

Psoriasis increases the risk of concurrent inflammatory bowel disease: A population-based nationwide study in Korea

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Abstract

Background: The epidemiology of the association between psoriasis and inflammatory bowel disease is poorly defined and remains controversial.

Aim: To evaluate the prevalence of inflammatory bowel disease in patients with psoriasis compared with the general population.

Methods: We searched the nationwide health claims database between 2011 and 2015 and evaluated the prevalence of inflammatory bowel disease, including Crohn's disease and ulcerative colitis.

Results: Prevalence of inflammatory bowel disease, Crohn's disease and ulcerative colitis in patients with psoriasis vs the general population in 2011 were 0.16, 0.05 and 0.12% vs 0.08, 0.03 and 0.06%, respectively, which increased significantly with time between 2011 and 2015. Patients with psoriasis consistently revealed higher standardized prevalence (age and sex adjusted) of inflammatory bowel disease, Crohn's disease and ulcerative colitis compared with the general population. Subgroup analysis revealed the highest risk of prevalent inflammatory bowel disease in patients younger than 19 years (crude odds ratio 5.33, 95% confidence interval 3.74–7.59). Severe psoriasis demonstrated higher odds of inflammatory bowel disease (odds ratio 2.96, 95% confidence interval 2.54–3.45) than mild psoriasis (odds ratio 1.68, 95% confidence interval 1.51–1.88).

Limitations: Limited data for doing adjustment and cross-sectional study design.

Conclusions: Psoriasis patients revealed higher risk of inflammatory bowel disease. In particular, young patients and those with severe psoriasis may require closer monitoring and comprehensive management.

Key words: Crohn's disease, epidemiology, inflammatory bowel disease, prevalence, psoriasis, ulcerative colitis

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Introduction

The association between psoriasis and inflammatory bowel disease has been repeatedly reported, which can be explained by common genetic and inflammatory pathways including tumor necrosis factor-alpha or interleukin-17.¹⁻⁴ However, the epidemiology of this relationship is poorly defined and remains controversial.⁵ Research from the United States, Germany and Israel reported increased prevalence of Crohn's disease or ulcerative colitis among patients with psoriasis compared with healthy subjects.⁶⁻¹⁰ On the other hand, research in Taiwan reported that psoriasis was not associated with increased risk of Crohn's disease.¹¹ Studies on newly incident inflammatory bowel disease associated with psoriasis are also conflicting. A nationwide Danish cohort study¹² revealed increased risk of both incident Crohn's disease and ulcerative colitis associated with psoriasis, whereas a US study¹³ in women nurses reported increased risk of Crohn's disease, but not ulcerative colitis. Some of these previous studies had limitations, however, including limited populations^{6,8,9,13} or specific patient groups (e.g. women nurses),¹³ which do not provide robust information of real-world patients. Given the concerns regarding inflammatory bowel disease in patients with psoriasis as a systemic inflammatory disease, we searched the nationwide health claims database of Korea and aimed to identify the risk of inflammatory bowel disease in patients with psoriasis compared with the general population.¹⁴

Methods

This study was exempt from approval by the Institutional Review Board.

Data source

We used the database of the Health Insurance Review and Assessment Service, an independent Government agency responsible for conducting reviews of health claims data and evaluating the appropriateness of medical benefits submitted by healthcare organizations. Health Insurance Review and Assessment Service's claims data include all medical utilization covered by insurance program of entire Korean population. National Health Insurance program covers the majority of the population and Medical Aid manages the remaining 3% (special population with low socioeconomic status).

Study population and operational definitions of psoriasis and inflammatory bowel disease

Patients with inflammatory bowel disease refer to those who have International Classification of Diseases, 10th revision, diagnostic codes of ulcerative colitis (K51.0, K51.1, K51.3, K51.5, K51.8, K51.9) or Crohn's disease (K50.x) from 2011 through 2015. Patients with psoriasis refer to those who have a diagnostic code of L40.x during the same period. We recategorized patients with psoriasis in 2015 into the severe group if they received phototherapy,

systemic agents (acitretin, cyclosporine, methotrexate) or biologic agents (infliximab, etanercept, adalimumab, ustekinumab). Otherwise, they were classified into the mild group.

