group had an increased risk for the following incident thyroid diseases: hyperthyroidism (adjusted HR [aHR] 1.22, 95% CI 1.11-1.33), Graves disease (aHR 1.26, 95% CI 1.13-1.41), acquired

Table II. Incident thyroid diseases in people with psoriatic disease

Category	Incident cases, n	No. person-years	Incidence per 1000 person-years (95% CI)	*P* value*	Crude HR (95% CI)	Adjusted HR (95% CI)†
Simple nontoxic goiter						
Nonpsoriasis controls	1814	1,156,090.74	1.57 (1.50-1.64)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	1764	1,057,633.89	1.67 (1.59-1.74)	.07	1.06 (0.996-1.14)	1.05 (0.99-1.12)
Psoriatic arthritis group	202	94,108.22	2.15 (1.86-2.46)	<.0001	1.37 (1.18-1.58)‡	1.44 (1.24-1.66)‡
					P_{trend} = .0003	P_{trend} = .0002
Hyperthyroidism						
Nonpsoriasis controls	872	1,155,940.74	0.75 (0.71-0.81)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	967	1,057,556.52	0.91 (0.86-0.97)	<.0001	1.21 (1.11-1.33)‡	1.22 (1.11-1.33)‡
Psoriatic arthritis group	90	94,084.41	0.96 (0.77-1.18)	.0315	1.27 (1.02-1.58)§	1.32 (1.07-1.65)§
					P_{trend} < .0001	P_{trend} < .0001
Graves disease						
Nonpsoriasis controls	584	1,156,136.72	0.51 (0.47-0.55)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	676	1,057,764.52	0.64 (0.59-0.69)	<.0001	1.27 (1.13-1.41)‡	1.26 (1.13-1.41)‡
Psoriatic arthritis group	64	94,103.44	0.68 (0.52-0.87)	.02	1.35 (1.04-1.75)§	1.38 (1.07-1.79)§
					P_{trend} < .0001	P_{trend} < .0001
Toxic nodular goiter (Plummer syndrome)						
Nonpsoriasis controls	71	1,155,874.91	0.06 (0.05-0.08)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	59	1,057,443.98	0.06 (0.04-0.07)	.59	0.91 (0.64-1.28)	0.89 (0.63-1.26)
Psoriatic arthritis group	7	94,084.64	0.07 (0.03-0.15)	.63	1.20 (0.55-2.62)	1.26 (0.58-2.74)
					P_{trend} = .88	P_{trend} = .85
Hypothyroidism						
Nonpsoriasis controls	482	1,156,134.42	0.42 (0.38-0.46)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	629	1,057,701.56	0.59 (0.55-0.64)	<.0001	1.43 (1.27-1.61)‡	1.38 (1.23-1.56)‡
Psoriatic arthritis group	63	94,113.33	0.67 (0.51-0.86)	.0004	1.60 (1.23-2.08)‖	1.74 (1.34-2.27)‡
					P_{trend} < .0001	P_{trend} < .0001
Thyroiditis						
Nonpsoriasis controls	313	1,155,949.66	0.27 (0.24-0.30)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	404	1,057,620.73	0.38 (0.34-0.42)	<.0001	1.41 (1.22-1.64)‡	1.42 (1.22-1.64)‡
Psoriatic arthritis group	49	94,091.10	0.52 (0.39-0.69)	<.0001	1.92 (1.42-2.60)‡	2.05 (1.51-2.77)‡
					P_{trend} < .0001	P_{trend} < .0001
Hashimoto thyroiditis						
Nonpsoriasis controls	143	1,155,900.27	0.12 (0.10-0.15)	—	1.00 (referent)	1.00 (referent)
Psoriasis group	193	1,057,498.27	0.18 (0.16-0.21)	.0004	1.48 (1.19-1.83)‖	1.47 (1.18-1.82)‖
Psoriatic arthritis group	23	94,074.86	0.24 (0.16-0.37)	.002	1.98 (1.27-3.07)‖	2.09 (1.34-3.24)‖
					P_{trend} < .0001	P_{trend} < .0001

CI, Confidence interval; *HR*, hazard ratio.
*Compared with nonpsoriasis controls.
†Adjusted for age, sex, and comorbidities, including type 2 diabetes mellitus, hypertension, and hyperlipidemia.
‡$P < .0001$.
§$P < .05$.
‖$P < .01$.

hypothyroidism (aHR 1.38, 95% CI 1.23-1.56), thyroiditis (aHR 1.42, 95% CI 1.22-1.64), and Hashimoto thyroiditis (aHR 1.47, 95% CI 1.18-1.82) compared with the nonpsoriasis controls after adjusting for potential confounders (Table II). Meanwhile, the psoriatic arthritis group had a 1.44 (95% CI 1.24-1.66)−fold increased risk for simple nontoxic goiter, 1.32 (95% CI 1.07-1.65)−fold increased risk for hyperthyroidism, 1.38 (95% CI 1.07-1.79)−fold increased risk for Graves disease, 1.74 (95% CI 1.34-2.27)−fold increased risk for hypothyroidism, 2.05 (95% CI 1.51-2.77)−fold increased risk for thyroiditis, and 2.09 (95% CI 1.34-3.24)−fold increased risk for Hashimoto thyroiditis compared with the nonpsoriasis control group. In addition, we found a stepwise increase in the risk for the aforementioned incident thyroid diseases from the nonpsoriasis control group to the psoriasis group to the psoriatic arthritis group ($P < .0001$, chi-squared test for trend).