Study outcomes

The primary endpoint was annual prevalence of inflammatory bowel disease in patients with psoriasis and the general population, respectively. The secondary outcome was risk of inflammatory bowel disease in psoriasis subgroups according to age, sex, insurance type and psoriasis severity.

Statistical analysis

Annual prevalence was calculated in two ways: (1) crude prevalence without adjustment and (2) standardized number per 100,000 population after adjusting for sex and age based on the 2013 population data from the Korea National Statistics Office.

Frequency analyses were conducted to describe the distribution of prevalence. We calculated crude odds ratios to identify the relative risk of prevalent inflammatory bowel disease in patients with psoriasis vs the general population. Next, we performed time-trend analyses using the Chi-squared test for trend method to investigate whether prevalence of inflammatory bowel disease increased over time. Lastly, the Cochran–Armitage test was used to identify whether different time trends existed between patients with psoriasis and the general population. All statistical tests were performed using SAS version 9.4 Enterprise Guide (SAS Institute, Inc., Cary, NC, USA). All tests were two-sided and a *P* value of < 0.05 was considered statistically significant.

Results

Characteristics of patients with psoriasis and the general population

The baseline characteristics of the study population are summarized in Table 1. We identified a total of 50,111,476 patients, including 219,429 patients with psoriasis, in 2011. There were 43,689 patients with inflammatory bowel disease in the general population and 357 patients with inflammatory bowel disease among patients with psoriasis in 2011. These numbers increased between 2011 and 2015. Approximately 60% of subjects were male.

Prevalence of inflammatory bowel disease in patients with psoriasis and the general population

Prevalence of inflammatory bowel disease in patients with psoriasis and the general population were 0.16–0.21% and 0.08–0.11%, respectively [Table 2]. Prevalence in each group increased significantly between 2011 and 2015 (*P* = 0.002 in patients with psoriasis; *P* < 0.0001 in the general population). There was no significant difference in increasing trend between groups (*P* = 0.2049). When inflammatory bowel disease was classified into Crohn's disease and ulcerative colitis, similar patterns were revealed.

Table 1: Characteristics of the study population

	2011		2012		2013		2014		2015	
	Psoriasis (n=219,429), n (%)	General population (n=50,111,476), n (%)	Psoriasis (n=221,704), n (%)	General population (n=50,345,325), n (%)	Psoriasis (n=228,842), n (%)	General population (n=50,558,952), n (%)	Psoriasis (n=231,888), n (%)	General population (n=50,763,158), n (%)	Psoriasis (n=233,909), n (%)	General population (n=50,951,719), n (%)
Total IBD patients	357	43,689	404	45,593	397	48,218	448	51,074	490	54,125
Sex										
Male	222 (62.2)	25,184 (57.6)	258 (63.9)	26,745 (58.7)	243 (61.2)	28,538 (59.2)	290 (64.7)	30,478 (59.7)	315 (64.3)	32,615 (60.3)
Female	135 (37.8)	18,505 (42.4)	146 (36.1)	18,848 (41.3)	154 (38.8)	19,680 (40.8)	158 (35.3)	20,596 (40.3)	175 (35.7)	21,510 (39.7)
Age										
0-9	2 (0.6)	380 (0.9)	2 (0.5)	392 (0.9)	2 (0.5)	360 (0.7)	1 (0.2)	286 (0.6)	2 (0.4)	258 (0.5)
10-19	10 (2.8)	2855 (6.5)	22 (5.4)	3008 (6.6)	16 (4.0)	3241 (6.7)	24 (5.4)	3286 (6.4)	29 (5.9)	3264 (6.0)
20-29	37 (10.4)	6996 (16.0)	55 (13.6)	7536 (16.5)	55 (13.9)	8069 (16.7)	63 (14.1)	8938 (17.5)	70 (14.3)	9746 (18.0)
30-39	77 (21.6)	8055 (18.4)	69 (17.1)	8463 (18.6)	71 (17.9)	8787 (18.2)	69 (15.4)	9174 (18.0)	75 (15.3)	9594 (17.7)
40-49	67 (18.8)	8239 (18.9)	84 (20.8)	8437 (18.5)	67 (16.9)	8935 (18.5)	83 (18.5)	9475 (18.6)	97 (19.8)	9938 (18.4)
50-59	73 (20.4)	7902 (18.1)	80 (19.8)	8214 (18.0)	74 (18.6)	8794 (18.2)	84 (18.8)	9162 (17.9)	83 (16.9)	9561 (17.7)
60-69	56 (15.7)	5139 (11.8)	59 (14.6)	5110 (11.2)	62 (15.6)	5372 (11.1)	62 (13.8)	5761 (11.3)	69 (14.1)	6426 (11.9)
70-79	30 (8.4)	3230 (7.4)	28 (6.9)	3511 (7.7)	43 (10.8)	3641 (7.6)	55 (12.3)	3866 (7.6)	56 (11.4)	4044 (7.5)
80~	5 (1.4)	893 (2.0)	5 (1.2)	922 (2.0)	7 (1.8)	1019 (2.1)	7 (1.6)	1126 (2.2)	9 (1.8)	1294 (2.4)
Type of health insurance										
NHI	330 (92.4)	41,936 (96.0)	378 (93.6)	43,911 (96.3)	372 (93.7)	46,536 (96.5)	419 (93.5)	49,406 (96.7)	459 (93.7)	52,310 (96.6)
Medical aid	27 (7.6)	1753 (4.0)	26 (6.4)	1682 (3.7)	25 (6.3)	1682 (3.5)	29 (6.5)	1668 (3.3)	31 (6.3)	1815 (3.4)

IBD: Inflammatory bowel disease, NHI: National Health Insurance

	2011			2012			2013			2014			2015		
	Prevalence	Crude OR (95% CI)		Prevalence	Crude OR (95% CI)		Prevalence	Crude OR (95% CI)		Prevalence	Crude OR (95% CI)		Prevalence	Crude OR (95% CI)	
IBD															
Psoriasis	357/219,429 (0.16%)	1.87 (1.69-2.08)	404/221,704 (0.18%)	2.02 (1.83-2.23)	397/228,842 (0.17%)	1.83 (1.66-2.02)	448/231,888 (0.19%)	1.93 (1.76-2.12)	490/233,909 (0.21%)	1.98 (1.81-2.17)					
General population	43,689/50,111,476 (0.08%)	Reference	45,593/50,345,325 (0.09%)	Reference	48,218/50,558,952 (0.10%)	Reference	51,074/50,763,158 (0.10%)	Reference	54,125/50,951,719 (0.11%)	Reference					
CD															
Psoriasis	105/219,429 (0.05%)	1.62 (1.34-1.96)	129/221,704 (0.06%)	1.82 (1.53-2.17)	116/228,842 (0.05%)	1.47 (1.23-1.77)	140/231,888 (0.06%)	1.68 (1.42-1.98)	168/233,909 (0.07%)	1.94 (1.66-2.25)					
General population	14,840/50,111,476 (0.03%)	Reference	16,133/50,345,325 (0.03%)	Reference	17,469/50,558,952 (0.03%)	Reference	18,304/50,763,158 (0.04%)	Reference	18,996/50,951,719 (0.04%)	Reference					
UC															
Psoriasis	264/219,429 (0.12%)	2.03 (1.80-2.29)	285/221,704 (0.13%)	2.14 (1.91-2.41)	290/228,842 (0.13%)	2.03 (1.81-2.28)	314/231,888 (0.14%)	2.05 (1.83-2.29)	331/233,909 (0.14%)	2.01 (1.80-2.23)					
General population	29,818/50,111,476 (0.06%)	Reference	30,377/50,345,325 (0.06%)	Reference	31,687/50,558,952 (0.06%)	Reference	33,777/50,763,158 (0.07%)	Reference	36,149/50,951,719 (0.07%)	Reference					