DISCUSSION

In this population-based cohort study, we found people with psoriasis had an increased risk for incident thyroid diseases, including hyperthyroidism, hypothyroidism, thyroiditis, and specific autoimmune thyroid diseases (such as Graves disease and Hashimoto thyroiditis). Although the exact causes for hyperthyroidism, hypothyroidism, and thyroiditis were not specified in the data source, they might have been related to autoimmune etiology.[7] The risk for incident thyroid diseases was further increased in people with concomitant psoriasis and psoriatic arthritis.

There are several explanations for the association between psoriatic disease and autoimmune thyroid diseases. First, T-helper 1 cell−mediated inflammation is involved in both psoriatic disease and autoimmune thyroid diseases and might be the immunopathogenic basis for the association of the 2 dieases.[20] Compared with psoriasis alone, the further increased inflammation in psoriatic arthritis could explain the higher risk for incident thyroid diseases found in this population. Second, shared predisposing genes might explain the association between thyroid diseases and psoriatic disease, especially psoriatic arthritis. In 1 study, the protein tyrosine phosphatase nonreceptor type 22 620W allele was found to be significantly associated with psoriasis and autoimmune thyroid disease.[21] In another study, a locus on chromosome 4q27 was found to be associated with both psoriatic arthritis and Graves disease.[22]

To the best of our knowledge, this study was the first to find a significant association between simple nontoxic goiter and psoriatic arthritis but not psoriasis alone. The mechanism of the association between psoriatic arthritis and simple nontoxic goiter is unclear. More studies are warranted to confirm this association.

Our cohort study was in agreement with previous studies that showed a significant association of psoriatic disease, especially psoriatic arthritis, with thyroid diseases.[8,23-26] Nevertheless, previous studies only collected data at a single time point and could not reflect long-term exposure to various biochemical factors that might have been important effect modifiers of thyroid disease.

In contrast, a few cross-sectional studies did not detect a significant association between psoriasis and thyroid diseases.[9-11,27] However, the sample size of these studies was generally limited, with resultant type 2 error. A meta-analysis that included 7 case-control studies with 77,563 patients with psoriatic disease and 340,096 controls showed significant associations between psoriatic disease and autoimmune thyroid disease, hyperthyroidism, and hypothyroidism.[26]

Our study has the strength of a cohort study and confirms the causal relationship between psoriatic disease and incident thyroid diseases. In addition, we used medication records to increase the accuracy of diagnosis of thyroid diseases. On the other hand, our study had several limitations. First, the data source of this study was the NHIRD, which lacks clinical variables, such as body mass index. Therefore, we were unable to control for these confounders. Although we only explored incidence of thyroid disease in patients with psoriatic disease, further evidence is still needed to establish the causality because age of onset of thyroid disease might be greater than that of psoriasis. Second, to avoid overestimating the risk for incident thyroid diseases, we excluded those with psoriasis diagnosed before 2000. Thus, patients with longer durations of psoriasis were excluded. The increased risk for thyroid diseases found in the psoriasis group might have been underestimated. Third, since patients with early-onset psoriasis might have a different genetic profile than those with late-onset psoriasis, further studies are needed to evaluate the risks in these 2 populations. Fourth, the exclusion of patients with a history of thyroid disease from the cohort with psoriatic disease led to an underestimation of the overall disease burden of thyroid diseases. Fifth, although we have mitigated confounding by matching and adjustment for known confounders, there might have been residual confounding. Sixth, the patients in this study were from an Asian population. More studies are warranted to confirm if the

risk for thyroid disease increases in psoriasis patients of other race/ethnicities. Last, this study found no substantial difference in the risk of developing thyroid diseases between patients with psoriasis and psoriatic arthritis. Therefore, it is difficult to select a specific group of patients to undergo screening for thyroid diseases. Psoriasis is not a rare disease, so further cost-effectiveness analysis is warranted.

In conclusion, the present study illustrates that patients with psoriatic disease have an increased risk for incident hyperthyroidism, hypothyroidism, thyroiditis, and specific autoimmune thyroid diseases, such as Graves disease and Hashimoto thyroiditis. Compared with patients with psoriasis alone, this risk is further increased in those with psoriatic arthritis. The findings of this study can be used as a guide for thyroid disease risk stratification for patients with psoriatic disease. An endocrinology consultation should be considered when thyroid symptoms are present in psoriasis patients, especially those with psoriatic arthritis.

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