P for trend in IBD: 0.002 (psoriasis), <0.001 (general population), 0.205 (psoriasis vs general population), 0.117 (psoriasis vs general population), <0.001 (general population), <0.001 (psoriasis vs general population), <0.001 (general population), 0.775 (psoriasis vs general population), 0.775 (psoriasis vs general population), (Cochran-Armitage Chi-square test for comparison between psoriasis and general population), CD: Crohn's disease, CI: Confidence interval, IBD: Inflammatory bowel disease, OR: Odds ratio, UC: Ulcerative colitis

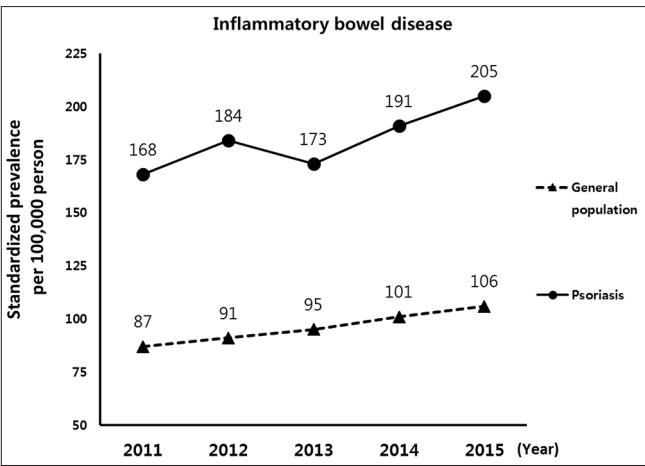


Figure 1a: Standardized prevalence (per 100,000 person) of inflammatory bowel disease in patients with psoriasis compared to that in general population. Total inflammatory bowel disease

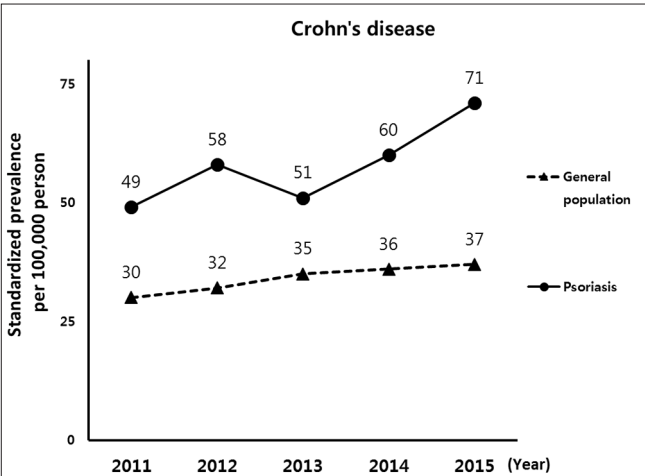


Figure 1b: Standardized prevalence (per 100,000 person) of inflammatory bowel disease in patients with psoriasis compared to that in general population. Crohn's disease

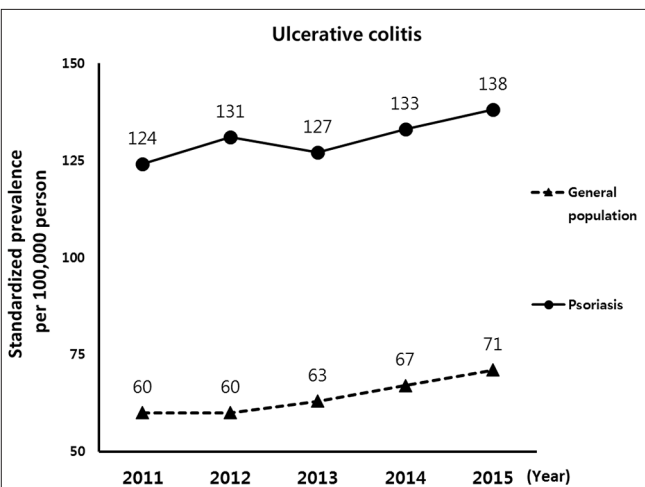


Figure 1c: Standardized prevalence (per 100,000 person) of inflammatory bowel disease in patients with psoriasis compared to that in general population. Ulcerative colitis

Table 3: Comparison of the prevalence of inflammatory bowel disease in the year of 2015 according to subgroups by sex, age and psoriasis severity

	Crude OR (95% CI)		
	IBD	CD	UC
Male			
Psoriasis	1.98 (1.81-2.17)	1.72 (1.43-2.07)	1.90 (1.65-2.18)
General population	Reference	Reference	Reference
Female			
Psoriasis	2.09 (1.80-2.42)	2.18 (1.67-2.84)	2.08 (1.74-2.48)
General population	Reference	Reference	Reference
Age ≤19 (years)			
Psoriasis	5.33 (3.74-7.59)	5.96 (4.02-8.85)	3.78 (1.80-7.95)
General population	Reference	Reference	Reference
Age 20-39 (years)			
Psoriasis	1.72 (1.46-2.02)	1.40 (1.09-1.81)	1.96 (1.58-2.42)
General population	Reference	Reference	Reference
Age ≥40 (years)			
Psoriasis	1.72 (1.54-1.92)	2.10 (1.69-2.60)	1.63 (1.44-1.86)
General population	Reference	Reference	Reference
National Health Insurance			
Psoriasis	2.02 (1.84-2.22)	1.97 (1.68-2.31)	2.04 (1.82-2.28)
General population	Reference	Reference	Reference
Medicaid			
Psoriasis	1.97 (1.38-2.82)	1.80 (1.02-3.18)	2.23 (1.45-3.44)
General population	Reference	Reference	Reference
Mild psoriasis (no systemic therapy)			
Psoriasis	1.68 (1.51-1.88)	1.44 (1.18-1.75)	1.81 (1.59-2.06)
General population	Reference	Reference	Reference
Severe psoriasis (all the systemic treatment)			
Psoriasis	2.96 (2.54-3.45)	3.61 (2.86-4.55)	2.64 (2.17-3.22)
General population	Reference	Reference	Reference
Severe psoriasis (systemic treatment excluding adalimumab and infliximab)			
Psoriasis	1.71 (1.40-2.09)	0.97 (0.62-1.52)	2.08 (1.66-2.59)
General population	Reference	Reference	Reference
Psoriatic arthritis			
Psoriasis	2.67 (1.70-4.19)	1.52 (0.97-2.38)	3.20 (2.04-5.01)
General population	Reference	Reference	Reference

CD: Crohn's disease, CI: Confidence interval, IBD: Inflammatory bowel disease, OR: Odds ratio, UC: Ulcerative colitis

Patients with psoriasis demonstrated significantly increased likelihood of prevalent inflammatory bowel disease during the study period (crude odds ratio, 1.87–2.02). Again, when inflammatory bowel disease was classified into Crohn's disease and ulcerative colitis, both entities revealed increased likelihood [Table 2].

Next, we calculated age- and sex-adjusted standardized prevalence of inflammatory bowel disease, Crohn's disease and ulcerative colitis per 100,000 person during the study period. Patients with psoriasis consistently revealed higher standardized prevalence of inflammatory bowel disease, Crohn's disease and ulcerative colitis compared with the general population [Figure 1].

Association between inflammatory bowel disease and psoriasis in psoriasis subgroups

Subgroup analyses [Table 3] were performed using the data from 2015. Both sexes demonstrated increased risk of inflammatory bowel disease, Crohn's disease and ulcerative colitis. Although psoriasis increased the risk of inflammatory bowel disease in all age groups, patients younger than 19 years of age revealed the highest likelihood of inflammatory bowel disease (odds ratio, 5.33; 95% confidence interval, 3.74–7.59). Furthermore, Crohn's disease (odds ratio, 5.96; 95% confidence interval, 4.02–8.85) revealed a stronger association than ulcerative colitis (odds ratio, 3.78; 95% confidence interval, 1.80–7.95) in this age group. Severe psoriasis demonstrated higher

likelihood of inflammatory bowel disease (odds ratio, 2.96; 95% confidence interval, 2.54–3.45) compared with mild psoriasis (odds ratio, 1.68; 95% confidence interval, 1.51–1.88). As adalimumab and infliximab are commonly used to treat both inflammatory bowel disease and psoriasis in Korea, we also performed an analysis after excluding patients who were treated with these medications. Severe psoriasis still demonstrated increased risk of ulcerative colitis (odds ratio, 2.08; 95% confidence interval, 1.66–2.59) but not Crohn's disease (odds ratio, 0.97; 95% confidence interval, 0.62–1.52). Similarly, patients with psoriatic arthritis revealed increased risk of inflammatory bowel disease (odds ratio, 2.67; 95% confidence interval, 1.70–4.19), especially ulcerative colitis (odds ratio, 3.20; 95% confidence interval, 2.04–5.01). Patients with psoriasis demonstrated increased prevalence of inflammatory bowel disease, Crohn's disease and ulcerative colitis, irrespective of socioeconomic status (National Health Insurance or Medicaid).

Discussion

Psoriasis was once considered as a mere localized cutaneous disease demonstrating well-demarcated erythematous plaque with silvery scales. However, intensive studies changed the main concept of the disease, which led to a new perspective of psoriasis as an immune-mediated disease with systemic inflammation and associated comorbidities, including inflammatory bowel disease, metabolic syndrome, cardiovascular disease, psoriatic arthritis, chronic kidney disease and mood disorders.^{4,5,15-18} Retrospective research from a large academic setting revealed that 73% of patients with psoriasis have at least one comorbidity.¹⁹ Another study revealed higher prevalence of selected comorbidities of interest in patients with psoriasis compared with control patients (odds ratio, 1.68; 95% confidence interval, 1.66–1.69), which was observed in all age groups.⁷ Therefore, comprehensive management of psoriasis and its comorbidities appears to be important.²⁰

Although inflammatory bowel disease is one of the representative comorbidities of psoriasis, the epidemiology of this association remains poorly defined.⁵ In Korea, even the nationwide prevalence of inflammatory bowel disease itself was not known, and only the prevalence in a localized district of Seoul (Songpa-Kangdong area, 1986–2005) had been reported.²¹ In this previous report, as of December 31, 2005, overall age- and sex-adjusted prevalence was 11.24/100,000 inhabitants (0.01%) for Crohn's disease and 30.87/100,000 inhabitants (0.03%) for ulcerative colitis.²¹ Other data from two teaching hospitals located in Seoul (1990–2012) revealed higher prevalence of Crohn's disease (0.043%) and ulcerative colitis (0.054%) among patients with psoriasis ($n = 9322$)²² compared with the general population²¹; however, the number of included patients was much too small ($n = 4$ for Crohn's disease; $n = 5$ for ulcerative colitis) to draw a definite conclusion. The present study demonstrated that the nationwide prevalence of Crohn's disease and ulcerative

colitis were 0.03–0.04% (49–71/100,000) and 0.06–0.07% (124–138/100,000), respectively, from 2011 through 2015, which increased with time. This pattern is compatible with a previous systematic review revealing increased incidence and prevalence of inflammatory bowel disease with time and in different areas around the world.²³ Notably, nationwide epidemiologic data of inflammatory bowel disease concurrent with psoriasis were scarce, but the present study identified the volume of patients with both diseases.

Previous epidemiologic studies demonstrated conflicting results regarding the association between inflammatory bowel disease and psoriasis. In particular, research from Taiwan using the National Health Insurance claims database reported that patients with psoriasis demonstrated lower risk of prevalent Crohn's disease compared with controls (adjusted risk ratio, 0.66; 95% confidence interval, 0.48–0.91).¹¹ They postulated that the discrepancies with previous studies were due to different ethnic backgrounds leading to differences in shared genetic susceptibility loci between psoriasis and inflammatory bowel disease. However, the present study does not suggest racial differences regarding the association between inflammatory bowel disease and psoriasis and demonstrated results consistent with previous studies from Western countries. In addition, a previous study in Korea demonstrated that patients with inflammatory bowel disease had higher risk of inflammatory skin disease, including psoriasis, which supports our findings in a way and helps to describe a bidirectional relationship between psoriasis and inflammatory bowel disease.²⁴

Whereas previous studies mostly included adult patients^{6,8,12,13} or did not perform subgroup analyses for underage patients,^{7,9,11} we further analyzed patients younger than 19 years of age. In 2015, patients with psoriasis younger than 19 years of age demonstrated the highest odds of prevalent Crohn's disease and ulcerative colitis, especially Crohn's disease, compared with the general population of the same age. Approximately one-fourth of patients with inflammatory bowel disease have onset before 20 years of age.²⁵ Additionally, pediatric patients with inflammatory bowel disease more frequently present with nonclassical symptoms²⁶ and extraintestinal manifestations, including anemia, uveitis, autoimmune hepatitis, arthritis, growth failure, osteopenia, pyoderma gangrenosum and erythema nodosum.^{26,27} Extraintestinal manifestations are more common in pediatric patients with Crohn's disease (15–25%) than ulcerative colitis (2–16%).^{28,29} These characteristics may explain the strong association between psoriasis and inflammatory bowel disease, especially Crohn's disease, in the younger age group.^{26,30} Although a thorough literature search by a psoriasis expertise panel found only a limited number of studies on pediatric psoriasis comorbidities, they recommended formal gastrointestinal evaluation in pediatric patients with psoriasis and unexplained growth retardation.³¹ It is noteworthy that our study added adequate evidence. Furthermore, patients

with concurrent psoriasis and inflammatory bowel disease in this age group may require a different treatment strategy to suppress autoimmunity, employing immune modulators or biologics, rather than conventional treatment.

Severe psoriasis demonstrated a higher association with concurrent inflammatory bowel disease (both Crohn's disease and ulcerative colitis) compared with mild psoriasis. In the present study, severe psoriasis was defined by the use of systemic psoriasis treatments or phototherapy. As some systemic antipsoriatic agents (biologics, cyclosporine, methotrexate) are also used for inflammatory bowel disease, the association between severe psoriasis and inflammatory bowel disease can be overestimated. Among biologics, infliximab and adalimumab are generally used to treat inflammatory bowel disease in Korea. Other overlapping agents, including cyclosporine and methotrexate, are scarcely used to treat inflammatory bowel disease in Korea. Therefore, we performed an additional analysis after excluding patients who had been treated with infliximab and adalimumab. As a result, the relationship between severe psoriasis and Crohn's disease was lost, whereas the association with ulcerative colitis was maintained. This may simply be because clinicians more frequently prescribe infliximab/adalimumab for Crohn's disease than for ulcerative colitis, or because patients with psoriasis and concurrent Crohn's disease truly had more severe psoriasis requiring treatment with infliximab/adalimumab, rather than only ulcerative colitis has true association.

Epidemiologic studies using a randomized psoriasis population or specific cohort may provide limited information. On the contrary, a very large insurance claims database provides more generalizable information on the prevalence of comorbidities. South Korea has been adopting a single mandatory national health insurance system and all types of healthcare institutions must submit health claims data to the Health Insurance Review and Assessment Service in order to receive reimbursement. In this way, the Health Insurance Review and Assessment Service has accumulated a vast amount of medical records since 2002 and has become one of world's largest medical databases. For example, the Health Insurance Review and Assessment Service gathered 1.3 billion health claims data from the entire Korean population in 2011.³²⁻³⁵ Similarly, the present study included the entire Korean population (approximately 50 million people) and can reflect real-world patients. Because a cross-sectional study using a health claims database usually targets the population of a specific country, further studies including a global population or a systematic review of various research is desired.

Our study has several limitations. First, we did not evaluate lifestyle factors, such as smoking, diet, alcohol intake or body mass index. Also, we had limited data for doing adjustment and multivariate analysis. Second, we did not evaluate causal

or temporal relationships due to the cross-sectional design. Third, detection or misclassification bias is possible. In spite of several limitations, this was a large-scale population-based study, including the entire Korean population, regarding prevalence of inflammatory bowel disease in patients with psoriasis compared with the general population. The present study suggests that prevalence of inflammatory bowel disease in patients with psoriasis significantly increased with time and patients with psoriasis revealed higher prevalence of inflammatory bowel disease compared with the general population. In addition, patients with psoriasis younger than 19 years of age demonstrated the highest risk of inflammatory bowel disease, especially Crohn's disease. Further work on these associations may enable us to better manage both inflammatory bowel disease and psoriasis and to reduce the burden.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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